The identification of at-risk patients ,prevention ,and management of thromboembolism in pediatric cancer

Peyman Eshghi
Prof. of Hematology and Oncology
Mofid Children Hospital

Urmieh
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ALL Study	No.	Time Period (yr)	Early Deaths		Deaths in CR	
			Total Deaths	Death Due to Bleeding	Total Deaths	Death Due to Bleeding
DCOG	875	1984–1996	9	6	14	1
SJCRH[6]	1011	1984–1999	14	0	22	0
MRC UK ALLX*[7]	1612	1985–1990	38	4	53	0
TPOG[8]	201	1993–1997	6	1	NA	NA
DFCI [13]	971	1985–1995	7	0	27	0
Total	4670		74	11	116	1

*X is the protocal number 10.
ALL, acute lymphoblastic leukemia; CR, complete remission; DCOG, Dutch Childhood Oncology Group; SJCRH, St. Jude Children's Research hospital; MRC UK, Medical Research Council of United Kingdom; TPOG, Taiwan Pediatric Oncology Group; DFCI, Dana-Farber Cancer Institute; NA, not available.

occurring either before starting therapy or

AML Study	No.	Time Period	Early Deaths		Deaths in CR	
			Total Deaths	Death Due to Bleeding	Total Deaths	Death Due to Bleeding
DCOG[4]	229	1982–1997	30	20	14	2
SJCRH[6]	260	1983–2002	8	1	22	0
ANZCCG[12]	280	1986–1999	14	4/10	NA	NA
UK MRC 10[9]	341	1988–1995	14	8	35	1
BFM 93 and 98[10]	901	1993–2002	49	17	35	0
Total	2011		115	50	106	3

AML, acute myelogenous leukemia; CR, complete remission; DCOG, Dutch Childhood Oncology Group; SJCRH, St. Jude Children's Research hospital; ANZCCG, Australian and New Zealand Children's Cancer Group; MRC UK, Medical Research Council of United Kingdom; BFM, Berlin-Frankfurt-Munster.

What about thromboembolism in pediatric cancer?

Main Topics to review in short time:

- **How frequent** is cancer-associated Venous Thromboembolism(VTE) and other TE events
- **Who to prevent:**
  - To identify children at risk of cancer-associated VTE and other TE events
- **How To prevent** :
  - Thromboprophylaxis: The use of anticoagulant agents, but not mechanical prophylaxis or antiplatelet agents
- **How to manage**

- Cancer alone has been reported to be associated with a 4.1-fold risk of thrombosis, whereas chemotherapy increases the risk 6.5-fold in adults due to:

✓ activation of the coagulation and fibrinolytic systems,

✓ perturbation of the vascular endothelium,

✓ Activation of monocytes and platelets

✓ surgery,

✓ bed rest,

✓ and infections

✓ central venous catheters(CVL)

✓ L-asparaginase (L-Asp) ;corticosteroids;etc.

- more complicated in pediatric patients:

✓ the hemostatic system is undergoing developmental changes

✓ cancers in children tend to have different biology and generally are treated differently

EPIDEMIOLOGY OF TE IN CHILDREN WITH HEMATOLOGIC MALIGNANCIES

- Thromboembolism (TE) is an uncommon entity in childhood
- Estimated incidence in general population:0.7 to 1.4 events per 100,000 children and 53 per 100,000 hospital admissions

Nowak-Gottl U, Kosch A, Schlegel N. Thromboembolism in newborns, infants and children. Thromb Haemost 2001; 86:464–474

- so far there are very little data describing the epidemiology of TE in children with cancer.

- 37 out Of 387 (9.5%) referred children with thrombosis -in Turkey during 7 years study- had malignancies:
- Thrombosis was detected :
  - ✓Pre diagnosis: No
  - ✓at the time of diagnosis:
    - ✓9 / 37 patients (25%);
      - ✓**Solid tumors** were present in 8 /9 patients (21%)
  - ✓during therapy: in 25 patients (67%)
  - ✓after the discontinuation: in 3 patients (8%)

Selma Ünal et al , Ann Hematol (2005) 84: 395–399

Type of malignancy:

- ALL , (9/37);
- NHL , (10/37);
- Hepatoblastoma ,(5/37);
- myelodysplastic syndrome (MDS) ,(3/37);
- Wilms' tumor, (3/37);
- acute myelogenous leukemia (AML), (2/37);
- recurrent pilocytic astrocytoma (1/37); cranial germinoma (1/37); Ewing's sarcoma (1/37);neuroblastoma (1/37); adrenocortical carcinoma (1/37);

Location of thrombosis:

- Deep venous thrombosis (DVT): 10
- Cerebrovascular Occlusion(CVO): 8
- Portal vein thrombosis (PVT): 5
- Cerebral Venous Sinus Thrombosis (CVST): 3
- Intracardiac:4
- Internal jugular vein:3
- Renal vein:2
- Radial vein:1
- Mesenteric vein thrombosis:1

Selma Ünal et al , Ann Hematol (2005) 84: 395–399

- All malignancies:
  - Symptomatic thrombosis : 2–16%
  - Asymptomatic thrombosis: 40%
  - Approximately 30% of VTE in this population is associated with central venous lines (CVL).
- In acute lymphoblastic leukemia (ALL) alone:
  - symptomatic/asymptomatic VTE has been reported to be as high as 36.7% , with subsequent VTE associated detrimental effects such as a 6.4% case fatality rate
- The most common location of VTE:
  - All cancers: is upper and lower extremity deep venous thrombosis (43 to 50% of events, respectively),
  - ALL : 50% of events patients occur in the central nervous system.
- Risk factor of thrombosis :include the type of cancer, age of the patient, the presence of a CVL, presence of pulmonary/intra thoracic disease, as well as the type of chemotherapy

Piovesan D, et al.Thromb Haemost 2014; 111: 1015–21

Mitchell LG, the PARKAA Group .Cancer 2003; 97:508–16.

Thromboembolism in Children with Hematologic Malignancies

	Type of Cancer: Patients with TEs/Total No. of Patients		
Authors	**ALL**	**AML**	**Lymphoma**
Wermes et al[16]	6/73	0/11	2/12
Glaser et al[17]	1/3	—	3/7
Knoffler et al[18]	4/25	1/5	—
Journeycake et al[19]	14/97*	3/20	2/23
Total	25/198 (12.6%)	4/36 (11.1%)	7/42 (16.7%)

*Includes patients with T-cell lymphoma.
TE, thromboembolism; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

Arterial Thrombosis in Patients with Cancer

- Association of Cance with arterial thromboembolism (ATE) is less well established
- the incidence of arterial thromboembolic events (ATEs) in patients with cancer at 6 months is 4.7%
  - lung, gastric, or pancreatic cancers had the highest rates of ATE
- Ischemic stroke was less common in cancer patients than myocardial infarction (2.0% at 6 month follow-up versus 3.0% respectively).
- Arterial thrombosis accounted for 5.6% of deaths in cancer patients receiving outpatient chemotherapy
- the presence of an ATE is predictive of worse outcomes.
- Risk factors:
  - Certain drugs such as :
    - Platinum-based agents,
    - Vascular endothelial growth factor inhibitors,
    - Tyrosine kinase inhibitors,
    - Taxanes
  - Radiation
  - Increased platelet reactivity appears crucial to development of arterial thrombosis in cancer patients.

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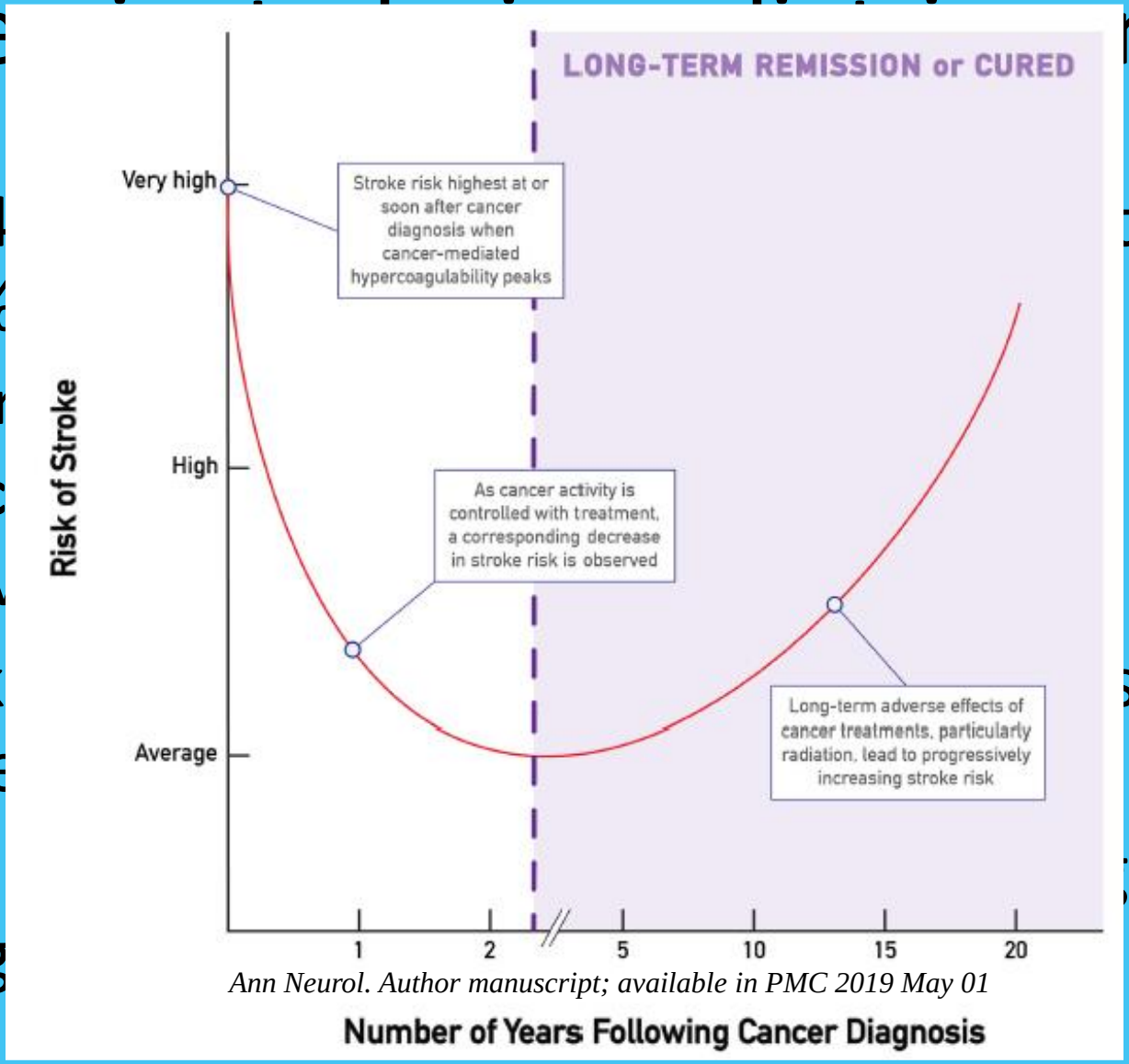

Ann Neurol. Author manuscript; available in PMC 2019 May 01

Corina Noje,et al.,Pediatric Neurology, October 2013Volume 49, Issue 4, Pages 237–242

Should we apply for primary prophylaxis in all patients?

- No study has demonstrated a significant benefit from **systemic primary prophylaxis** for the prevention of VTE in pediatric cancer patients
- **Risk assessment** plays an important role in identifying patients who may benefit from thromboprophylaxis.
- Prediction models for adult oncology patients are of limited utility in pediatric cancer patients
- Pediatric oncology-specific risk prediction models have yielded **low sensitivities**

Schoot RAU,et al.Cochrane Database Syst Rev 2013; 9
Brandao LR, et al.Cochrane Database Syst Rev 2014; 3

Risk assessment of TE in pediatric cancer

Journal of Thrombosis and Haemostasis, **16**: 175–180 DOI: 10.1111/jth.13895

RECOMMENDATIONS AND GUIDELINES

The identification of at-risk patients and prevention of venous thromboembolism in pediatric cancer: guidance from the SSC of the ISTH

B. P. TULLIUS,* U. ATHALE,† C. H. VAN OMMEN,‡ A. K. C. CHAN,† J. S. PALUMBO,§and J. M. S. BALAGTAS¶ FOR THE SUBCOMMITTEE ON HEMOSTASIS AND MALIGNANCY AND THE SUBCOMMITTEE ON PEDIATRIC/NEONATAL THROMBOSIS AND HEMOSTASIS

**Division of Pediatric Hematology/Oncology and BMT, Nationwide Children's Hospital, Columbus, OH, USA; †Pediatrics, McMaster University and Division of Paediatric Hematology/Oncology, McMaster Children's Hospital, Hamilton Health Sciences, Hamilton, ON, Canada; ‡Department of Pediatric Hematology, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands; §Division of Pediatric Hematology, University of Cincinnati, Cincinnati, OH, ; and ¶Division of Pediatric Hematology/Oncology, Stanford University, Stanford, CA, USA*

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Table 1 Risk factors for venous thromboembolism in pediatric cancer

Risk factors	Affected age group	Clinical context
Patient-specific risk factors		
Age > 10	Adolescents	Inpatient and outpatient
Inherited thrombophilia	All age groups	Inpatient and outpatient
History of prior VTE	All age groups	Inpatient and outpatient
Use of combined hormonal contraception	Adolescents	Inpatient and outpatient
Obesity*	All age groups, although predominantly adolescent	Inpatient and outpatient
Disease-related risk factor		
Leukemia confers higher risk than other malignancies	All age groups	Inpatient and outpatient
Intrathoracic/metastatic tumor burden in solid tumor malignancies	All age groups	Inpatient and outpatient
Treatment-related risk factors		
Presence of CVC	All age groups	Inpatient and outpatient
Treatment with asparaginase	All age groups	Inpatient and outpatient
Treatment with corticosteroids	All age groups	Inpatient and outpatient
Treatment with bevacizumab	All age groups	Inpatient and outpatient
Recent surgery/hospitalization	All age groups	Inpatient

Postpubertal age is a well-established risk factor

*Based on evidence in general pediatric population. VTE, venous thromboembolism; CVC, central venous catheter.

- Inherited thrombophilia:

- A metaanalysis of five studies on pediatric ALL reported: *Place et.al Lancet Oncol 2015; 16: 1677–90.*
  - 20% prevalence of at least one prothrombotic defect in pediatric ALL
  - eight times higher risk of VTE in ALL children with thrombophilia
- IT dose not increase VTE risk in pediatric cancers other than ALL (role of chemotherapy?)
  - *Wermes C, et al. Eur J Pediatr 1999; 158: S143–6.*
- Evidences does not support routine screening of children with cancer for IT.

Summary of Studies Evaluating the Prevalence of inherited Thrombophilia in Children with ALL and Its Impact on Development of TE

			Prevalence of Thrombophilia			Incidence of TE	
Authors	No.	Ethnicity	Overall	>1 Defect	Thrombophilia Studied	Overall	With Thrombophilia (%)
Nowak-Gottl et al[46]	301	German	55/301 (18%)	10/55	AT, PC, PS deficiency, FVL, PT, and MTHFR mutation, Lp(a), Hcy	32/289 (11%)	27/58 (46.5%)
Mauz-Korholz et al[47]	108	German	35/108 (32%)	UK	AT, PC, PS deficiency, FVL, PT, and MTHFR mutation, Lp(a)	3/108 (3%)	0/35
Mitchell et al[69]	60	North American	11/60 (18%)	1/11	FVL, PT, APLA	22/60 (37%)	4/11 (36.4)
Rudd et al[70]	60*	Scandinavian	20 (33%)	UK	AT, PC, PS deficiency, FVL, PT, and MTHFR mutation, Lp(a), Hcy	2/60 (3.3%)	UK
Sfakaki et al[71]	31†	Cretan	N/A	3/14	AT, PC, PS deficiency, FVL, PT, and MTHFR mutation,‡ Lp(a), Hcy, APLA	1/31 (3.2%)	0/31
Elhasid et al[67]	27	Arabs 13 Jews 14	11†/27 (41%)	1†/11	FVL, PT, MTHFR	N/A§	N/A
Kishi et al[68]	53	American	21/53‖	N/A	MTHFR	5/53 (9.4%)	3†/21 (14.3%)

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High rate of VTE recurrence among pediatric cancer patients, even when appropriate anticoagulation has been implemented:

- a prospective cohort study following 2183 consecutive children with cancer at a single institution noted that of the 87 patients who developed VTE,:
  - 12/87 (15.4%) developed recurrent VTE
    - 7/12(58.33%%) developed recurrence while on prophylactic/therapeutic anticoagulation.
      - *Klaassen ILM, et al.J Thromb Haemost 2016; 14: 90.*

B . P . TULLIUS et al. ,JTH 2018, 16: 175–180

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Risk factors	Affected age group	Clinical context

tumor types :

- Certain pediatric cancers (e.g. leukemia) are associated with higher VTE incidence rates as compared with others.

- Interestingly, children with brain tumors have a significantly lower incidence of VTE as compared with other pediatric tumor types

Athale U, et al. Epidemiology and clinical risk factors predisposing to thromboembolism in children with cancer. Pediatr Blood Cancer 2008; 51: 792–7.

*Based on evidence in general pediatric population. VTE, venous thromboembolism; CVC, central venous catheter.

- Children with non-ALL malignancies with TE (compared to children with ALL) tend to be:

✓ older

✓ more likely to develop TE at sites distant from CVL,

✓ less likely to be associated with inherited prothrombotic mutations.

Wermes C, et al. Clinical relevance of genetic risk factors for thrombosis in paediatric oncology patients with central venous catheters. Eur J Pediatr 1999;158(suppl 3):S143–S146

Seminars in thrombosis and hemostasis/volume 33, number 4 2007

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Table 1 Risk factors for venous thromboembolism in pediatric cancer

- CVC is **the most common** pediatric risk factor associated with VTE :symptomatic and asymptomatic VTE reported a rate of 37–50%

Athale et al.Expert Rev Hematol 2013; 6: 599–609

- The risk appears to be **independent of pediatric cancer type**

Wiegering V, et al. BMC Hematology 2014; 14: 18.

- Increased (6.4 times higher) in pediatric cancer patients who developed CVC **occlusion and infection** .
- Pharmacological thromboprophylaxis **does not appear to reduce** the incidence of CVC-associated VTE .

Schoot RAU,et al.Cochrane Database Syst Rev 2013; 9
Brandao LR, et al.Cochrane Database Syst Rev 2014; 3

[illegible] Based on evidence in general pediatric population. VTE, venous thromboembolism; CVC, central venous catheter.

CVL-Related Thrombosis

- the Prophylactic Antithrombin Replacement in Children with ALL on Asparaginase study (PARKAA) identified **37%** incidence of CVL-related **asymptomatic** thrombosis in children with ALL

- Compared with adults, the incidence of CVL-related TE is **significantly increased in children** with cancer

- It is important to clearly define **CVC-specific features**, including line type, material, insertion site, and tip placement location.

- Significantly higher risk of CVL-related complications in:

✓ younger age of the patients **(<6 years**),
✓ underlying **hematologic** disease,
✓ External double-lumenHickman line

Feratino et al.Ann Oncol 2005;16:648–654

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*Based on evidence in general pediatric population. VTE, venous thromboembolism; CVC, central venous catheter.

- Longer duration of asparaginase therapy significantly increased the VTE incidence rate
  - *Athale U, et al.. Semin Thromb Hemost 2007; 33: 416–26.*
- No difference in risk comparing E. coli asparaginase vs Erwinia asparaginase And E. coli asparaginase vs PEG-asparaginase
  - Caruso V, Blood 2006; 108: 2216–22. Place et.al Lancet Oncol 2015; 16: 1677–90.
- The relative contributions of dose, duration and type of corticosteroid to the overall risk of VTE remains unclear.

- **Asparaginase therapy:**
  - Causes **suppression of natural anticoagulants:** (**antithrombin [AT]**, protein C [PC], and protein S [PS])
- **Corticosteroid therapy:**
  - **Induces a prothrombotic state** mainly by elevations in procoagulant factors(**factor II and VIII**) and by reduction in fibrinolytic potential (with elevation of plasminogen activator inhibitor type 1 and reduction of a2-macroglobulin and tissue-type plasminogen activator)
- concomitant administration of asparaginase and corticosteroids increases the risk of TE in children with ALL

Nowak-Gottl U, Heinecke A, von Kries R, Nurnberger W, Munchow N, Junker R. Thrombotic events revisited in children with acute lymphoblastic leukemia: impact of concomitant Escherichia coli asparaginase/prednisone administration. Thromb Res 2001;103:165–172

Continuation of Asparaginase Therapy in a Child with TE

- there is no need to discontinue asparaginase permanently in a child with hematologic malignancy and TE. We reinstate asparaginase after the TE is under control with continuation of anticoagulant therapy

SEMINARS IN THROMBOSIS AND HEMOSTASIS/VOLUME 33, NUMBER 4 2007

Replacement of Antithrombin or FFP in Patients Receiving Asparaginase Therapy

- **AT** is believed to be mainly responsible for asparaginase-induced prothrombotic state,
- several investigators have studied the usefulness of fresh frozen plasma or AT supplements in the prevention of TE or hypercoagulability in patients receiving asparaginase.
- the available data **do not support routine use** of fresh frozen plasma or AT therapy in children receiving asparaginase.

SEMINARS IN THROMBOSIS AND HEMOSTASIS/VOLUME 33, NUMBER 4 2007

- Anthracyclines:
  - A meta-analysis showed an increased risk of TE in children with ALL treated with anthracyclines (**6.1%)** compared with those without anthracyclines **(2.7%; p=0.05%)**; there was **no difference in the type of anthracycline used.**

Caruso V, Iacoviello L, Di Castelnuovo A, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. Blood 2006;108:2216–2222

- Growth factors (e.g., granulocyte colony-stimulating factor), are shown to increase the risk of thrombosis

Lee AY, Levine MN. The thrombophilic state induced by therapeutic agents in the cancer patient. Semin Thromb Hemost 1999;25:137–145

ROLE OF CHEMOTHERAPY

- Chemotherapeutic agents are shown to directly activate platelets and monocyte-macrophage tissue factor (TF).
- In addition, chemotherapy-induced cellular apoptosis and release of cytokine molecules can lead to increased expression and activation of TF

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Recent surgery/hospitalization	All age groups	Inpatient

*Based on evidence in general pediatric population. VTE, venous thromboembolism; CVC, central venous catheter.

Surgery is an additional risk factor for VTE formation.

VTE in elective orthopedic surgery in children without cancer is reported to be only 0.06%

Georgopoulos G, et al. J Pediatr Orthop 2015; 00: 1–9.

sarcoma patients undergoing surgery reported an overall VTE rate of 4.1%

Damron TA, et al. J Surg Oncol 2011; 103: 643–7.

Who to prevent:
ISTH SSC guidance

1. We recommend that a **comprehensive risk assessment** performed on each pediatric cancer patient **at the initiation of cancer therapy.**

2. We recommend **against routine primary thromboprophylaxis** in pediatric cancer patients **without a history of prior thrombosis**.

1. We recommend **thromboprophylaxis** in pediatric cancer patients **with prior thrombosis** who are **continuing to receive intensive therapy,** so long as there are no contraindications to anticoagulation.

2. We suggest that **thromboprophylaxis** should be considered, on a **case-by-case basis**, for pediatric cancer patients **with no history of VTE,** but with significant **combinatorial risk factors** (e.g. CVC, asparaginase therapy, obesity, adolescence, hormonal contraceptives or hospitalization for surgery).

How to prevent

Journal of Thrombosis and Haemostasis, **16**: 175–180 DOI: 10.1111/jth.13895

REC

STATE OF THE ART ISTH2017 BERLIN

Anticoagulant prophylaxis and therapy in children: current challenges and emerging issues

F. NEWALL,* B. BRANCHFORD† and C. MALE‡

**Clinical Haematology & Nursing Research, Royal Children's Hospital, Haematology Research Group, Murdoch Childrens Research Institute and Departments of Paediatrics and Nursing, The University of Melbourne, Melbourne, Australia; †Department of Pediatrics, Section of Hematology/Oncology/Bone Marrow Transplant and the Hemophilia and Thrombosis Center, School of Medicine and Center for Cancer and Blood Disorders, Children's Hospital Colorado, University of Colorado, Aurora, CO, USA; and ‡Haemostasis and Thrombosis Unit, Department of Paediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria*

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Table 1 Clinical characteristics associated with increased venous

Pharmacological primary prophylaxis may be used in the following risk groups:

- **CANCER**

+

CCU admission & CVC

- **CANCER**

+

CCU admission OR CVC

+

ONE another risk factor

- **CANCER**

+

TWO other risk factors

How to prevent

- children with cancer and VTE may not benefit

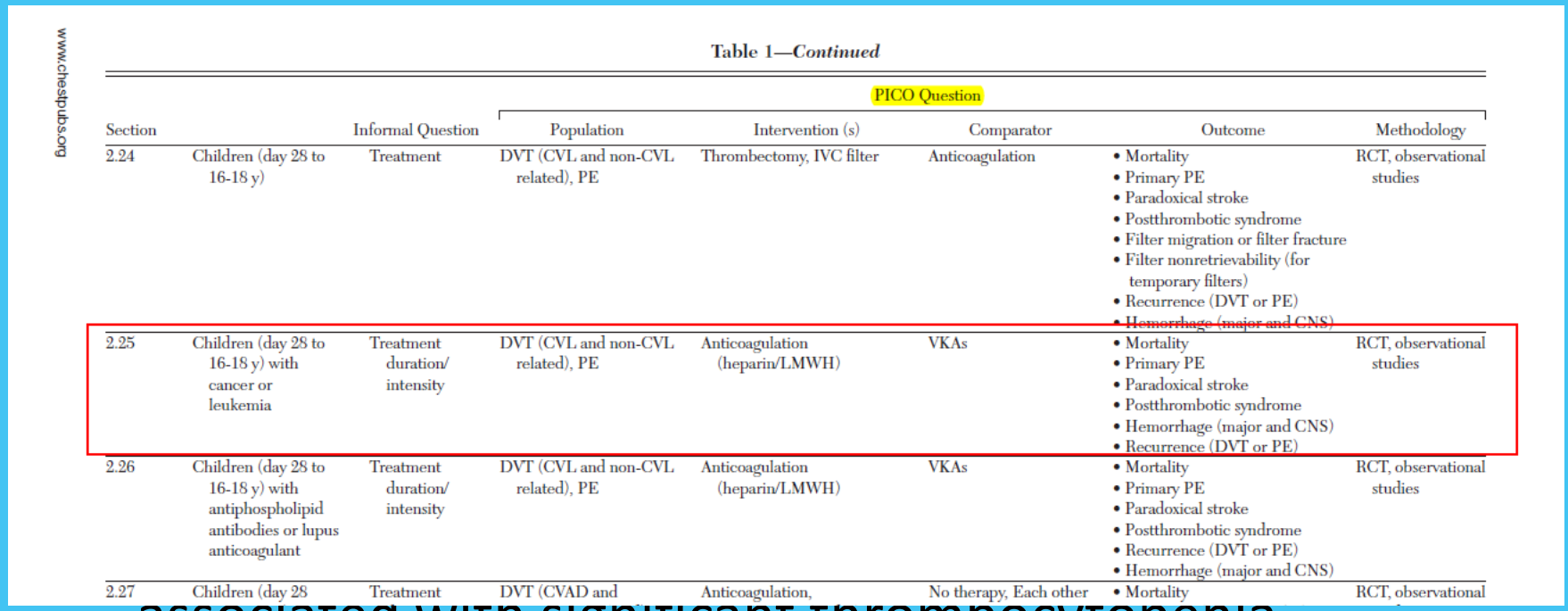

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Table 1—*Continued*

Section		Informal Question	PICO Question: Population	Intervention (s)	Comparator	Outcome	Methodology
2.24	Children (day 28 to 16-18 y)	Treatment	DVT (CVL and non-CVL related), PE	Thrombectomy, IVC filter	Anticoagulation	• Mortality • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Filter migration or filter fracture • Filter nonretrievability (for temporary filters) • Recurrence (DVT or PE) • Hemorrhage (major and CNS)	RCT, observational studies
2.25	Children (day 28 to 16-18 y) with cancer or leukemia	Treatment duration/ intensity	DVT (CVL and non-CVL related), PE	Anticoagulation (heparin/LMWH)	VKAs	• Mortality • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Hemorrhage (major and CNS) • Recurrence (DVT or PE)	RCT, observational studies
2.26	Children (day 28 to 16-18 y) with antiphospholipid antibodies or lupus anticoagulant	Treatment duration/ intensity	DVT (CVL and non-CVL related), PE	Anticoagulation (heparin/LMWH)	VKAs	• Mortality • Primary PE • Paradoxical stroke • Postthrombotic syndrome • Recurrence (DVT or PE) • Hemorrhage (major and CNS)	RCT, observational studies
2.27	Children (day 28	Treatment	DVT (CVAD and	Anticoagulation,	No therapy, Each other	• Mortality	RCT, observational

associated with significant thrombocytopenia, increasing the bleeding risks of anticoagulant therapy.

How to prevent

ACCP and ISTH guideance statement

- **In children with cancer;**
  - we suggest that management of VTE follow the **general recommendations** for management of VTE in children.
  - We suggest the use of LMWH in the treatment of VTE for **a minimum of 3 months** until the precipitating factor has resolved (eg, use of asparaginase)(Grade 2C) .
- *Remarks:* The presence of cancer, the need for surgery,chemotherapy, or other treatments may modify the risk-benefit ratio for treatment of VTE, and clinicians should consider these factors **on an individual basis.**

Why LMWH

- LMWHs are advantageous because of their predictable pharmacokinetics, long half-life, lack of drug–drug interactions, and favorable side-effect profile.

- It is required just to withhold LMWH for 24 h prior to the procedure

- The incidence of major bleeding while on enoxaparin has been reported to be between 0% and 6% in pediatric patients

LMWH dosage and monitoring

ISTH guidance statement

- We recommend that LMWHs be administered as per standard pediatric prophylactic dosing guidelines, with subsequent dose adjustments based

Anti-Xa level	Withhold next dose?	Dose change	Timing of next anti-Xa level
<0.35 IU/ml	no	increase by 25%	after next dose
0.36–0.49 IU/ml	no	increase by 15%	after next dose
0.5–1.0 IU/ml	no	no	after one week if hospitalized, one month if outpatient
1.01–1.25 IU/ml	no	decrease by 15%	after next dose
1.26–1.5 IU/ml	no	decrease by 25%	after next dose
1.51–2.0 IU/ml	yes	decrease by 30%	when next dose is due; if >1.5, continue to withhold dose and repeat after 12 h
>2.0 IU/ml	yes	decrease by 40%	when next dose is due; if >1.5, continue to withhold dose and repeat after 12 h

those struggling with compliance on twice-daily dosing.

- We suggest that, once started, thromboprophylaxis be continued until predisposing conditions are resolved or ameliorated. (e.g. achievement of remission or completion of chemotherapy).
  - Several studies suggest 3-month treatment period due to lower rate of bleeding complications

Tousovska K,et al. Blood Coagul Fibrinolysis 2009; 20: 583–9.
Massicotte P, et al.: the REVIVE trial. Thromb Res 2003; 109: 85–92.

Use of LMWHs during thrombocytopenia in pediatric cancer patients

ISTH guidance statement

- full therapeutic dosing in patients with platelets > 50 X 10^9/ L (with transfusion as nece… ^{9}/ L in the …
- redu… pati… ^{9}/ L and …
- Withholding LMWH if platelet counts are < 20 X 10^9/ L

	Therapeutic dose	Prophylactic dose
Enoxaparin		
≤2 months of age	1.5 mg/kg s.c. bid	1.5 mg/kg s.c. od
>2 months of age	1 mg/kg s.c. bid	1 mg/kg s.c. od

Anticoagulation and Invasive Procedures

- prior to lumbar puncture or epidural procedures, at least two doses of LMWH should be withheld and anti-Xa levels should be determined prior to the procedure, if possible

- *Monagle et al. the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:645S–687S*

Mechanical prophylaxis

ISTH guidance statement

- We suggest that mechanical prophylaxis be considered in older, higher-risk patients in hospitalized settings associated with prolonged immobility.
- We further suggest that additional pharmacological thromboprophylaxis be considered in patients with :
  - significant additional risk factors (obesity,OCP,etc.) or
  - for whom mechanical prophylaxis is not feasible or is inappropriate

Mechanical prophylaxis

- Sequential compression devices are preferred over compression stockings , with the exception of a known thrombus
- Not been well established for upper and central venous system VTE, particularly if CVC-associated.
- Additional risks :
  - Pressure ulcer or other skin irritation
- Contraindications :
  - Acute VTE,
  - Fracture,
  - Burns, wound, postoperative site,
  - Peripheral intravenous access, or
  - Inappropriate fit

DOACs in children

Table 4 Indications targeted by current Pediatric Investigation Plans for direct oral anticoagulants

	Prevention of VTE	Prevention of cardiac, arterial TE	Treatment of VTE
Rivaroxaban	–	Post-Fontan surgery, versus aspirin	Acute VTE
Dabigatran	–	–	1. Acute VTE 2. Extended secondary prevention
Apixaban	Acute leukemia with central venous catheter, versus placebo	Various cardiac diseases, versus LMWH/VKA	Acute VTE
Edoxaban	–	Various cardiac diseases	Acute VTE
Betrixaban	1. Medical illness or surgery 2. Neonates/preterms with umbilical catheter	–	–

LMWH, low molecular weight heparin; TE, thromboembolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Treatment considerations for ATE in cancer

- **Anti-platelet agents**:
- Central role to the treatment of arterial thrombosis, with careful consideration about the bleeding risk due to thrombocytopenia which is common in cancer patients:
  - Adults:
    - Aspirin :platelet count is >10,000,
    - DAPT with aspirin and clopidogrel :platelet counts between 30 and 50,000
    - P2Y12 receptor inhibitors such as ticagrelor and prasugrel: platelet count >50000

Cilingiroglu M, Charitakis K, et al. SCAI expert consensus statement: evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory. Catheter Cardiovasc Interv. 2016;87:E202–23.

- Children: APA is considered for platelet count >50000

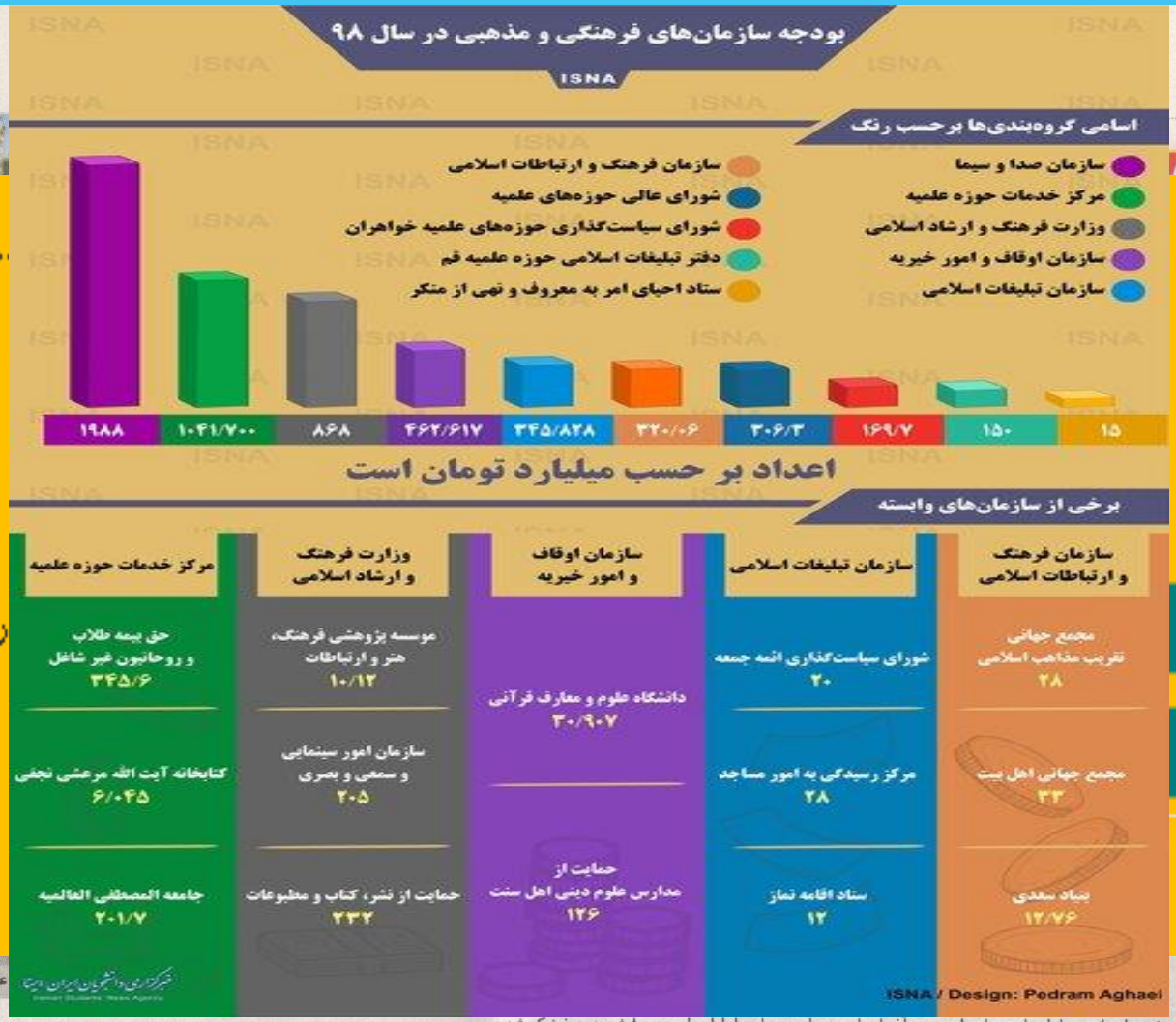
- May have direct anti-neoplastic properties through inhibition of tumor growth and spread .

Treatment considerations for ATE in cancer

- Thrombolysis
  - Systemic
  - Catheter related
- Endovascular Thrombectomy

CVAD

- **For CVADs, we suggest flushing with normal saline or heparin or intermittent recombinant urokinase (rUK) to maintain patency as compared with no therapy** (Grade 2C)
- **For blocked CVADs, we suggest tPA or rUK to restore patency** (Grade 2C) **. If after at least 30 min following local thrombolytic instillation CVAD patency is not restored, we suggest a second dose be administered. If the CVAD remains blocked following two doses of local thrombolytic agent, we suggest radiologic imaging to rule out a CVAD-related thrombosis** (Grade 2C) **.**
- **For children with short- or medium-term CVADs, we recommend against the use of routine systemic thromboprophylaxis** (Grade 1B) **.**



- Thanks for your attention