Thrombosis in childhood ALL

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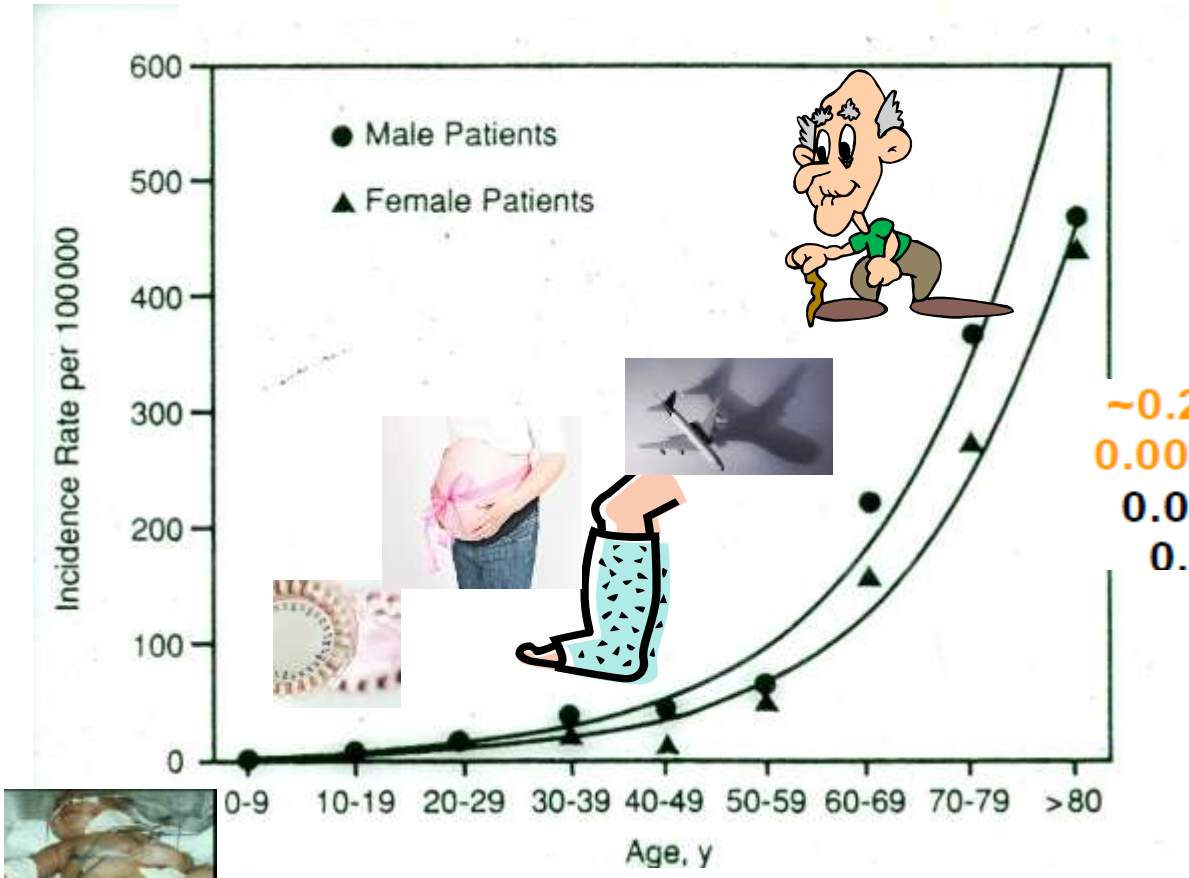
Case report

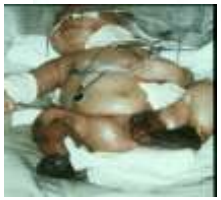
6 years old boy with ALL
started chemotherapy 1 month ago.
Central catheter difficulty of drawing blood
What are the options? And how to proceed?

Incidence of venous thrombotic events per 100,000 according to age

Figure 1. Annual incidence of VTE among residents of Worcester MA 1986, by age and sex. (Reproduced by permission from Anderson FA, et al. *Arch Intern Med.* 1991;151:933–938.)



~0.2 neonates
0.001 children
0.03 15-35 years
0.4 > 70 years



Among children neonates exhibit the highest risk for thrombosis

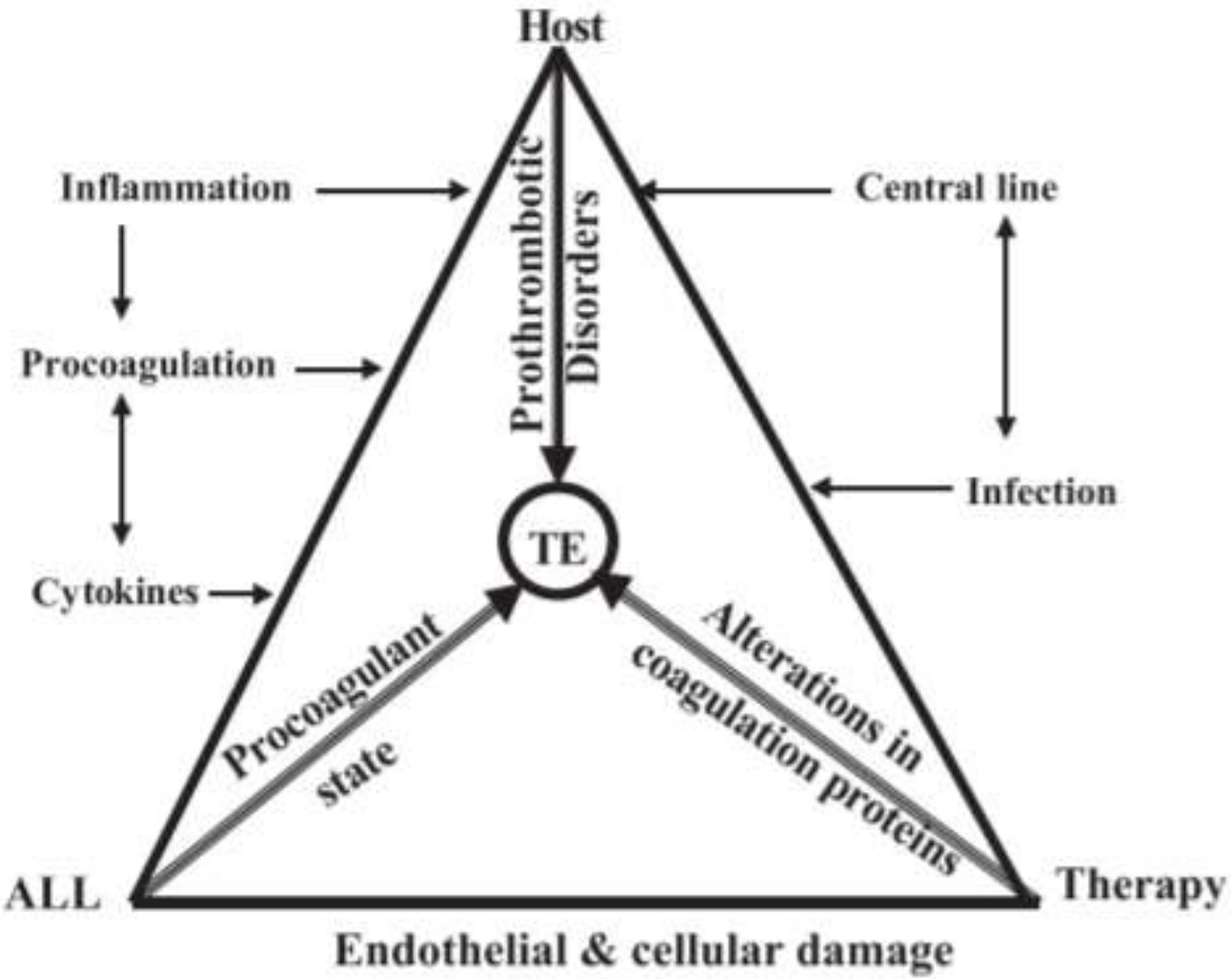
Thrombotic Disorders

- Genetic
  - Factor V Leiden mutation
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin III deficiency
  - prothrombin 20210 mutation
- Acquired
  - Antiphospholipid antibodies
    - (Anti-Cardiolipin antibodies)
  - Cancer
  - Atherosclerosis
  - Hyper-homocysteinemia
  - Infection
  - Stasis
  - Injury

Virchow's triad in cancer patients

- **Endothelial damage**
  - *Shift to procoagulant endothelium*
  - *Invasion of cancer cells into vessel wall*
- **Stasis of blood**
  - *Frequent immobilization, surgery*
  - *Compression of blood vessels by tumor*
- **Changes in the blood constituents**
  - *Activation of clotting proteins and blood cells*

Rudolf Virchow
1821–1902



U.H. Athale, A.K.C. Chan / Thrombosis Research 111 (2003) 125–131

Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients

Vanesa Caruso, Licia Iacoviello, Augusto Di Castelnuovo, Sergio Storti, Guglielmo Mariani, Giovanni de Gaetano, and Maria Benedetta Donati

The risk of thrombosis in children with acute lymphoblastic leukemia (ALL) reportedly ranges between 1% and 37%. Epidemiologic studies have usually been hampered by small numbers, making accurate estimates of thrombosis risk in ALL patients very difficult. The aim of this study was to better estimate the frequency of this complication and to define how the disease, its treatment, and the host contribute to its occurrence. We made an attempt to combine and analyze all published data on the association between pediatric ALL and thrombosis, by using a meta-analytic method. The rate of thrombosis in 1752 children from 17 prospective studies was 5.2% (95% CI: 4.2-6.4). The risk varies depending on several factors. Most of the events occurred during the induction phase of therapy. Lower doses of asparaginase (ASP) for long periods were associated with the highest incidence of thrombosis, as were anthracyclines and prednisone (instead of dexamethasone). The presence of central lines and of thrombophilic genetic abnormalities also appeared to be frequently associated with thrombosis. In conclusion, the overall thrombotic risk in ALL children was significant, and the subgroup analysis was able to identify high-risk individuals, a finding that will hopefully guide future prospective studies aimed at decreasing this risk. (Blood. 2006;108:2216-2222)

A Prospective Cohort Study Determining the Prevalence of Thrombotic Events in Children with Acute Lymphoblastic Leukemia and a Central Venous Line Who are Treated with L-Asparaginase

Results of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study

Lesley G. Mitchell, M.Sc. and the PARKAA Group

Population Health Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada.

Presented in part at the meeting of the American Society of Hematology, New Orleans, Louisiana, December 4, 1999. Also presented in part at the International Congress on Thrombosis, Porto, Portugal, May 7, 2000.

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L.G.M. is a research scholar of the Canadian Institutes of Health Research. M.A. and J.G. are a career investigators of the Heart and Stroke Foundation of Ontario.

Members of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) group are: Maureen Andrew MD, Population Health Sciences, The Hospital for Sick Children, Toronto, Canada; Kim Hanna M.Sc, Bayer Inc., Toronto, Canada; Thomas Abshire MD, Hematology/Oncology, Emory University School of Medicine, Atlanta, USA; Jacqueline Halton MD, Hematology/Oncology, Children's Hospital of Eastern Ontario, Ottawa, Canada; Ron Andurson MD, Dept Hematology/Oncology, Alberta Children's Hospital, Calgary, Canada; Irene Chortick MD, Dept Hematology/Oncology, University Hospital, Syracuse, USA; Sunil Sood MD, Dept Hematology/Oncology, W MacKenzie Health Sciences Centre, Edmonton, Canada; Donald Mahoney MD, Dept Hematology/Oncology, Texas Children's Hospital, Houston, USA; Patricia McCusker MD, Hematology/Oncology, Children's Hospital of Western, London, Canada; John Wu MD, Hematology/Oncology, B.C. Children's Hospital, Vancouver, Canada; Gary Dahl MD, Hematology/Oncology, Stanford University School of Medicine, Palo Alto, USA; Peter Chait MD, Radiology, Hospital for Sick Children, Toronto, Canada; Gabriella de Veber, Neurology, Hospital for Sick Children, Toronto, Canada; Kyong-Jin Lee MD, Cardiology, Hospital for Sick Children, Toronto, Canada; David Mikulis, Neurology, Toronto General Hospital, Toronto, Canada; Jeffrey Ginsberg MD, Medicine, McMaster University, Hamilton, Canada; Clifford Way MD, Cardiology, McMaster University, Hamilton, Canada.

The authors acknowledge and thank the study coordinators: Patsy Vogh, Monica Adams, Karen Billynsky, Alex Blay, Tracy Corr, Elaine Dollard, Christine McDonald, Julie Nichols, Judy Powers, Chris Trombley, and Hanna Zahn.

BACKGROUND. Thrombotic events (TEs) are serious secondary complications in children with acute lymphoblastic leukemia (ALL) who receive L-asparaginase (ASP) therapy; however, the prevalence of TEs has not been established. The primary objective of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study was to determine the prevalence of TEs. The secondary objective was to detect any association of TEs with the presence of congenital or acquired prothrombotic disorders.

METHODS. Children with ALL were screened for TEs at the end of ASP treatment using bilateral venograms, ultrasound, magnetic resonance imaging, and echocardiography. Symptomatic TEs were confirmed by appropriate radiographic tests. All tests were read by a blinded central adjudication committee.

RESULTS. Twenty-two of 60 children had TEs, a prevalence of 36.7% (95% confidence interval, 24.4–48.8%). TEs were located in the intravenous system of the brain in 1 patient, the right atrium in 3 patients, and the upper central venous system in 19 patients. TEs detected by venography resulted in 1) 25–100% occlusion, with 1 in 3 patients showing occlusion of > 75% of the greatest vessel dimension, and 2) the presence of collaterals in 60% of patients, with 40% categorized as major. No children with TEs were positive for factor V Leiden or prothrombin gene 20210A, and four of eight children with antiphospholipid antibodies had a TE.

The authors are all deeply saddened by the loss of their colleague and friend, Dr. Maureen Andrew, who passed away suddenly on August 26, 2001. Dr. Andrew was instrumental in the work reported here, and the authors respectfully dedicate this article to her memory.

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Thrombosis and acute lymphoblastic leukaemia

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Epidemiology

- **Cancer is found in 20% of pediatric patients with VTE**
- The most common malignancy in children is ALL, therefore it has an important role and impact on the pathogenesis and occurrence of VTE in children.
- **The reported prevalence of symptomatic VTE in children with ALL ranges from 2-3% (retrospective BFM study)and 14% (prospective study)**, however the prevalence of all reported cases including asymptomatic cases may range in some studies to up to 73%.
- There is a high incidence of PTS in survivors of childhood ALL. A significant proportion of ALL survivors develop PTS, indicating previously undiagnosed DVT

Sutor AH et al: Bleeding and thrombosis in children with ALL treated according to the ALL-BDM-90 protocol, Klinpadiatr. 211 (1999) 201-204. Mitchel L et al, Cancer 2003; Caruso, V. et al. Blood 2006;108:2216-2222 ; Pyne et al BJH 2007; Nowak Gottl et al, Best Prac Hemat 2011

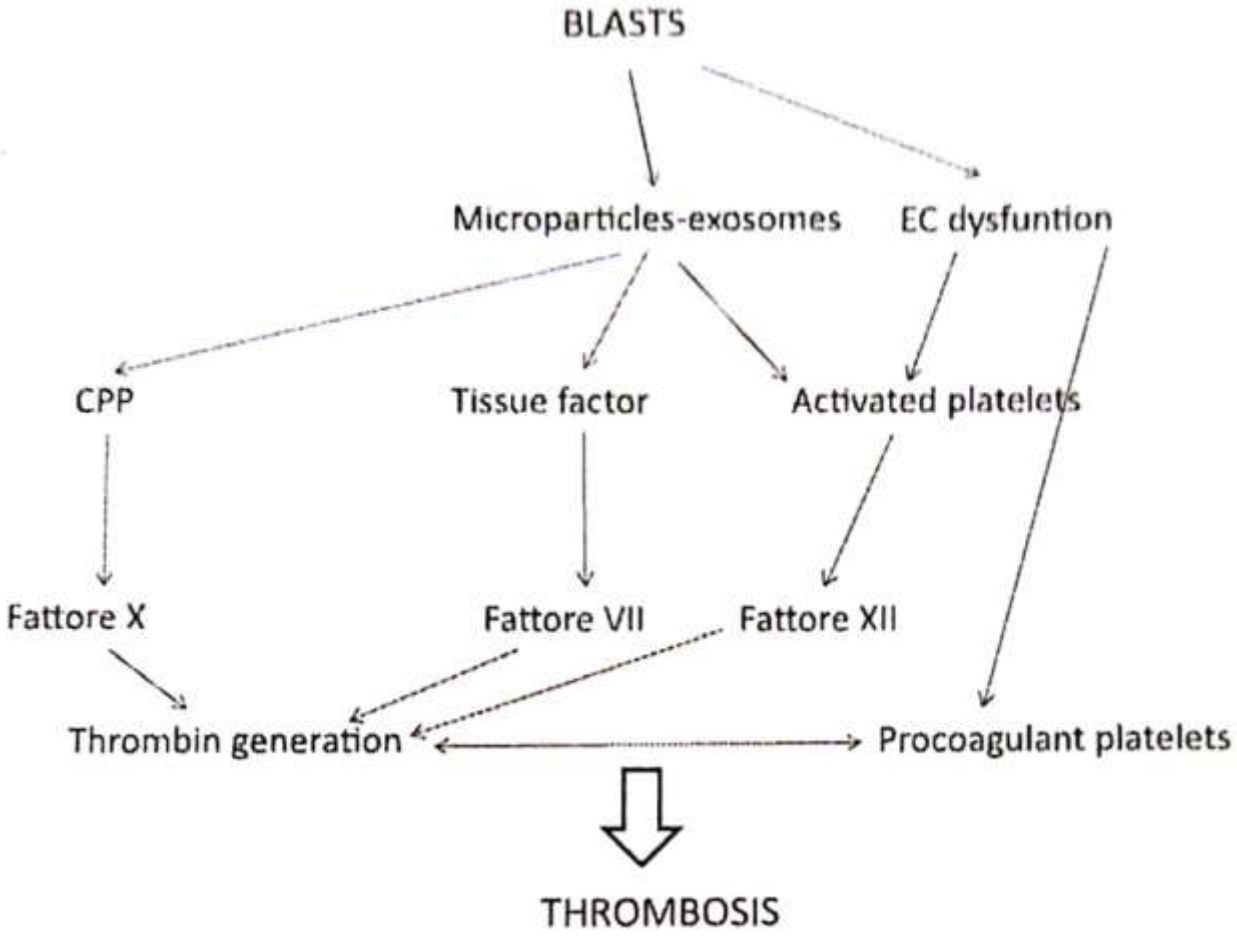

RISK

VTE risk factors in paediatric ALL

- treatment with *Escherichia coli* asparaginase
- concomitant use of steroids
- presence of central venous lines
- thrombophilic genetic abnormalities

[Caruso et al 2006 ; Payne 2007 ;Mitchell 2010; Nowak-Gottl 2011]

Hemostatic changes in leukemia – pre- therapy



Principe et al . Thrombosis in adult patients with acute leukemia. CurrOpinOncol 29 (2017) 448-454

Post therapy: Steroids

- Increase production of pro-coagulant FXII, FXI, FIX, FX, FVIII,FVII,FV,FII and inhibitors of proteolysis (PAI-I , anti-plasmin)
- Reducese fibrinolysis (tpa, plasminogen)

- N- Gottl et al. demonstrated that dexamethaonse may have some protective role vs prednisone in induction therapy
- Changes in protocols entail a different risk of thrombosis

- Athale et al. Evaluation for inherited and acquired prothrombotic defects predisposing to symptomatic thromboembolism in children with acute lymphoblastic leukemia: a protocol for a prospective, observational, cohort study, BMC Cancer. 2017 May 4;17(1):313
- Nowak Gottl U et al; Thromboembolic events in children with ALL (BFM protocol): prednisone vs dexamethasone administration. Blood. 2003:

L-asparaginase

- An increase in thrombotic events has been observed with the use of L-asp in a variety of chemotherapy protocols

(Mitchell, Semin Thromb Hemost, 1995)

- Thrombosis is mainly venous with a predilection to the central nervous system

(Kieslich, Pediatr Oncol, 2003.

Alberts,

Leuk Lymphoma, 1999)

Increased Endogenous Thrombin Generation in Children With Acute Lymphoblastic Leukemia: Risk of Thrombotic Complications in L'Asparaginase-Induced Antithrombin III Deficiency

By L. Mitchell, R. Hoogendoorn, A.R. Giles, P. Vegh, and M. Andrew

Table 1. Plasma Concentration of Coagulation Proteins

Test	Pretreatment at Diagnosis (n = 14)	After Treatment With ASP Only (n = 15)	Combination Therapy Without ASP (n = 15)	Combination Therapy With ASP* (n = 12)	Normal Controls (n = 14)
II (μ/mL)	0.94 ± 0.07	0.79 ± 0.05	1.19 ± 0.06†	1.22 ± 0.08†	0.88 ± 0.02
ATIII (μ/mL)	0.98 ± 0.03	0.58 ± 0.04†	0.95 ± 0.04	0.70 ± 0.06†	0.99 ± 0.03
α_2M (μ/mL)	1.8 ± 0.12	1.57 ± 0.08	1.49 ± 0.1	1.60 ± 0.11	2.25 ± 0.1
HCII (μ/mL)	1.35 ± 0.13†	0.68 ± 0.06†	1.37 ± 0.13†	0.85 ± 0.10	0.97 ± 0.06
Protein C (μ/mL)	0.89 ± 0.07	0.61 ± 0.09†	1.30 ± 0.1†	1.07 ± 0.1	0.9 ± 0.05
Total protein S (μ/mL)	0.96 ± 0.09	0.68 ± 0.04	1.11 ± 0.07†	1.03 ± 0.05†	0.78 ± 0.03
Free protein S (μ/mL)	0.28 ± 0.03†	0.24 ± 0.03†	0.47 ± 0.02	0.33 ± 0.03	0.41 ± 0.03

Data are presented as mean ± one standard error of the mean.

* Represents time in therapy that the patients are at risk for thrombotic events.

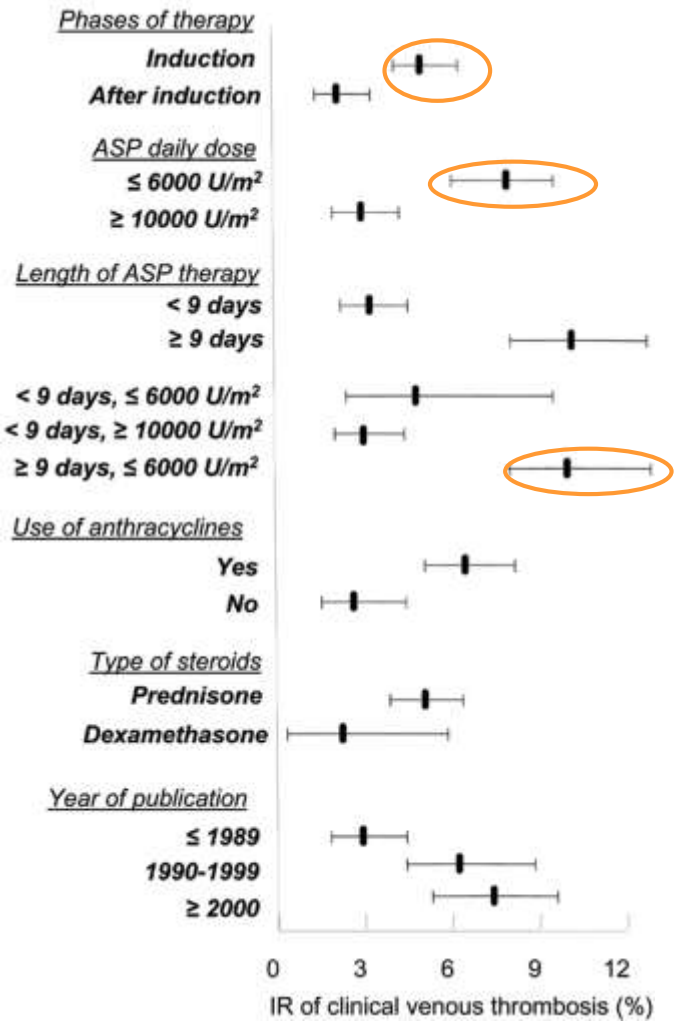
† Indicates a significant difference from healthy controls of at least $P < .01$.

Asparaginase- MOA

- Decrease of natural anticoagulants such as anti-thrombin, protein C and S following which there is an increase in thrombin generation.

- Risk of thrombosis does not seem to be significantly affected by type of ASP utilized. However, different commercial preparations exhibit various half life of ASP enzymes and may result in prolonged periods of hemostatic impairment

IRs of clinical thrombotic events in different subgroups of studies

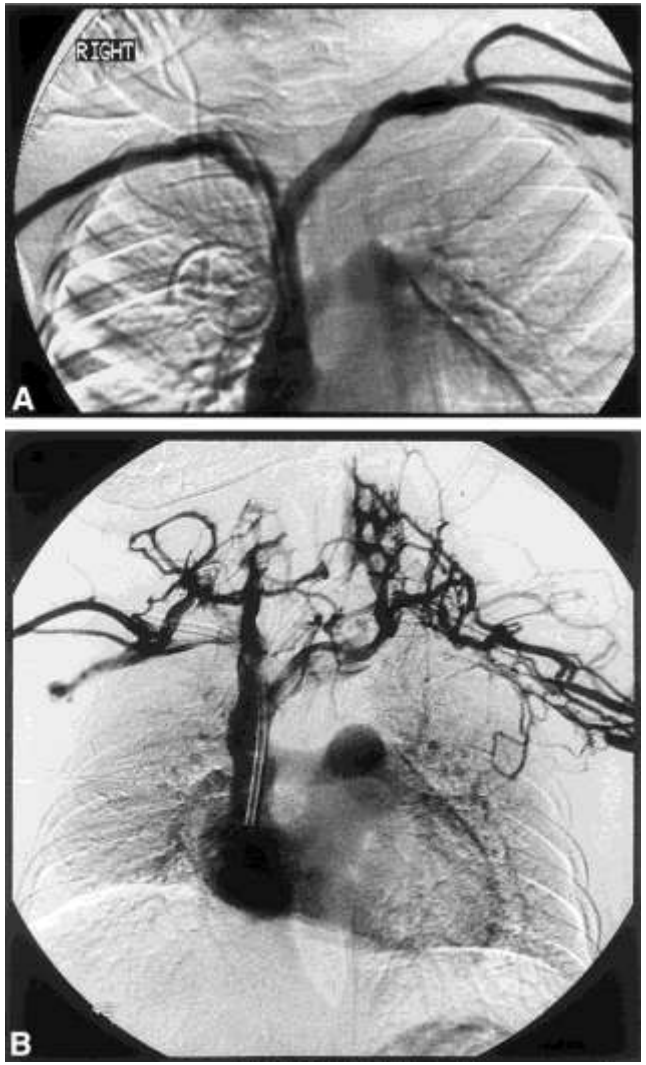


equivalent dosages:

Erwinia
E. Coli A [Crasnitin]
E. Coli B [Kyowa, Japan]

Caruso, V. et al. Blood 2006;108:2216-2222

A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase



Cancer 2003; 97(2): 508-516

More clinical data?

Clinical presentation – *Location of thrombosis*

- Most thrombotic events are of a venous origin
- most common location for thrombosis was CNS in 50% of cases, of which the majority were cerebral venous thrombosis.

- upper limb DVT associated with CVL comprised 27.5% cases.

- The rest : PE=1% Right atrium (1%) , superficial (2.2%)

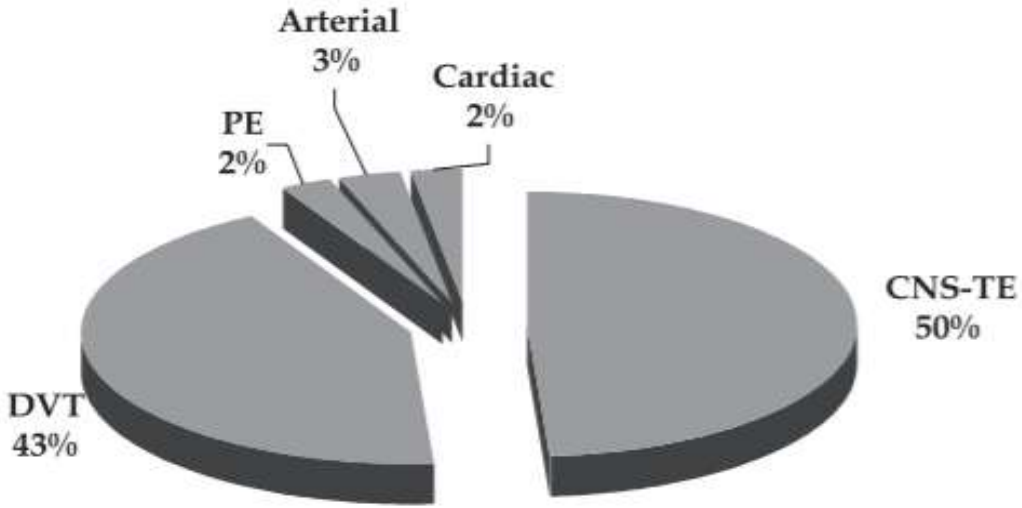


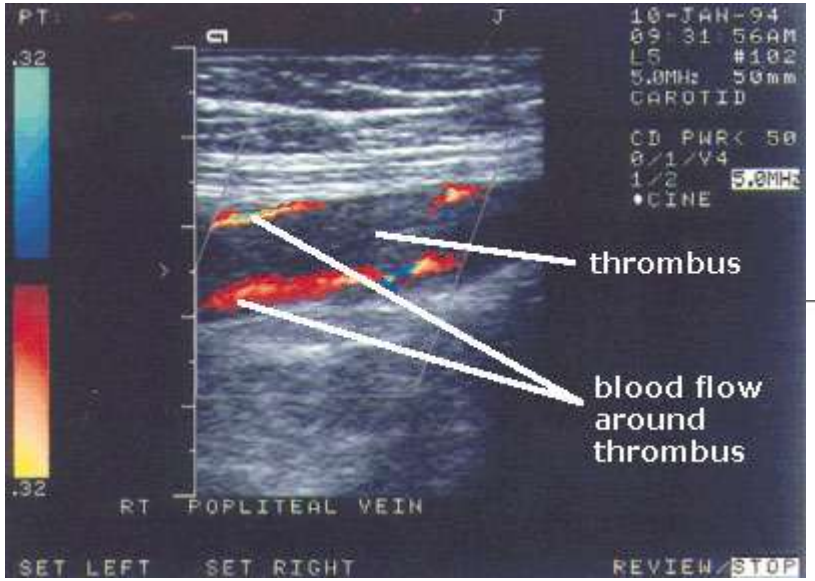
Fig. 1. Anatomical distribution of symptomatic TE in children with ALL; ...bus. Over 50% of TEs are reported in ...ike CNS, right atrium and pulmonary ...lism; DVT = deep venous thrombosis; CNS-TE = central nervous system thromboembolism.

U.H. Athale, A.K.C. Chan / Thrombosis Research 111 (2003) 125–131

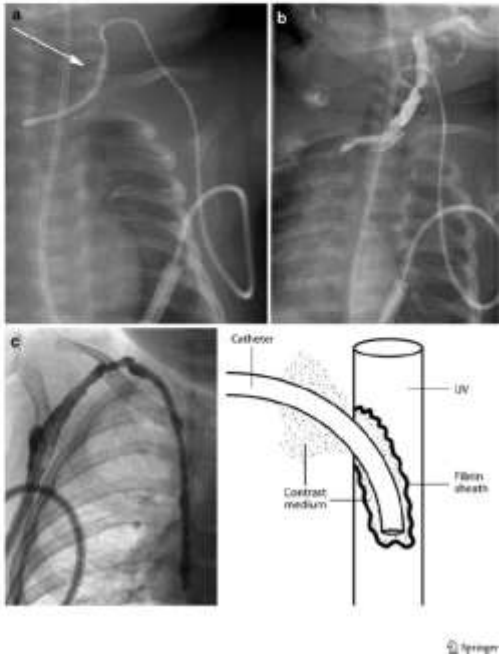
Arterial thrombosis

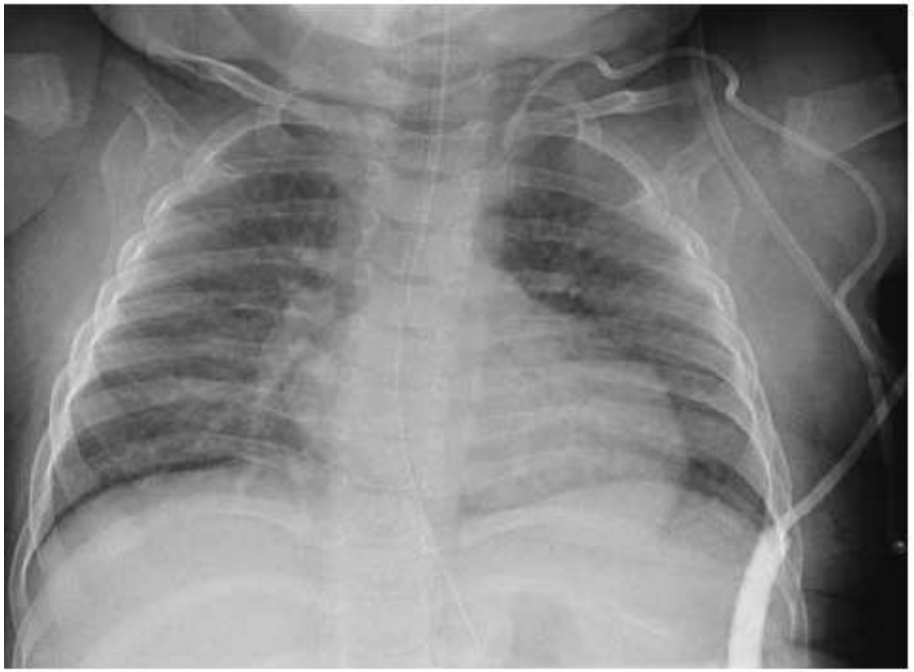
- Acute ischemic stroke (AIS) in the context of childhood ALL has been reported
- In large retrospective study looking at ischemic stroke among children treated for ALL, of a total of 2,318 ALL patients, 11 symptomatic ischemic strokes occurred in 11 patients (0.47%)
- Moyamoya syndrome occurs in increased frequency in survivors of childhood ALL. This may be attributed to treatment with cranial irradiation


your
next
step



- What are the options? And how to proceed?





Pediatric Blood & Cancer

RESEARCH ARTICLE

Need for tissue plasminogen activator for central venous catheter dysfunction is significantly associated with thrombosis in pediatric cancer patients

Jessica MacLean, Tamara MacDonald, Carol Digout, Nadine Smith, Krista Rigby, Ketan Kulkarni

First published: 14 March 2018
https://doi.org/10.1002/pbc.27015

Abstract

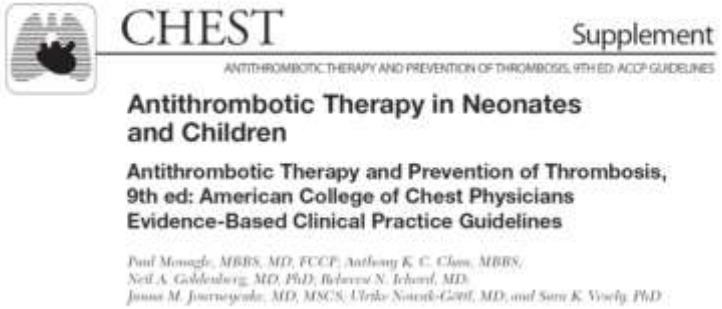
1 Background

Treatment of malfunctioning CVAD

- Malposition→remove.
- Fibrin sheath→ Urokinase
- Thrombus → Anticoagulation (ACT):

In children with CVAD in place who have a VTE, if CVAD no longer required or nonfunctioning-> remove, after at least 3-5 days ACT.

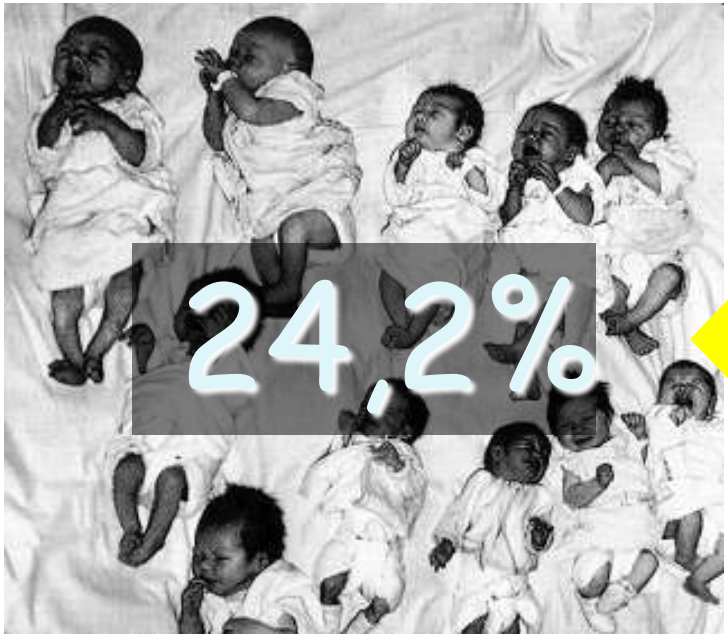
If CVAD still required and functioning, should remain in situ, and patient given ACT

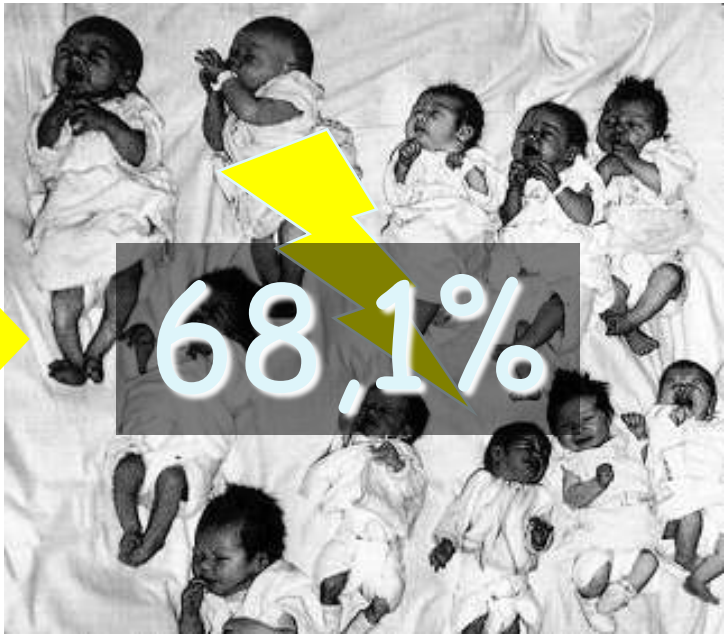


Role of Thrombophilia? Should we test?

Ped VTE– Statistics

(%IT)

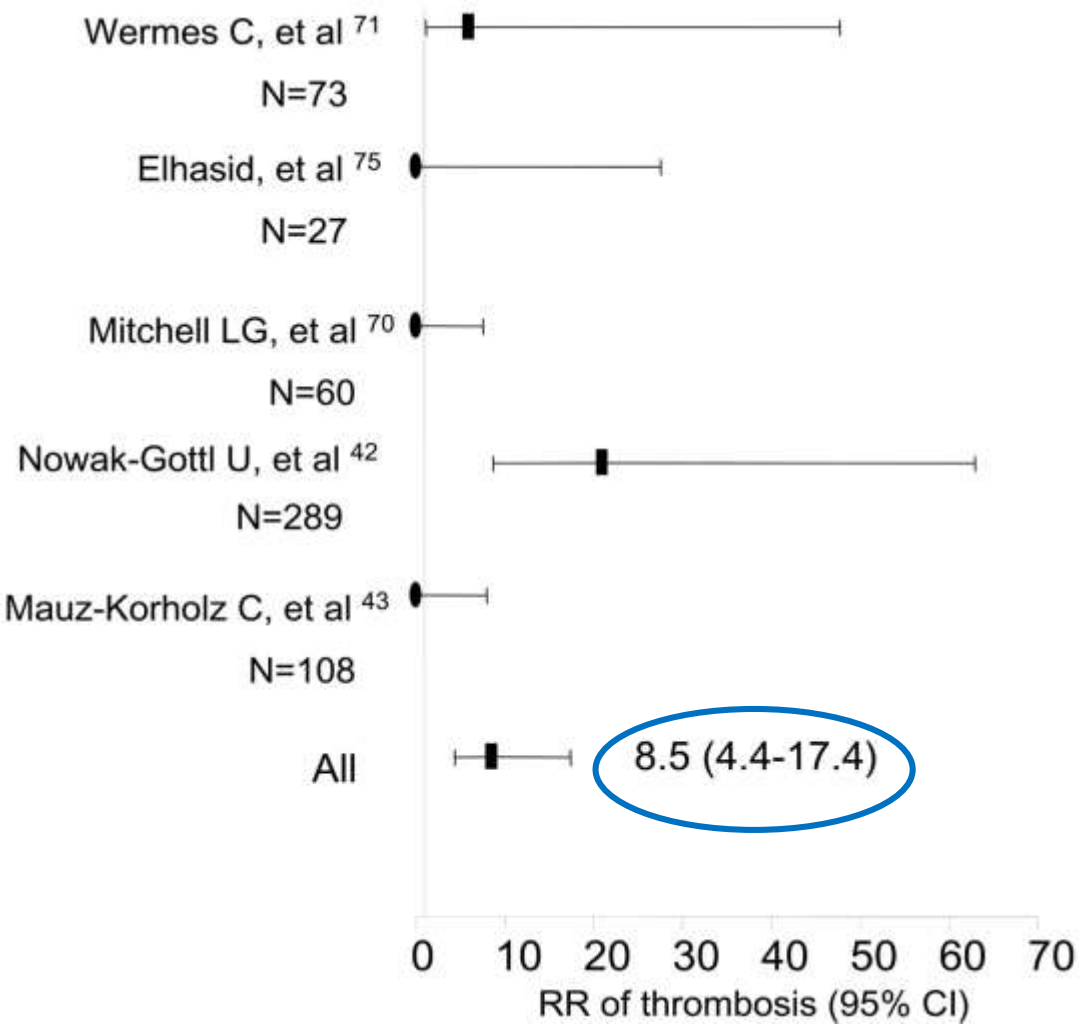




controls (healthy)

patients

Relative risk of thrombotic events in ALL children with at least one prothrombotic genetic defect



Caruso, V. et al. Blood 2006;108:2216-2222

- **Asp** therapy may exacerbate inherited deficiency of AT, PC and PS even in hetrozygous patients. FV Leiden may exacerbate the suppression of PC and PS as a result of ASP therapy.

- **Steroids** increase prothrombin levels, thus, PTM may render patients to even higher levels and increased risk of DVT.

- MTHFR C677T homozygousity in presence of folic acid deficiency may lead to endothelial activation due to increased Homocysteine levels- MTX.

1) Treat with LMWH
2) Check for thrombophilia?
3) Consider antithrombotic prophylaxis for high risk patients/situations
4) Neither FFP nor routine use of AT recommended in order to reduce thrombosis risk

BJH, Jan 2018: BSH guidelines : management of thrombosis in pediatric malignancy

Pediatric Thrombosis–Treatment

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy in Neonates and Children

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Paul Monagle, MBBS, MD, FCCP; Anthony K. C. Chan, MBBS; Neil A. Goldenberg, MD, PhD; Rebecca N. Ichord, MD; Janna M. Journeycake, MD, MSCS; Ulrike Nowak-Göttl, MD; and Sara K. Vesely, PhD

CHEST / 141 / 2 / FEBRUARY, 2012 SUPPLEMENT

Treatment

- 3 month of anticoagulation for DVT associated with cancer followed by 6 month of therapy if no clot resolution has occurred.
- Prophylaxis should be continued as long as any of the following risk factors exist: active cancer, CVL and chemotherapy.
- It has been previously recommended that patients that have suffered from DVT when re-introduced to ASP should receive anticoagulant prophylaxis prior to administration and for 48 hours post ASP exposure

Anti Coagulant Treatment

Low molecular weight heparin is the most commonly used treatment for DVT in children.

There are no evidence based studies of VTE treatment in children with hematological malignancies.....

Anti Xa should be monitored !

Should ACT prophylaxis be applied to children with ALL?

	BFM	COALL	FRALLE
Scoring system A			
Induction starting day 8			
PDN 40 mg/m^2 DEXA or	+ (0.5 points)	—	+ (0.5 points)
PDN 60 mg/m^2 and ASP 5000–6000 IU/m^2	++ (1 point)		
Maximum score	1.0	0	0.5
Scoring system B			
CVL, Broviac/Port	+ (1 point)	+ (1 point)	+ (1 point)
Genetics			
Thrombophilia (n = 1)	+ (1 point)	+ (1 point)	+ (1 point)
Thrombophilia (> 1)	+ (2 points)	+ (2 points)	+ (2 points)
Maximum score	3	3	3
Total score, minimum	0.5	0	0.5
Scoring systems A and B, maximum score	4.0	3.0	3.5

Pediatric ALL population:

Pilot cohort- 465 of 552 / Validation cohort- 339 of 347

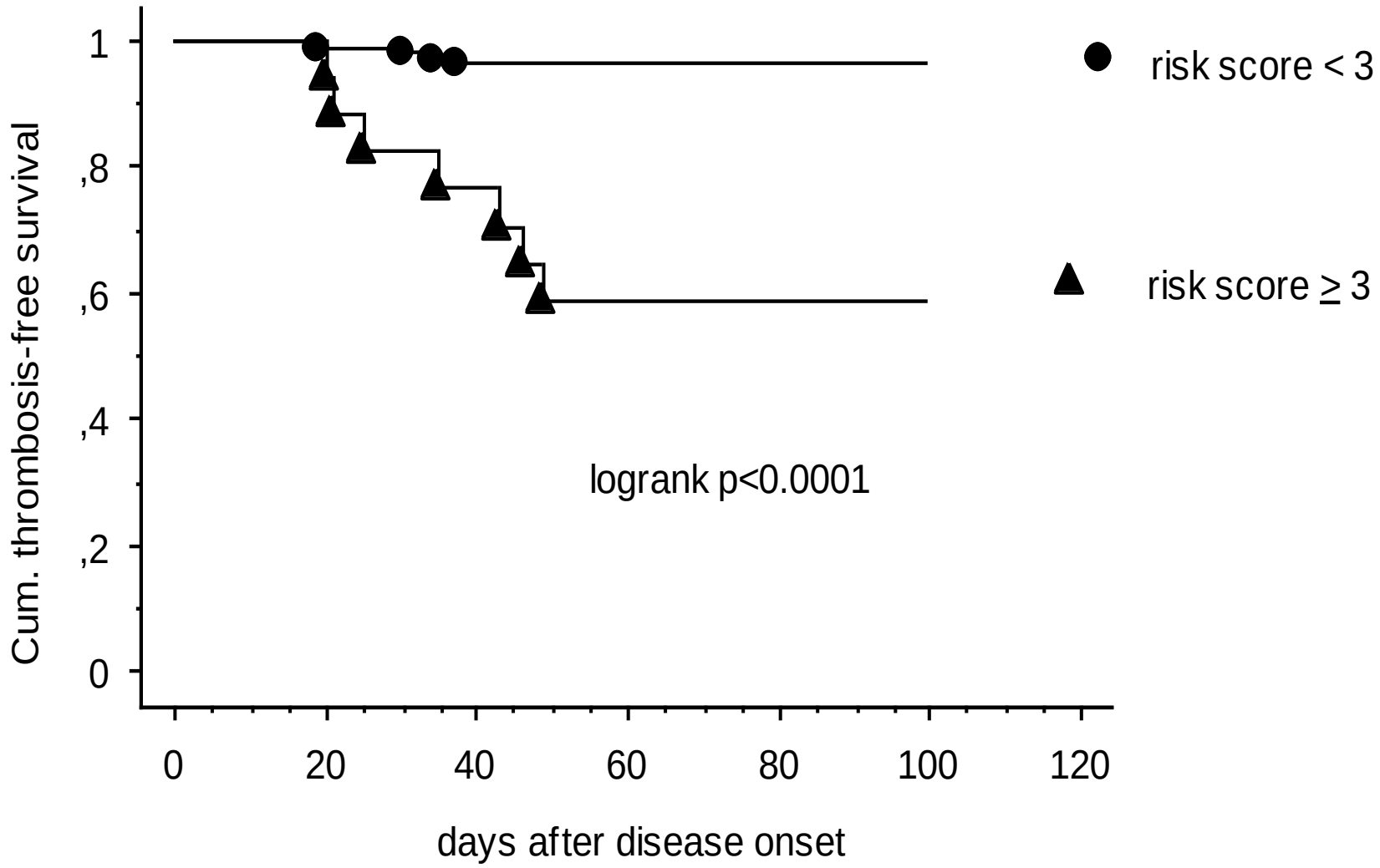
MITCHELL ET AL; BLOOD 2010 Scoring system for children with ALL according to different treatment protocols - BFM, Berlin-Frankfurt-Münster; COALL, Cooperative ALL; FRALLE, French ALL

Pediatric VTE: Primary prophylaxis - Suggested prophylaxis score

Points	Risk factor
1	ALL
1	positive family history/single thrombophilia
2	or combined thrombophilia/APS
1	central venous line

Σ	Risk score
≤ 1	low risk
2	medium risk
≥ 3	high risk

**E. coli B ASP 5000/m² x8; prednisone 60 mg/m²*

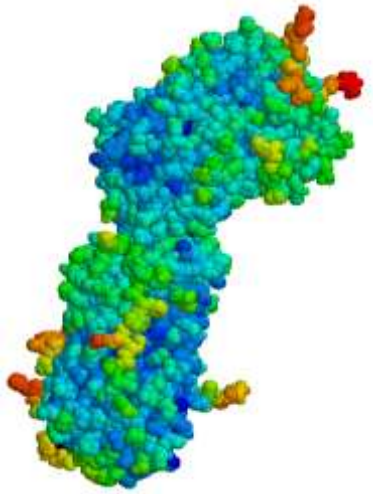

Cum. thrombosis-free survival
1
,8
,6
,4
,2
0
0
20
40
60
80
100
120
days after disease onset
risk score < 3
risk score ≥ 3
logrank p<0.0001

Consider VTE prophylaxis in ALL [high risk VTE patients]

- risk score ≥ 3
- enoxaparin 1 mg/kg/24h
  - prophylaxis start: days 8-12 (induction therapy)

→ platelet count < 20.000/µl: stop

AT Treatment- PARKAA



- PARKAA was an open, randomised, controlled study in children with ALL being treated with ASP.
- Children were randomised to receive antithrombin infusions or no antithrombin treatment. All thrombotic events were confirmed using bilateral venography, ultrasound, echocardiography and MRI.
- The incidence of thrombosis in patients treated with antithrombin was 28% (95% CI 10-46%), compared to 37% (95% CI 24-49%) in the non treated arm. Two minor bleeds occurred in patients in the treated arm, but were not considered to be related to antithrombin. No significant differences were seen in plasma markers by the treatment group.
- In conclusion, treatment with antithrombin concentrate shows a trend to efficacy and safety. In contrast, there was no difference in surrogate markers for thrombosis. Carefully designed clinical trials are needed to test the efficacy and safety of antithrombin in this population

Thromb Haemost 2003; 90(02): 235-244

Alternative anticoagulants

- Unfractioned heparin has the limitations of continuous administration, increased bleeding tendency however it is easily reversed.

- Warfarin, the only currently approved oral anticoagulant has a narrow therapeutic index, is affected by drug interactions and dietary changes that render it difficult for use in pediatric cancer patients.

	Discovered	Adult use	Ped Use
Heparin	1916	1937	1954
Warfarin	1929	1954	1976
LMWH	1970	1980	1990
Fundaparinux	1985	2001	2004

Bartolozzi G, Guazzelli C. [Two cases of septic thrombosis of the cavernous sinus cured by antibiotics and **heparin**.]Riv Clin Pediatr. 1954; Carpentieri U, Nghiem QX, Harris LC. Clinical experience with an **oral anticoagulant** in children. Arch Dis Child.1976; Massicotte P, Adams M, Mazinotto V, Brooker LA, Andrew M. **Low-molecular-weight heparin** in pediatric patients with thrombotic disease: a dose finding study. J Pediatr.1996; Young G, Nugent DJ. Use of argatroban and **fondaparinux** in a child with heparin-induced thrombocytopenia. Pediatr Blood Cancer. 2004;42:S542.

DOAC

- Direct oral anticoagulants (DOAC) have become widely used in adult patients with DVT.

- However, their use in active cancer associated DVT is still limited

- Currently DOAC are not approved for children and are only administered within clinical studies

Take home messages: Pediatric ALL thrombosis

- Epidemiology varies with study type
- Etiology:multifactorial
- Thrombophilia should not be routinely screened
- Different protocols yield variable risks
- Insufficient evidence to support replacement
- LMWH is the only drug for ACT
- Prophylaxis-individually tailored

Thanks!

Albisetti M, Bonduel M, Brandao L, Chalmers L, Chan A, Goldenberg NA, Heller C, Holzhauer S, Journeycake J, Male C, Mollinari AC, Manco-Johnson M, Mitchel L, Monagle P, van Ommen CH, Raffini L, Ravel Vilk S, Simioni P, Young G, Nowak-Göttl U