

Thrombosis in childhood ALL



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Case report

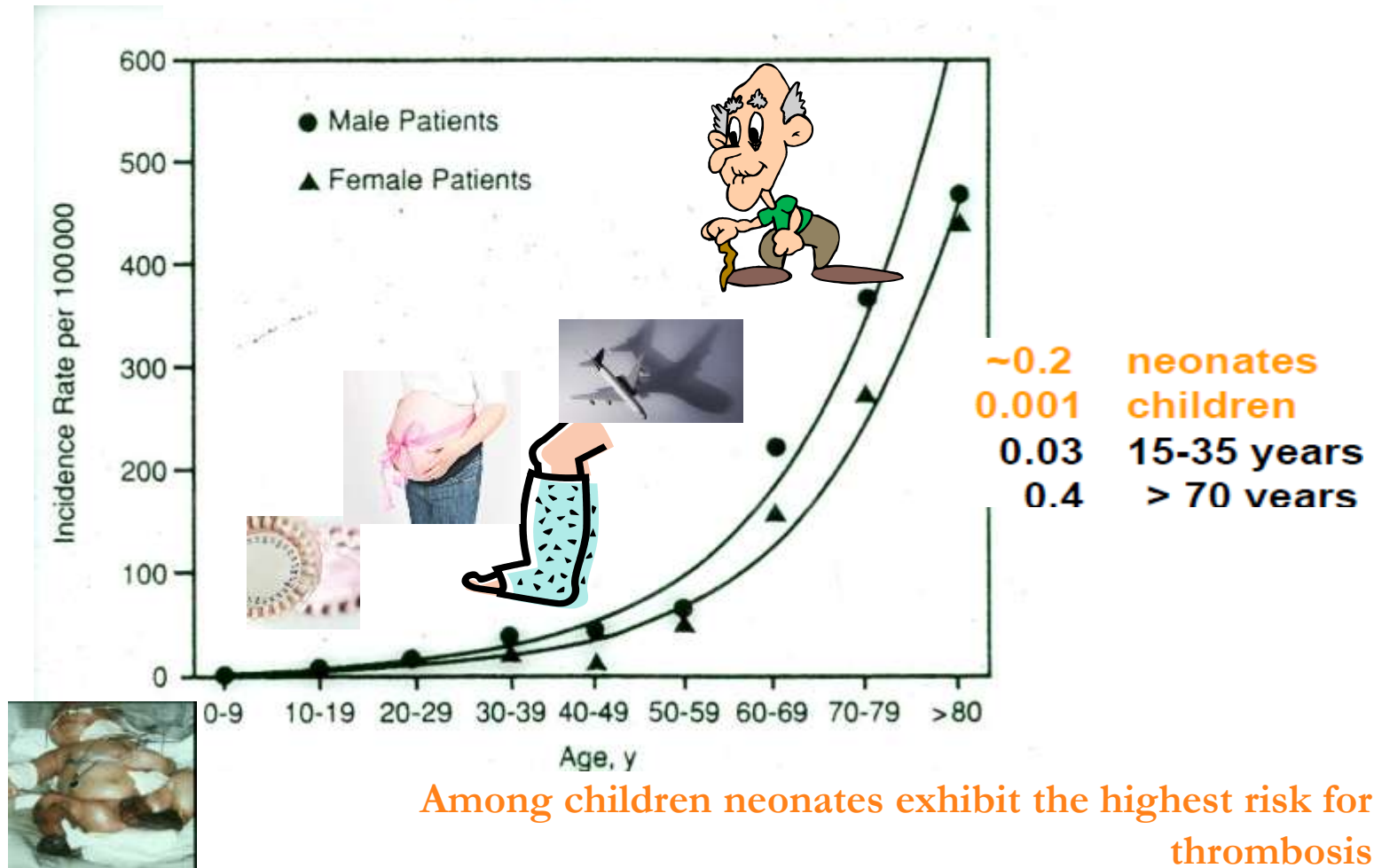
6 years old boy with ALL
started chemotherapy 1 month ago.
Central catheter difficulty of drawing
blood

**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.)



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

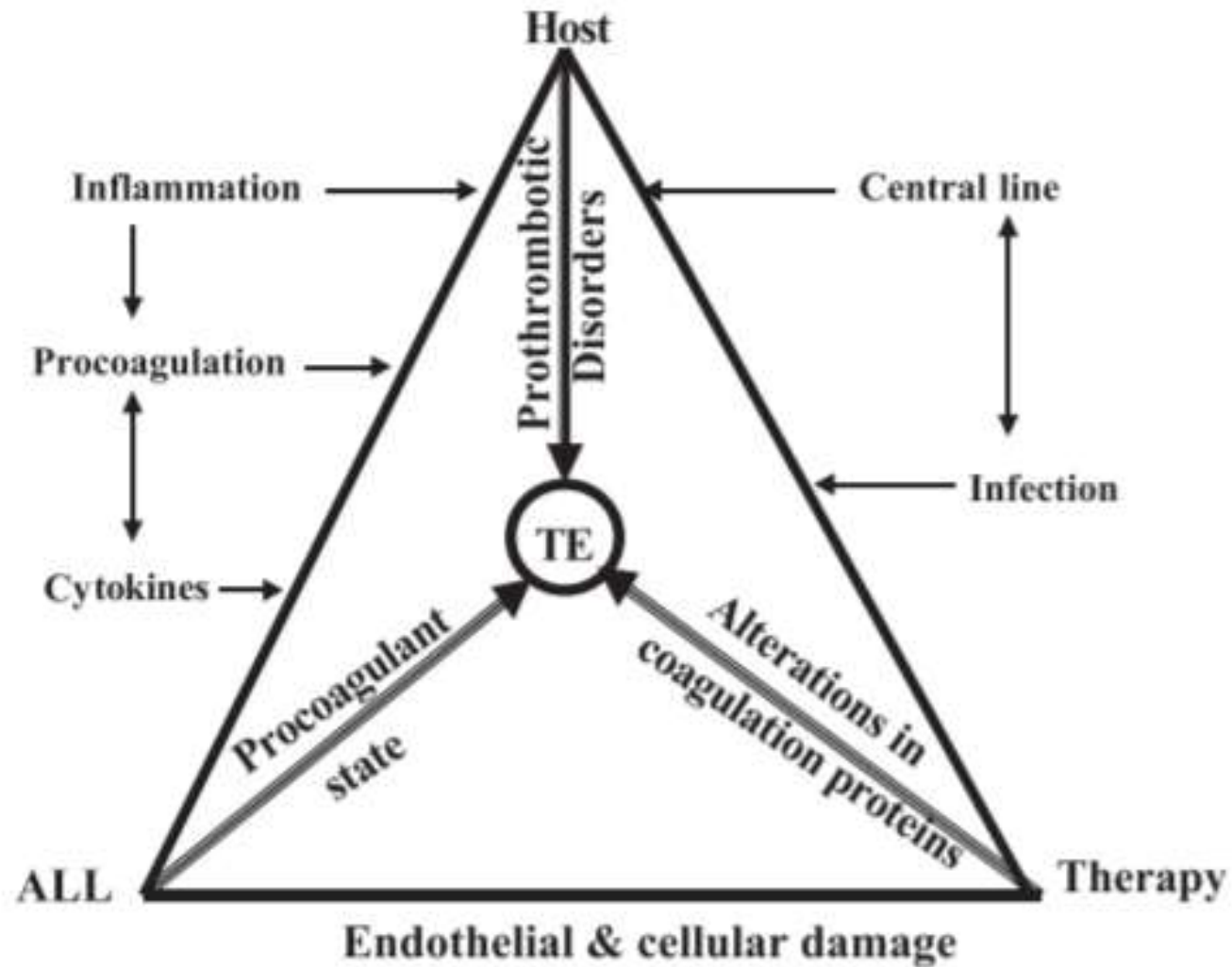
- *Frequent immobilization, surgery*
- *Compression of blood vessels by tumor*

▶ Changes in the blood constituents

- *Activation of clotting proteins and blood cells*



Rudolf Virchow
1821–1902



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

Vanessa 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)

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Thrombosis and acute lymphoblastic leukaemia

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Department of Paediatric Haematology, Sheffield Children's Hospital, Sheffield, UK

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 Anderson MD, Dept Hematology/Oncology, Alberta Children's Hospital, Calgary, Canada; Irene Chenikoff MD, Dept Hematology/Oncology, University Hospital, Syracuse, USA; Sunil Desai MD, Dept Hematology/Oncology, W MacKenzie Health Sciences Centre, Edmonton, Canada; Donald Mahoney MD, Dept Hematology/Oncology, Texas Children's Hospital, Houston, USA; Patricia McDougal MD, Hematology/Oncology, Children's Hospital of Western, London, Canada; John Wu MD, Hematology/Oncology, B.C. Children's Hospital, Vancouver, Canada; Gary Dahl

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 venous 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 diameter, 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 antithrombotic antibodies had a TE.

MD, Hematology/Oncology, Stanford University School of Medicine, Palo Alto, USA; Peter Chait MD, Radiology, Hospital for Sick Children, Toronto, Canada; Gabrielle de Volder, Neurology, Hospital for Sick Children, Toronto, Canada; Kwang Jin Lee MD, Cardiology, Hospital for Sick Children, Toronto, Canada; David Mikulis, Neurology, Toronto General Hospital, Toronto, Canada; Jeffrey Sinsberg MD, Medicine, McMaster University, Hamilton, Canada; Clifford Way MD, Cardiology, McMaster University, Hamilton, Canada.

The authors acknowledge and thank the study coordinators: Patsy Vogt, Monica Adams, Karen Blynsky, Alex Blay, Tracy Cor, Elaine Doffard, Christine McDonald, Julie Nichols, Judy Power, Chris Tromblay, and Hanna Zahra.

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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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**

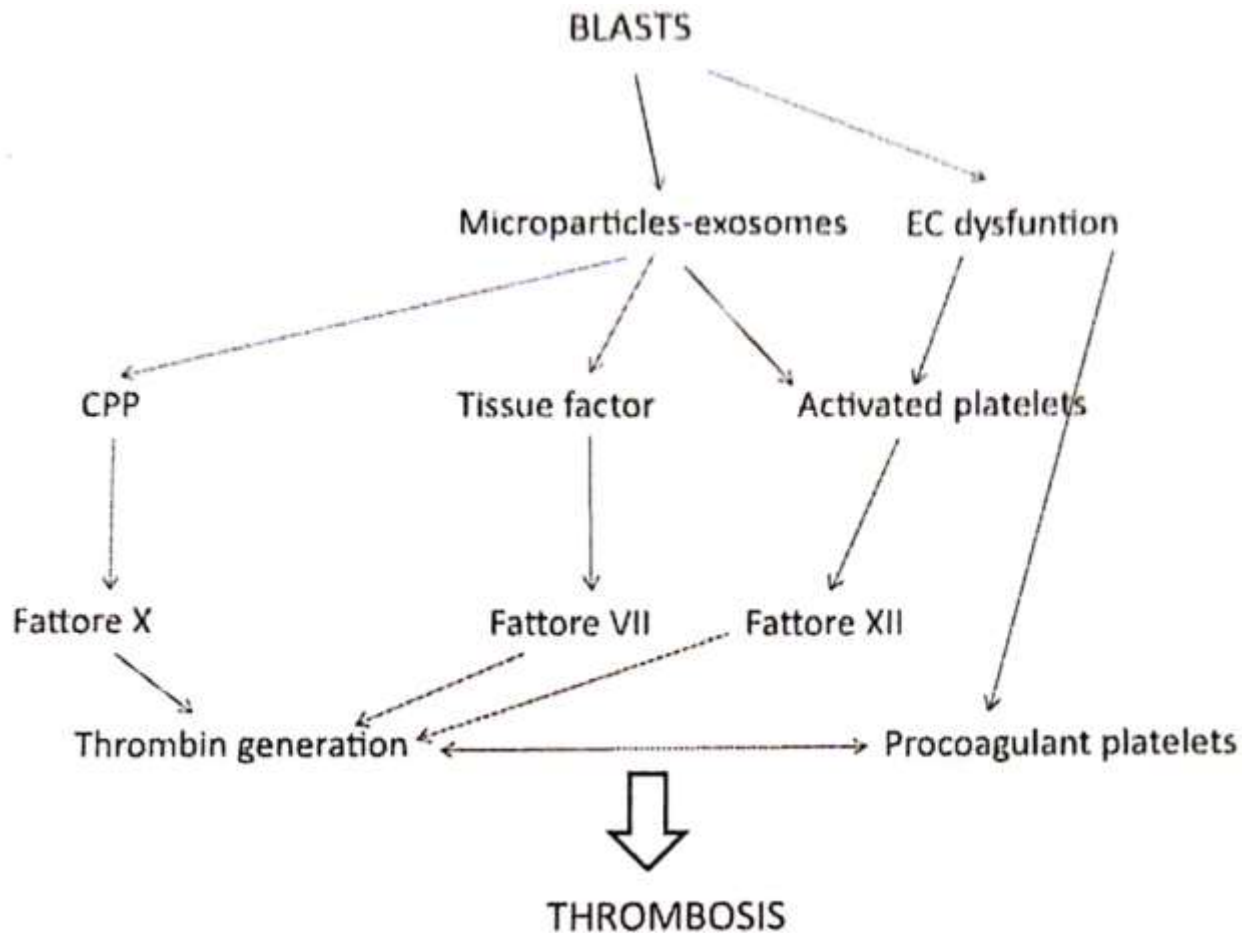


VTE risk factors in paediatric ALL

- ▶ 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)
 - ▶ Reduce fibrinolysis (tpa, plasminogen)
 - ▶ N- Gottl et al. demonstrated that dexamethasone 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-asparaginase 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, D. Hongreghien, A. B. Gane, P. Vajda, and M. Andrew

Pediatric patients with acute lymphoblastic leukemia (ALL) are at an increased risk of thrombotic events. Patient plasma concentrations indicate the disease process itself, treatment with chemotherapeutic agents (particularly L-Asparaginase [ASP]), or a combination of the disease and treatment. We studied thrombin generation in 28 pediatric patients with ALL and 18 healthy age-matched controls by: (1) plasma concentrations of pro-thrombin, (2) plasma titration of 125 I-thrombin, and (3) four biochemical markers of *in vitro* thrombin activation (thrombin compared to its inhibitor antithrombin III [AT], F1+2, prothrombin fragments 1+2 [F1+2], activated protein C compared to the inhibitors C1-inhibitor [APC/C1], and protein C inhibitor [APC/PCI]). Measurements were made at presentation, before treatment, after treatment with ASP alone, and during combination chemotherapy with and without ASP. At presentation, the capacity to generate thrombin (reflected by plasma prothrombin concentration) and the capacity to inhibit thrombin (AT—thrombin) in these samples (obtained) were similar in children with ALL compared with those for healthy children. After ASP alone or as part of combination chemotherapy, pro-

thrombin levels were preserved, whereas plasma inhibition of 125 I-thrombin decreased significantly (measure of a decrease in plasma concentrations of inhibitor, most importantly AT). After combination chemotherapy without ASP, plasma concentrations of AT and the capacity to inhibit 125 I-thrombin returned to normal values. In contrast, after combination chemotherapy with ASP, plasma concentrations of AT and the capacity to inhibit 125 I-thrombin were decreased from healthy controls. At presentation, plasma concentrations of three of four markers of *in vitro* thrombin activity (F1+2, APC/C1, but not APC/PCI) were increased in children with ALL. After ASP alone or combination chemotherapy with or without ASP, significantly altered values of these three markers. In summary, although the *in vitro* capacity to generate thrombin was preserved, the *in vitro* capacity to inhibit 125 I-thrombin decreased after ASP therapy. Evidence for increased endogenous thrombin generation was documented in children with ALL at presentation and throughout treatment. We speculate that poor regulation of this thrombin may contribute to thrombotic complications in children with ALL.

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and is used aggressively in the circulation phase of the F1+2 ALL protocols. ASP interferes with protein synthesis, thereby impairing the production of some coagulation proteins.

The F1+2 ALL protocols have an investigational window at diagnosis, facilitating evaluation of the effect of a single chemotherapeutic agent on untreated lymphoblasts *in vivo*. For the F1+2 protocol 87-001, the single drug was ASP. This provided an ideal opportunity to assess the effects of ASP on blood coagulation independent of previous or concurrent chemotherapy. In addition, blood coagulation was assessed in children before any intervention and after combination chemotherapy with and without ASP.

The generation and inhibition of thrombin constitute key steps in blood coagulation. Sensitive measures of endogenous generation of thrombin have been developed and include release of prothrombin fragments 1+2 (F1+2) by prothrombinase, thrombin complexed to its main inhibitor antithrombin III (AT) (F1+2-AT), and the generation of activated protein C, an antidote to circulating protein C complexes with its inhibitor C1-inhibitor and protein C inhibitor. The capacity of plasma to generate thrombin is reflected by the level of prothrombinase.^{1,2} Plasma capacity to inhibit thrombin can also be assessed by measuring the 125 I-thrombin assay to assess thrombin regulation in children with ALL at presentation, after treatment with ASP alone, and after treatment with combination chemotherapy with or without ASP.

MATERIALS AND METHODS

Patient population. The patient population was comprised of 28 consecutive children, aged 1 to 14 years, with ALL, referred to the Children's Hospital of Chukchee-Ma-Ma between March 1998 and July 1999. Their ages ranged from 2 to 13 years with a median age of 6 years. All patients were diagnosed with ALL as previously published³ and placed on the F1+2 protocol 87-001.

THE EFFECTS OF childhood acute lymphoblastic leukemia (ALL) have advanced to the extent that 5-year event-free survival (EFS) rates of approximately 80% have been achieved. The chemotherapeutic protocols for childhood ALL developed at the Dana-Farber Cancer Institute (DFCI, Boston, MA) are currently among the most successful. Children with standard risk (SR) ALL, defined by age and white blood cell count, have an 80% chance of a 5-year EFS, and children with high risk (HR) disease, a 75% 5-year EFS.⁴ The Children's Hospital at McMaster University Medical Centre (Hamilton, Ontario, Canada) has participated in the DFCI study group since 1985 and has achieved rates similar to the entire group.⁵ The successful treatment of ALL has been accompanied by an increase in thrombotic events have been linked to the drug L-Asparaginase (ASP). However, ASP is a very effective chemotherapeutic agent

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0885-0666/99/0808-1000\$10.00/0

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	$1.19 \pm 0.06^\dagger$	$1.22 \pm 0.08^\dagger$	0.88 ± 0.02
ATIII (μ /mL)	0.98 ± 0.03	$0.58 \pm 0.04^\dagger$	0.95 ± 0.04	$0.70 \pm 0.06^\dagger$	0.99 ± 0.03
α_2 M (μ /mL)	1.8 ± 0.12	1.57 ± 0.08	1.49 ± 0.1	1.60 ± 0.11	2.25 ± 0.3
HClII (μ /mL)	$1.35 \pm 0.13^\dagger$	$0.68 \pm 0.06^\dagger$	$1.37 \pm 0.13^\dagger$	0.85 ± 0.10	0.97 ± 0.06
Protein C (μ /mL)	0.89 ± 0.07	$0.61 \pm 0.09^\dagger$	1.30 ± 0.11	1.07 ± 0.1	0.9 ± 0.05
Total protein S (μ /mL)	0.96 ± 0.09	0.68 ± 0.04	$1.11 \pm 0.07^\dagger$	$1.03 \pm 0.05^\dagger$	0.78 ± 0.03
Free protein S (μ /mL)	$0.28 \pm 0.03^\dagger$	$0.24 \pm 0.03^\dagger$	0.47 ± 0.02	0.33 ± 0.03	0.41 ± 0.03

Data are presented as mean \pm one standard error of the mean.

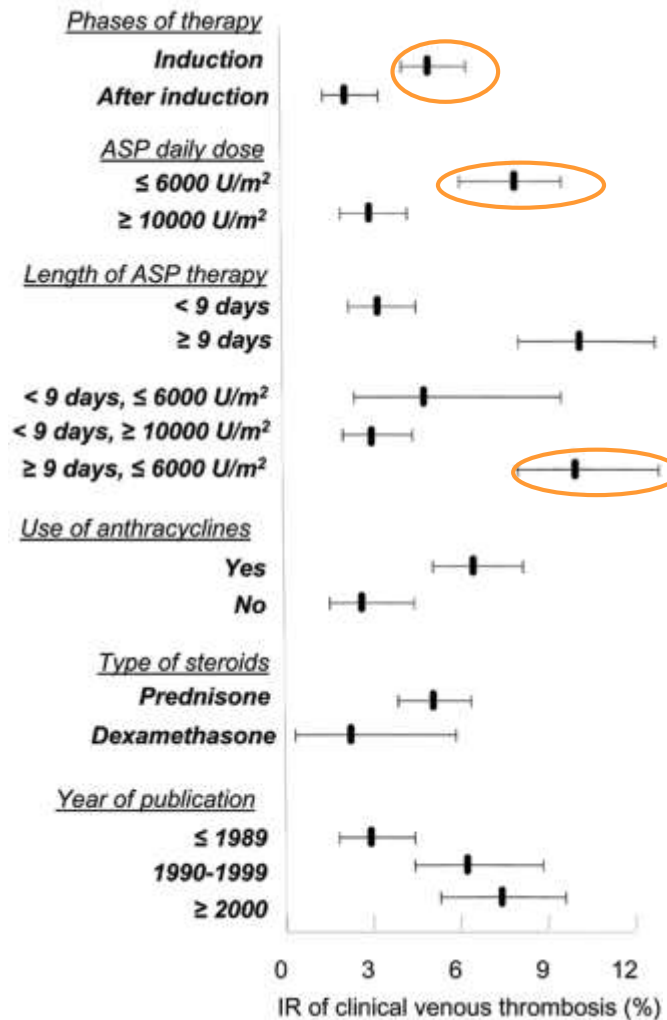
* Represents time in therapy that the patients are at risk for thrombotic events.

† 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

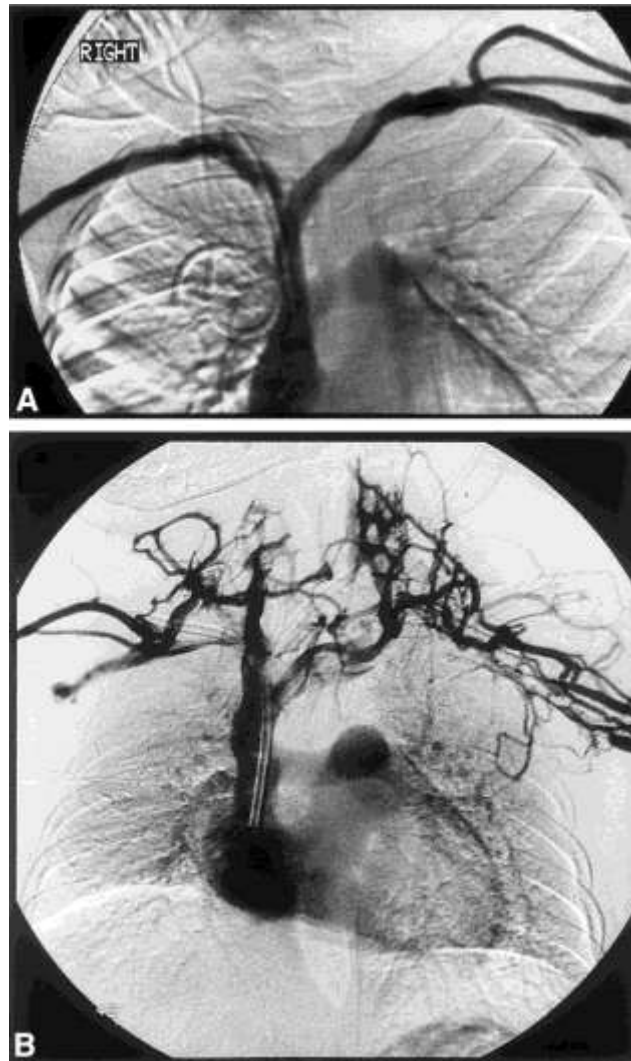


equivalent dosages:


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?

MEDICAL HISTORY FORM

Patient's name _____ DOB _____ Weight _____

ALLERGIES
If yes, please specify _____
Latex/Rubber/Eggs/Soybeans/Peanuts/Other _____
Please list all medications you are allergic to _____

CURRENT SYMPTOMS
Cough/Sputum > 3 weeks Yes / No
Fever, unexplained Yes / No
Weight loss / anorexia Yes / No
Night sweats Yes / No
Fatigue Yes / No

MEDICAL HISTORY
Asthma Yes / No
Cancer Yes / No
Depression Yes / No
Epilepsy Yes / No
Ear throat Yes / No
Ear problems Yes / No
Heart disease Yes / No
Liver disease Yes / No

FAMILY HISTORY
Heart Disease Yes / No
Cancer Yes / No
Diabetes Yes / No

SOCIAL HISTORY
Do you smoke? Yes / No
Do you drink? Yes / No
Do you live? Yes / No

Pressure Yes / No
Diabetes Yes / No
Cancer Yes / No
Heart problems Yes / No
Other Yes / No

Breast cancer Yes / No
Thyroid disease Yes / No
High blood pressure Yes / No
Depression Yes / No

wiseGEEK

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%)

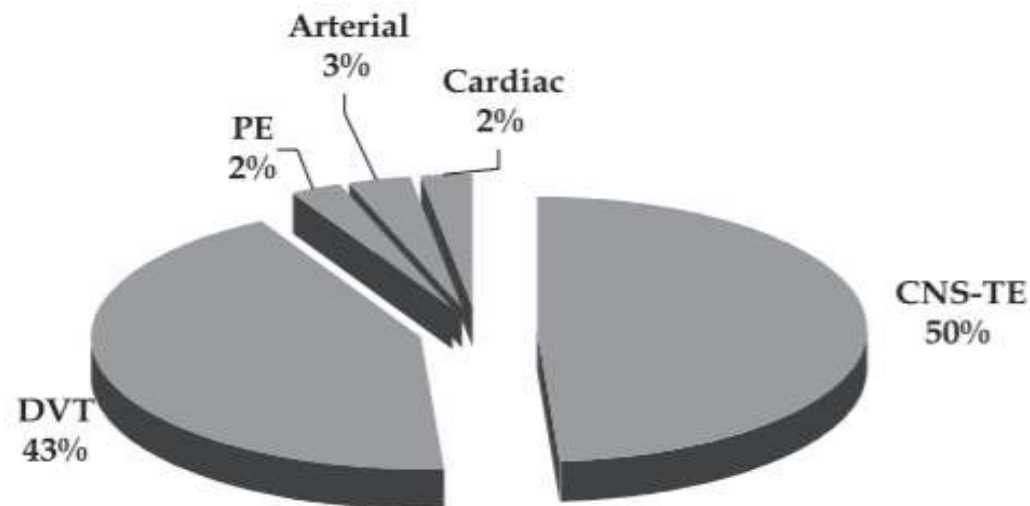


Fig. 1. Anatomical distribution of symptomatic TE in children with ALL; DVT=deep venous thrombosis. Over 50% of TEs are reported in venous locations like CNS, right atrium and pulmonary thromboembolism; DVT=deep venous thrombosis;

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

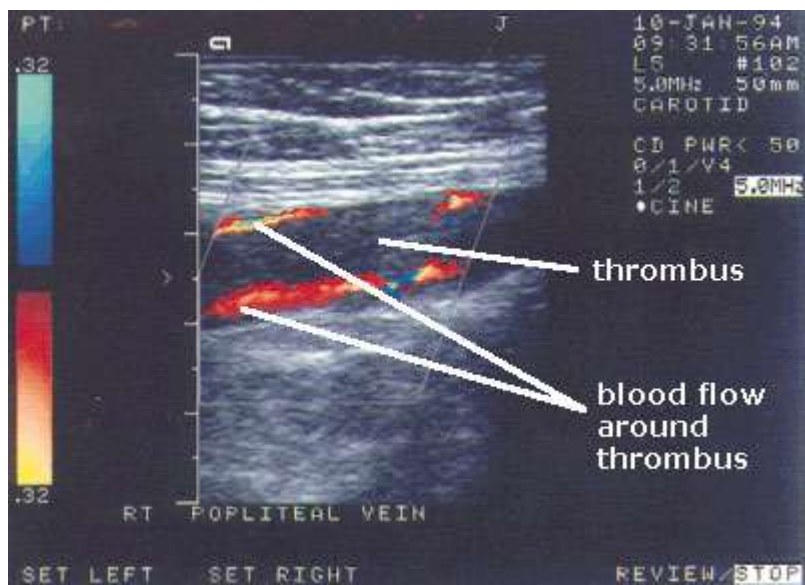
CNS-TE = central nervous system thromboembolism.

Arterial thrombosis

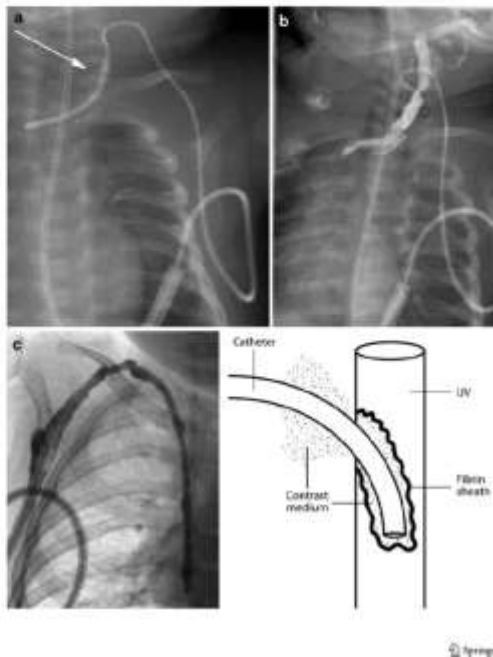
- ▶ Acute ischemic stroke (AIS) in the context of childhood ALL has been reported
- ▶ In large retrospective study looking at ischemic stroke among children treated for ALL, of a total of 2,318 ALL patients, 11 symptomatic ischemic strokes occurred in 11 patients (0.47%)
- ▶ **Moyamoya** syndrome occurs 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?



a



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



CHEST

Supplement

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

**Antithrombotic Therapy in Neonates
and Children**

**Antithrombotic Therapy and Prevention of Thrombosis,
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Evidence-Based Clinical Practice Guidelines**

Paul Monagle, MBBS, MD, FCCP; Anthony K. C. Chan, MBBS,
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Janus M. Journeay, MD, MSc; Ulrike Noack-Greif, MD; and Sara K. Vasey, PhD

Role of Thrombophilia? Should we test?

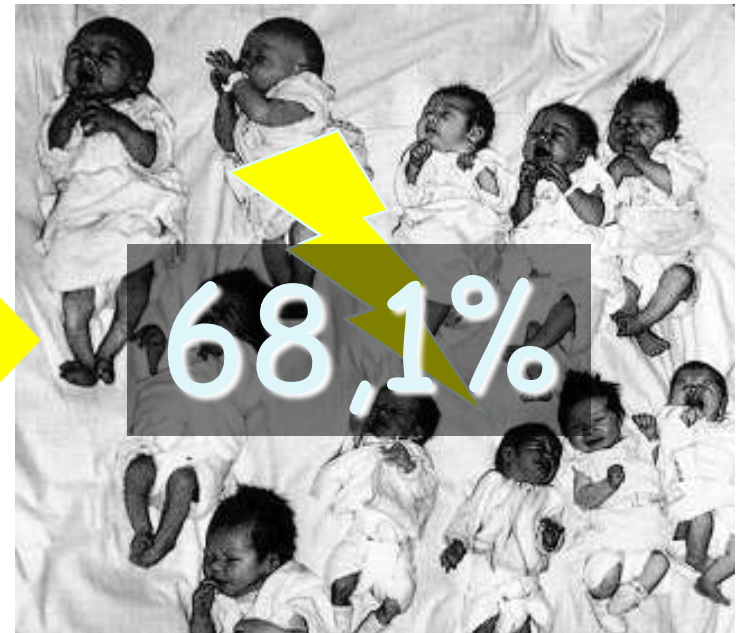


Ped VTE– Statistics

(%IT)

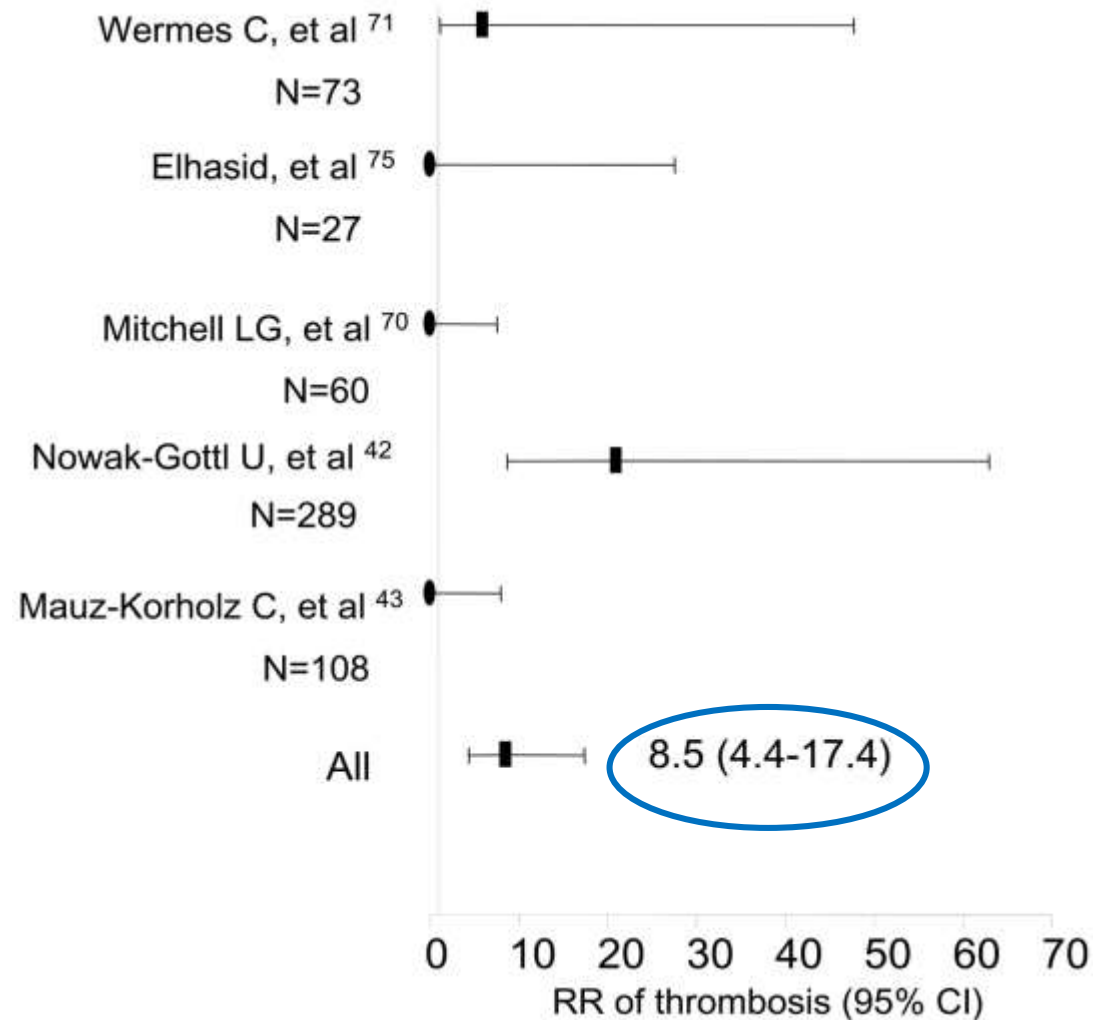


controls (healthy)



patients

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



- ▶ **Asp** therapy may exacerbate inherited deficiency of **AT**, **PC** and **PS** even in heterozygous 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 homozygosity 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,
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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			
DEXA or PDN 40 mg/m ²	+ (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

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

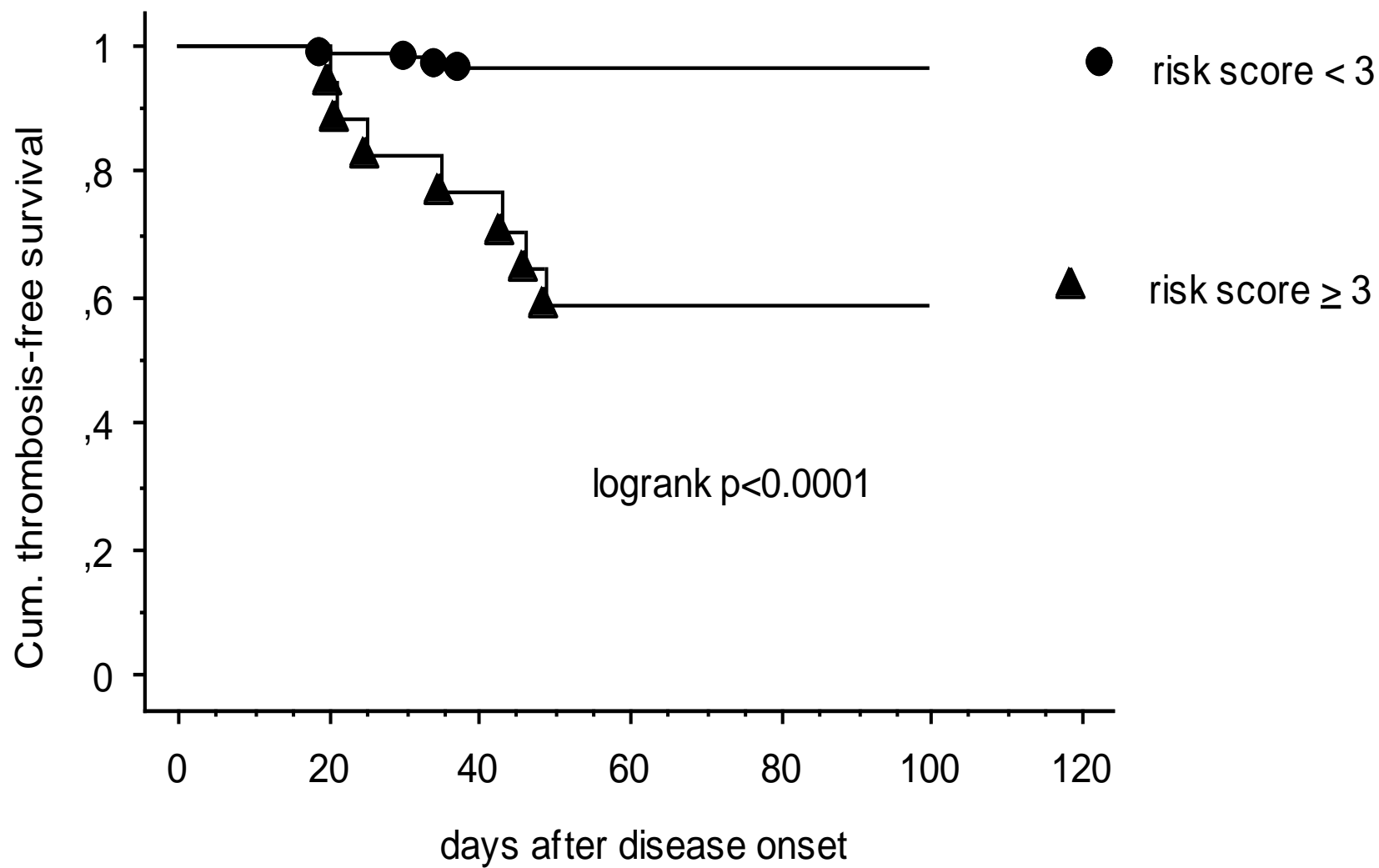
2

medium risk

≥ 3

high risk

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



Consider VTE prophylaxis in ALL [high risk VTE patients]

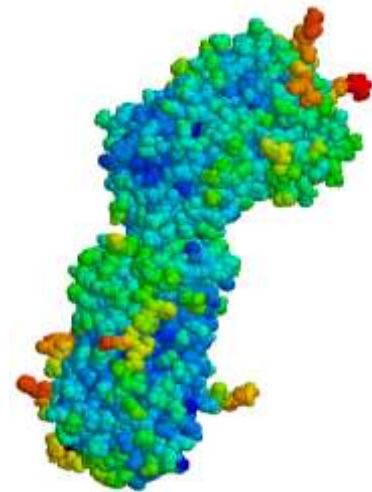
- ▶ risk score ≥ 3
- ▶ enoxaparin 1 mg/kg/24h
 - prophylaxis start: days 8–12 (induction therapy)



platelet count $< 20.000/\mu\text{l}$: 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

Alternative anticoagulants

- ▶ Unfractionated **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
Fondaparinux	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!

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