Trombosi in età pediatrica

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Varese, 15 Marzo 2017

Pediatric thrombosis is peculiar

- has become a substantial health hazard
- may be associated with significant morbidity and mortality
- impact imposed on the child's family members
- greater life expectancy compared with affected elderly
- lack of large carefully conducted clinical trials
- necessity for improved diagnosis, better definition of outcomes, adapted treatment and prophylactic regimens

• newer anticoagulant drugs

Incidence of VTE in pediatric patients

Canadian Registry 1994 → 0.07- 0.14/10,000 children per year

→ 5.3/10,000 hospital admission

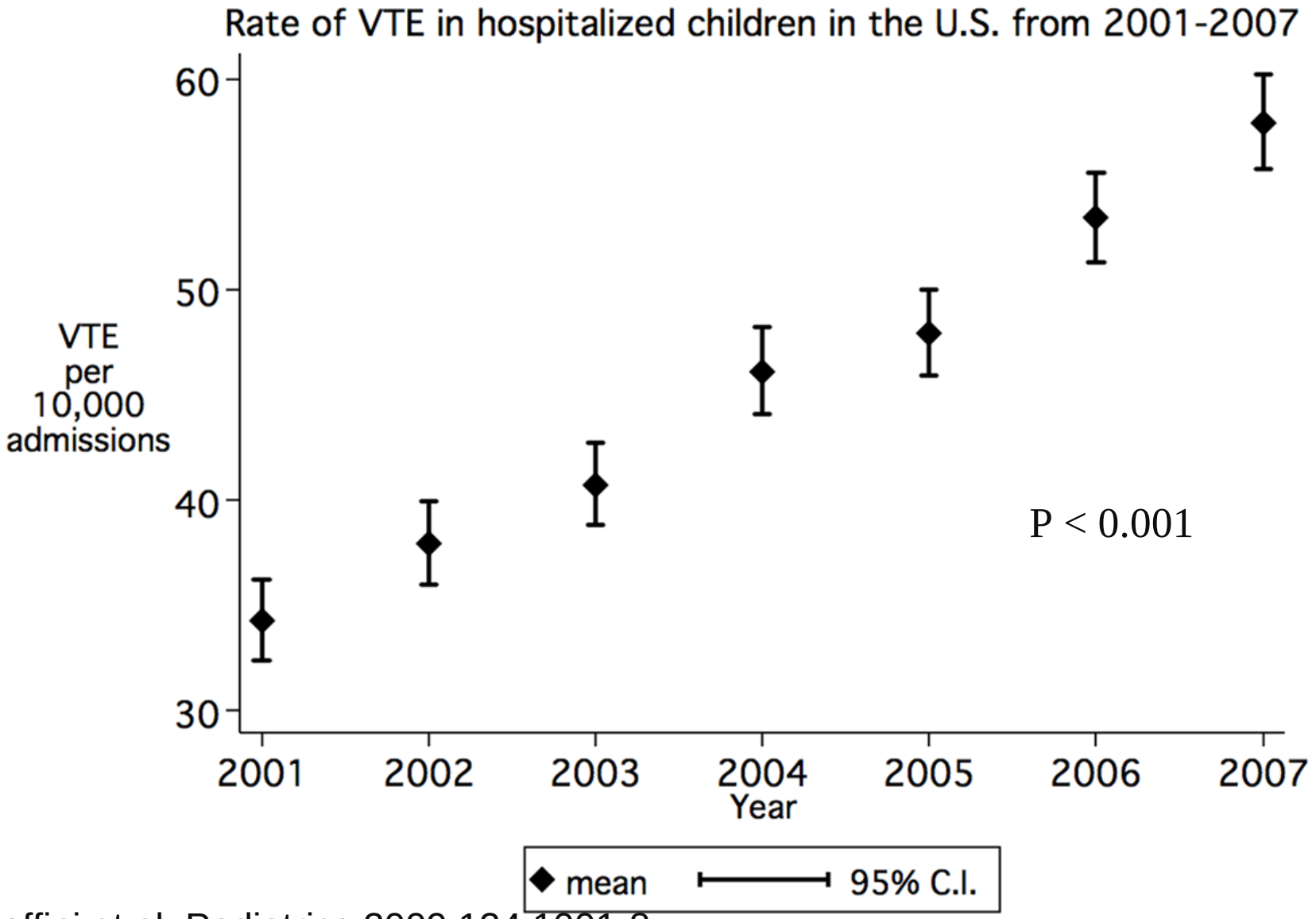
↓

Incidence now → 1/10,000 children per year

→ 42-58/10,000 hospital admissions

Andrew et al. Blood 1994
Kim et al. J Pediatr Orthop 2014
Raffini et al, Pediatrics 2009

VTE Admissions Over Time

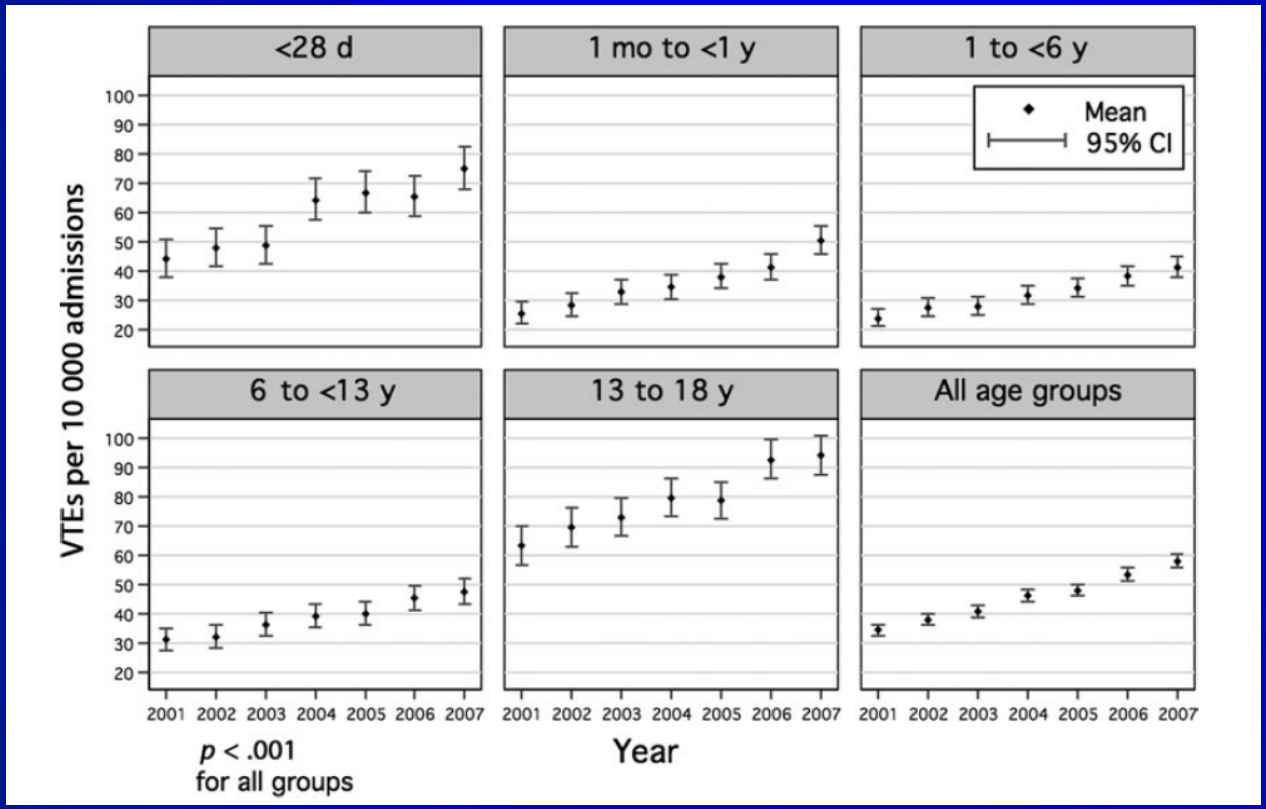


Raffini et al. Pediatrics 2009;124:1001-8

Dramatic Increase in Venous Thromboembolism in Children's Hospitals in the United States From 2001 to 2007

Leslie Raffini, Yuan-Shung Huang, Char Witmer and Chris Feudtner

Pediatrics 2009;124;1001; originally published online September 7, 2009;
DOI: 10.1542/peds.2009-0768



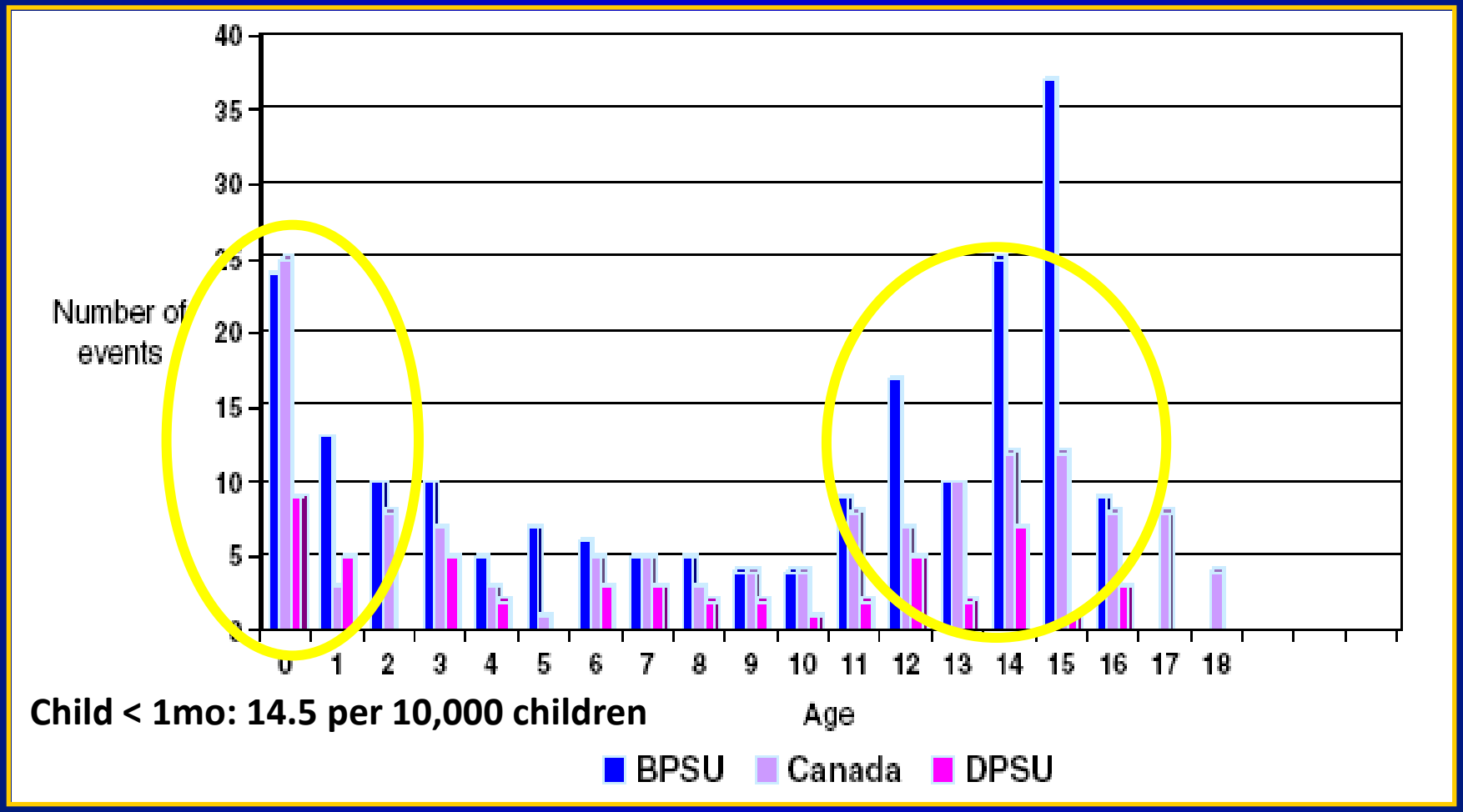
The annual rate of VTE increased by 70% [from 34 to 58 cases per 10 000 hospital admissions (*P* .001)].

This increase was observed in neonates, infants, children, and adolescents.

Reason for increasing incidence

- Increasing use of CVC for supportive care
- Better imaging techniques for thrombus detection
- Increasing awareness of the problem
- Increasing incidence of critically sick children

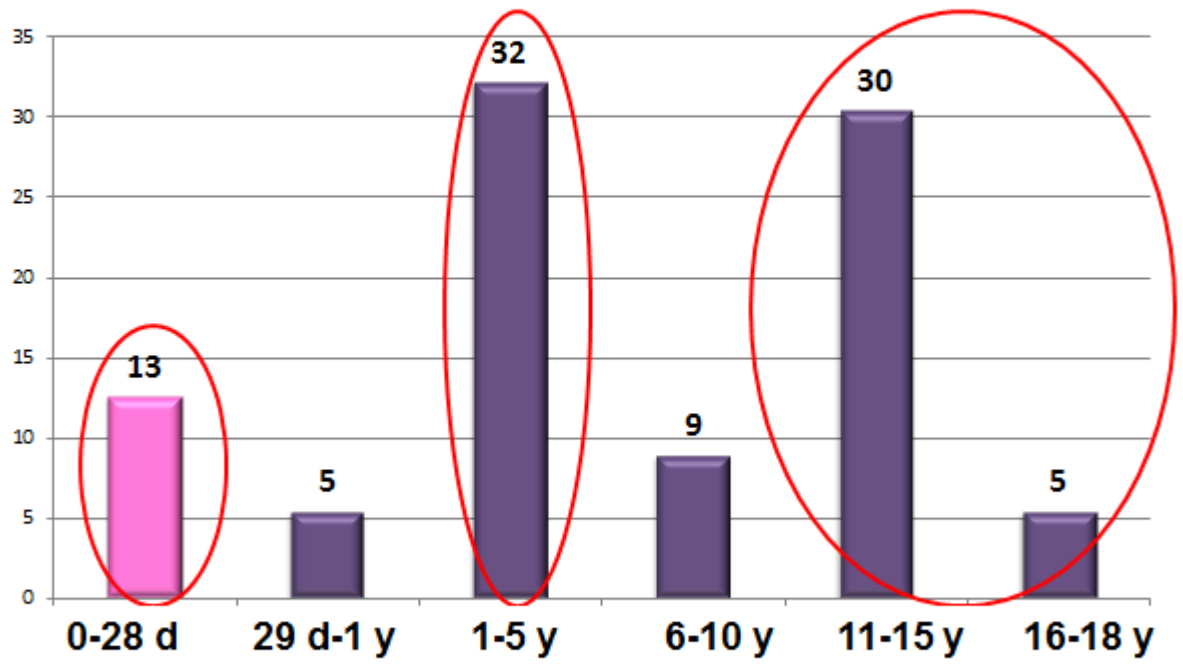
Age distribution of thrombotic events in published registries from the UK (BPSU), Canada and The Netherlands (DPSU)



Child < 1mo: 14.5 per 10,000 children

Chalmers et al., Thrombosis Research 2006

RITI: systemic venous TE



…35% in adolescence, 32% in preschool

Sites of thrombosis in child

Site of thrombosis	Canada	BPSU	DPSU
Upper limb (UL) DVT	47 (34%)	48 (30%)	5 (14%)
Lower limb (LL) DVT	68 (50%)	95 (59%)	21 (60%)
PE alone	8 (6%)	5 (3%)	4 (11%)
UL DVT+PE	3 (2%)	6 (4%)	2 (6%)
LL DVT+PE	11 (8%)	6 (4%)	3 (9%)
Total	137	160	35

Chalmers et al., Thrombosis Research 2006

Etiology and risk factors

1. Patient-related	
• **Age**	Highest risk in children <1mo and ≥11y
• **Thrombophilia**	PC,PS,AT deficiencies, FVL, PT20210A, hyperhomocysteine
• **Anatomic anomalies**	May-Thurner or Paget–Schroetter syndrome
2. Hospital-related	
• **CVC**	femoral vein (vs subclavian vein), upper left extremity (vs upper right) and multilumen
• **Prolonged hospitalization**	Each additional day increases risk by 3%
• **ICU admission**	
• **Surgery**	Most commonly after cardiac surgery
• **Trauma**	
• **Immobility**	Immobilization for >72 hr

Adapted from Pediatr Blood Cancer. 2018;65:e26881

Etiology and risk factors

3. Disease-related	
• **Infection/inflammation**	Highest risk with systemic blood stream infection
• **Cancer**	Highest risk for leukemia, lymphoma, and sarcoma
• **Congenital heart disease**	Abnormal levels and function of pro- and anticoagulants
• **Intestinal failure**	Patients with CVCs and parental nutrition
• **Neuromuscolar disease**	Immobility
• **Nephrotic syndrome**	Urinary loss of anticoagulants, mostly AT
4. Medications	
• **Asparaginase**	Reduces levels of AT, protein C, and protein S
• **Steroids**	Increases and decreases the levels of many pro- and anticoagulans
• **Estrogen**	Increases the levels of many pro-coagulant and decreases many anticoagulants

Adapted from Pediatr Blood Cancer. 2018;65:e26881

Risk factors in children

True idiopathic VTE, which implies an absence of of either a provoking risk factor or an undelying prothrombotic condition, is rare in children.

The majority of VTE is associated with an underlying associated disorder → 76.2%

Pediatric thombotic disorders, edited by Goldenberg NA and Manco-Jhonson MJ, Cambrudge Medicine 2015

Etiology and risk factors

Table 4 Risk factors in paediatric registries

Risk factors	Canada (%)	DPSU (%)	BPSU (%)
CVL	33	37	48
Sepsis	7.3	46	32
Immobility	NA	17	28
Malignancy	23	8	26
Surgery	5.8	15	15
CHD	15	19	8
Trauma	15	8	8
TPN	8	NA	12
Renal disease	6	6	11
Contraceptives	5	4	5
Idiopathic	3.6	2	8.5

CHD=congenital heart disease.

Chalmers et al., Thrombosis Research 2006

CVC-related DVT

DVT rates range from 2.6–34% in children

Contradictory studies:

1. A meta-analysis: lowest in PICCs and umbilical lines (vs tunneled lines), without a difference in DVT rates between CVCs placed in the upper or lower extremity

2. a systematic review: tunneled lines (vs nontunneled and PICCs) have the lowest rate of DVT

(retrospective study designs, the various patient populations, endpoint was symptomatic DVT or asymptomatic VTE)

Vidal E et al. J Thromb Haemost. 2015;13(1):161 and Ullman AJ Pediatrics. 2015;136(5):e1331

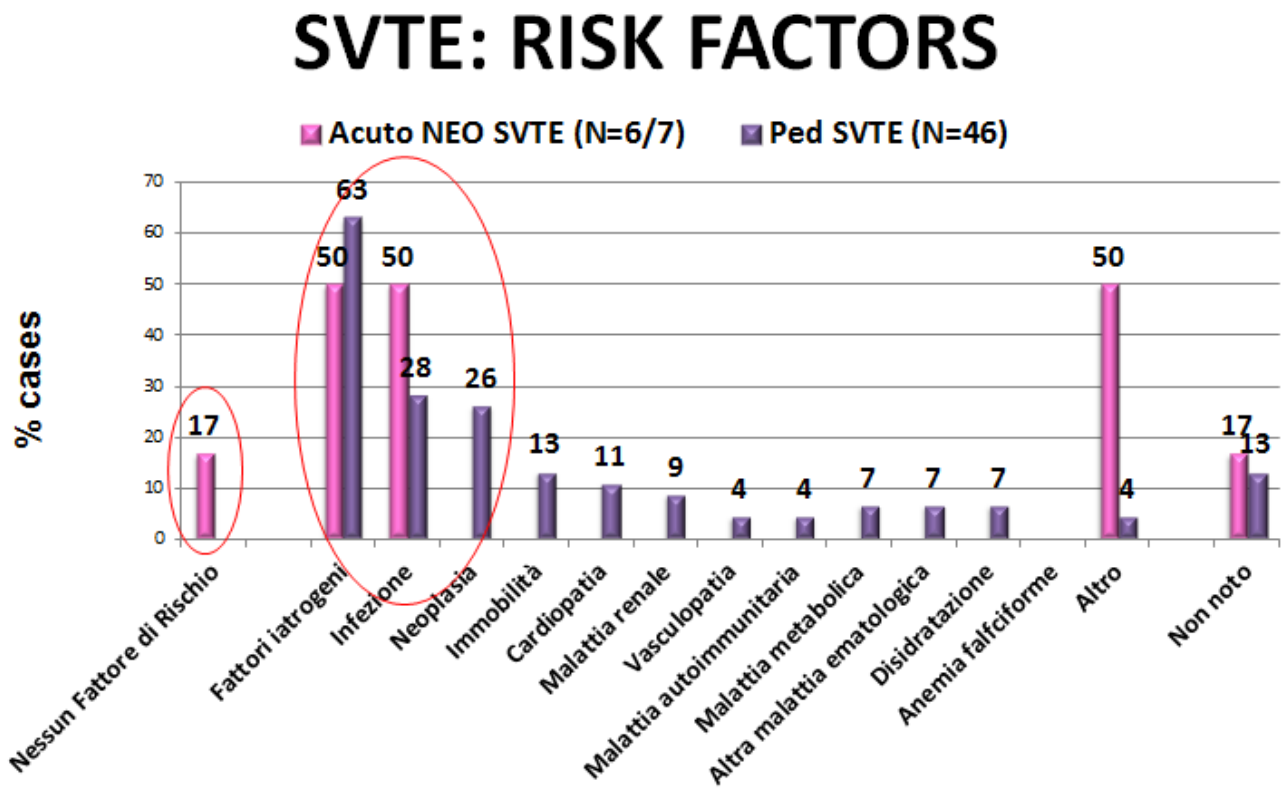
CVC-related DVT

Significant increase in incidence associated with the following risk factors:

- Increasing age
- Advanced renal disease
- Dyalisis
- Inflammatory bowel disease
- Total parenteral nutrition

Smitherman et al. Hosp Pediatr 2015

RITI: systemic venous TE



Paed CVL related TE: 54 % (25/46) ; Neon CVL related TE 43 % (3/7)

Hospital-associated venous thromboembolism in pediatrics: a systematic review and meta-analysis of risk factors and risk-assessment models

Arash Mahajerin,[1] Brian R. Branchford,[2] Ernest K. Amankwah,[3] Leslie Raffini, [4] Elizabeth Chalmers,[5] C. Heleen van Ommen,[6] and Neil A. Goldenberg[7,8]

Risk Factor	Number of studies	Case control studies Pooled OR (95% CI)	I^2 (%)
Admission to ICU	3	2.14 (1.97-2.32)	95.9
Any CVC	8	2.12 (2.00-2.25)	97.9
Mechanical ventilation	4	1.56 (1.42-1.72)	90.9
Length of stay in hospital	3	1.03 (1.03-1.03)	46.9

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Impact of Inherited Thrombophilia on Venous Thromboembolism in Children: A Systematic Review and Meta-Analysis of Observational Studies

Guy Young, Manuela Albisetti, Mariana Bonduel, Leonardo Brandao, Anthony Chan, Frauke Friedrichs, Neil A. Goldenberg, Eric Grabowski, Christine Heller, Janna Journeycake, Gili Kenet, Anne Krümpel, Karin Kurnik, Aaron Lubetsky, Christoph Male, Marilyn Manco-Johnson, Prasad Mathew, Paul Monagle, Heleen van Ommen, Paolo Simioni, Pavel Svirin, Daniela Tormene and Ulrike Nowak-Göttl

ublished online September 8, 2008;

Role of APLA & IT in children with a first TE onset * [Odds ratio]

TE-type	Stroke/CSVT	DVT
APLA	6.58	4.87
FV G1691A	3.26	3.55
FII G20210A	2.43	2.64
PC def.	9.31	7.72
PS def.	3.20	5.77
AT def.	7.06	9.44
combined ITs	11.86	9.5

Young et al. Circulation 2008; Kenet et al. Circulation 2010

Inherited thrombophilia and RECURRENT thrombotic event in children

Table 2. Summary ORs (95% CIs; Meta-Analysis) Including Testing for Heterogeneity (I^2) and Publication Bias for Genetic Traits Associated With Recurrent VTE in Children

Genetic Traits (No. of Studies)	Patients With Recurrence/Patients With No Recurrence, n	OR (95% CI), Fixed Model	OR (95% CI), Random Model	I^2, %	Bias Indicator[114]
Protein C deficiency (13)	152/1296	2.39 (1.21–4.36)	2.53 (1.30–4.92)	0	
P		0.012	0.006	0.74	0.67
Protein S deficiency (11)	132/857	3.12 (1.50–6.45)	3.76 (1.76–8.04)	0	
P		0.001	0.0006	0.51	0.41
Antithrombin deficiency (12)	150/969	3.01 (1.43–6.33)	3.37 (1.57–7.20)	0	
P		0.003	0.001	0.74	0.59
Factor V G1691A (12) **NO**	115/1160	0.64 (0.35–1.18)	0.77 (0.40–1.45)	0	
P		0.18	0.42	0.68	0.48
Factor V G1691A including children with idiopathic/spontaneous VTE only (13)	179/1397	1.35 (0.91–1.98)	1.43 (0.91–2.24)	4.3	
P		0.107	0.114	0.40	0.004
Factor II G20210A (12)	171/1397	1.88 (1.01–3.49)	2.15 (1.12–410)	0	
P		0.049	0.020	0.66	0.52
Lipoprotein(a) (6) **NO**	135/1020	0.81 (0.49–1.36)	0.84 (0.50–1.40)	0	
P		0.51	0.50	0.90	0.78
≥2 Genetic traits (10)	144/1127	4.46 (2.89–6.89)	4.91 (3.12–7.74)	0.7	
P		0.0001	0.0001	0.43	0.82

Young G et al. Circulation 2008; 118:1373-1382

Manifestations and clinical impact of pediatric inherited thrombophilia

Irene L. M. Klaassen,[1,2] C. Heleen van Ommen,[1] and Saskia Middeldorp[2]

(*Blood.* 2015;125(7):1073-1077)

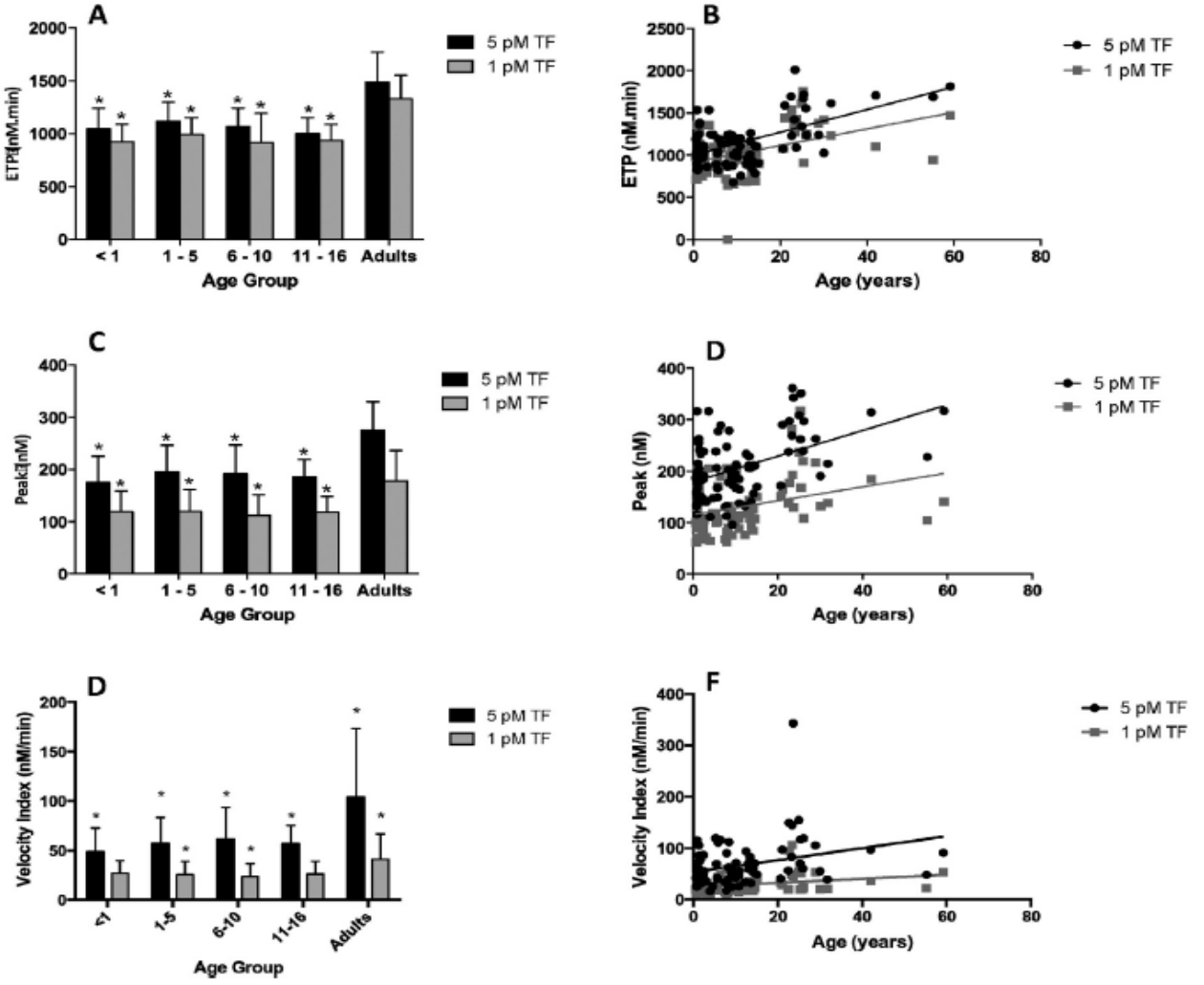
Albisetti et al studied 114 children with malignancies

→ No association between thrombophilia and CVC-related thrombosis

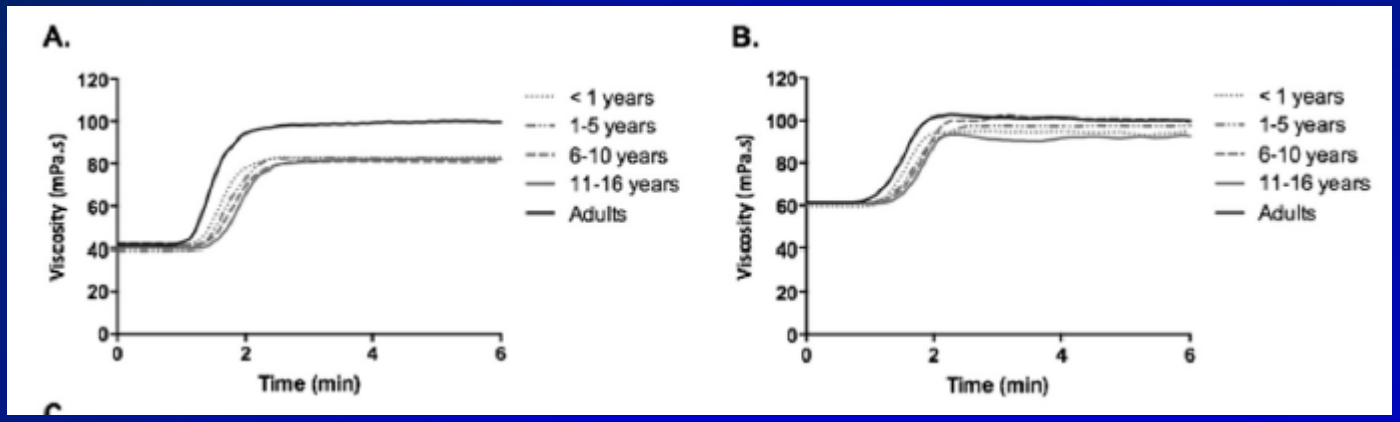
KIDs with Catheter associated Study studied 90 children with heart disease → no association between thrombophilic factors and CVC-related VTE

Differences in the mechanism of blood clot formation and nanostructure in infants and children compared with adults

Vera Ignjatovic [a,b,*,1], Leonie Pelkmans [c], Hilde Kelchtermans [c], Raed Al Dieri [c], Coen Hemker [c], Romy Kremers [c], Saartje Bloemen [c], Vasiliki Karlaftis [a], Chantal Attard [a,b], Bas de Laat [c], Paul Monagle [a,b,d]



Thrombosis Research xxx (2015) xxx–xxx



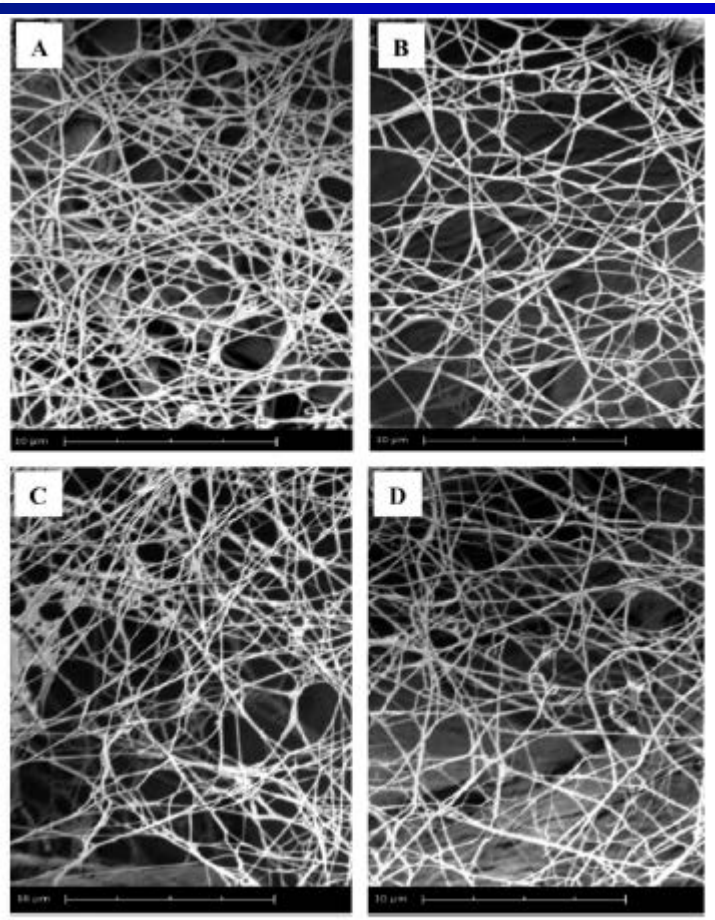


Fig. 4. *Representative images of fibrin clots.* (A) Adult at baseline; (B) < 1 year old at baseline; (C) Adult in the presence of tPA; (D) < 1 year old in the presence of tPA.

+ tPA			
Fibrin fibres (nm)	Fibrin fibres (% baseline)	Pore size (μM^2)	Pore size (% baseline)
345 (300–397)	97.46	0.050**** (0.035–0.071)	80.65
360 (290–440)	101.41	0.059***** (0.042–0.081)	86.76
363 (317–418)	100.83	0.060 (0.041–0.101)	92.31
362 (296–399)	102.84	0.056***** (0.033–0.094)	83.58
349 (319–514)	96.94	0.051 (0.034–0.084)	94.44

Diagnosis – PRE-test probability

Univariate and Multivariable ORs for VTE

Univariate ORs

Characteristic	Crude OR	95% CI	*p*-value
Male	2.96	(1.80, 4.87)	<0.001
CVAD[a]	2.51	(1.53, 4.14)	<0.001
Active Cancer	2.35	(1.19, 4.63)	0.014
Asymmetric Extremity[b]	1.76	(1.05, 2.97)	0.033
Alternative Diagnosis[c]	0.42	(0.24, 0.76)	0.004

Multivariate ORs

Characteristic	Estimate	SE	Adjusted OR	95% CI	*p*-value
Intercept	-2.03	0.28	--	--	--
Male	1.09	0.29	2.96	(1.68, 5.22)	<0.001
CVAD[a]	0.64	0.30	1.90	(1.07, 3.39)	0.029
Asymmetric Extremity[b]	0.60	0.31	1.81	(0.99, 3.31)	0.052
Active Cancer	0.55	0.40	1.73	(0.79, 3.78)	0.169
Alternative Diagnosis[c]	-1.11	0.35	0.33	(0.16, 0.66)	0.002

Radiology reports utilized to identify children imaged for suspected VTE

91 with VTE and 298 without

ROC analysis showed reasonable ability to discriminate VTE probability in the training cohort (AUC 0.73; $p<0.001$) and moderate discrimination in a separate validation cohort of 149 children (AUC 0.64; $p=0.011$)

Pediatr Res. 2015 March 12; 77(3): 463–471.

D-Dimer in children

Only 1 retrospective study in patients < 21 yrs (Strouse JJ et al. AmJ Hematol 2009) → sensitivity 92%, specificity 57%

TABLE 3. Pediatric Reference Values of Fibrinolysis Parameters Compared With Adults

Test	Children			
	Ages 1-5 (n = 19)	Ages 6-10 (n = 26)	Ages 11-18 (n = 25)	Adults (n = 26)
D-dimer (mg/mL)				
Mean	0.41*	0.37*	0.23	0.21
Range	(0.1-0.85)	(0.1-0.58)	(0.1-0.54)	(0.1-0.4)
t-PA (ng/mL)				
Mean	1.21	1.1	1.16	1.21
Range	(0.54-1.88)	(0.68-1.52)	(0.60-1.72)	(0.93-1.49)
PAI-1 (ng/mL)				
Mean	21.0	25.3	20.0	17.5
Range	(0.8-31.2)	(2.6-48.0)	(0.1-39.9)	(0.5-34.5)
TAFIa (μg/mL)				
Mean	40.1	43.9	46.8	41.9
Range	(20.6-59.6)	(30.8-57.1)	(35.2-58.3)	(30.8-53.1)

(*J Pediatr Hematol Oncol* 2007;29:19–22)

D-Dimer in children

Only 1 retrspective study in patients < 21 yrs (Strouse JJ et al. AmJ Hematol 2009) → sensitivity 92%, specificity 57%

Diagnostic Test Characteristics by Cut-Off (95% CI)

D-Dimer	Sensitivity	Specificity	PPV	NPV	Area under ROC
≥1.5 mg/dl	96% (80-100)	43% (10-82)	86% (68-96)	75% (19-99)	0.86 (0.72-1.0)
≥1.75 mg/dl	92% (75-99)	57% (18-90)	89% (71-98)	67% (22-96)	0.86 (0.72-1.0)
≥ 2 mg/dl	77% (56-91)	71% (29-96)	91% (71-99)	45% (17-77)	0.86 (0.72-1.0)

Am J Hematol. 2009 January ; 84(1): 62–63. doi:10.1002/ajh.21311.

Abnormal renal and liver function testing can be seen with hepatic, portal, and renal vein thrombosis.

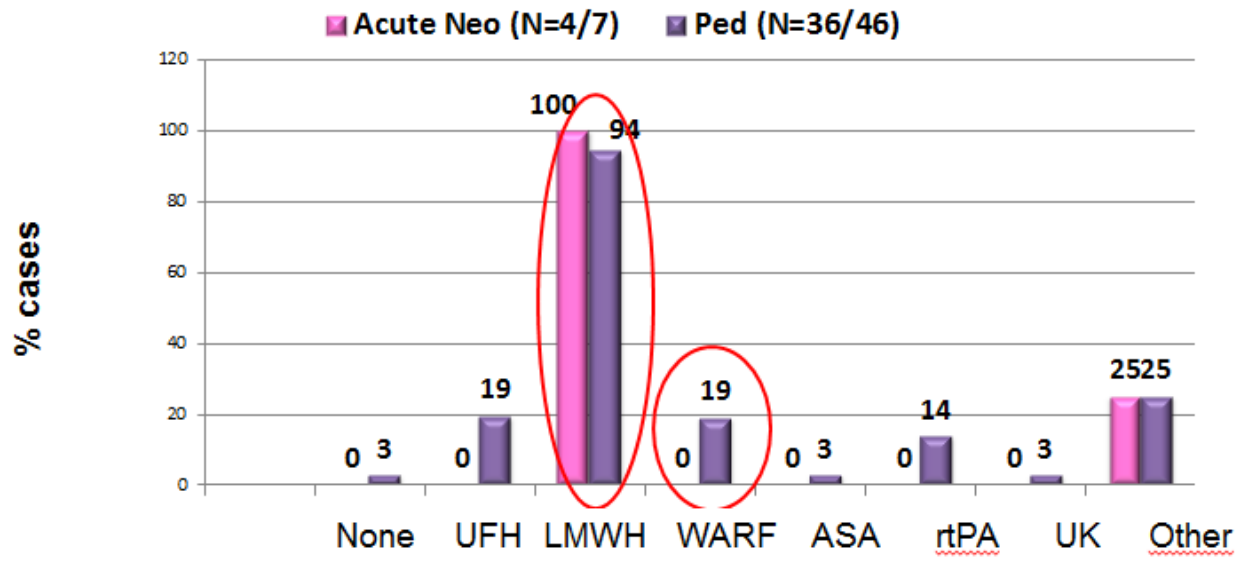
Treatment

Anticoagulant	Dose	Route of administration and frequency	Monitoring
UFH	28 units/kg/hr (age <1 year) 20 units/kg/hr (age ≥1 year)	Intravenous, bolus then continuous infusion	Antifactor Xa assay or aPTT
LMWH	1.5 mg/kg/dose (age <2 months) 1 mg/kg/dose (age >2 months)	Subcutaneous injection, twice daily	Antifactor Xa assay
Bivalirudin	0.125 mg/kg/hr	Intravenous, bolus then continuous infusion	aPTT
Argatroban	1 μg/kg/min	Intravenous, continuous infusion	aPTT
Fondaparinux	0.1 mg/kg/day	Subcutaneous injection, once daily	Factor Xa assay
VKA	0.1 mg/kg/day	Oral, once daily	INR
DOACs	Not determined in children	Oral once or twice daily	Unknown at this time

Jaffray and Young, Pediatr Blood Cancer. 2018;65:e26881

RITI: systemic venous TE

SVTE: ANTITHROMBOTIC TREATMENT



First VTE → standard approach
First VTE idiopathic → 6-12 months VKA

2.22.1. In children with first VTE (CVAD and non-CVAD related) we recommend acute anticoagulant therapy with either UFH or LMWH (Grade 1B). We recommend initial treatment with UFH or LMWH for at least 5 days (Grade 1B). For ongoing therapy, we recommend LMWH or UFH. For patients in whom clinicians will subsequently prescribe VKAs, we recommend beginning oral therapy as early as day 1 and discontinuing UFH/LMWH on day 6 or later than day 6 if the INR has not exceeded 2.0 compared with no therapy (Grade 1B).

2.22.2. We suggest that children with idiopathic VTE receive anticoagulant therapy for 6 to 12 months compared with no therapy (Grade 2C).

Chest 2012

Secondary VTE → 3 months
Ongoing reversible risk factor → beyond 3 months (therapeutic or prophylactic)

2.22.3. In children with secondary VTE (ie, VTE that has occurred in association with a clinical risk factor) in whom the risk factor has resolved, we suggest anticoagulant therapy be administered for 3 months (Grade 2C) as compared with no further therapy. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing asparaginase therapy, we suggest continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved (Grade 2C).

Chest 2012

Recurrent idiopathic VTE → indefinite
- Recurrent secondary VTE , reversible risk factor → at least 3 months (until resolution of risk situation)

2.22.4. In children with recurrent idiopathic VTE, we recommend indefinite treatment with VKAs (Grade 1A).

2.22.5. In children with recurrent secondary VTEs with an existing reversible risk factor for thrombosis, we suggest anticoagulation until resolution of the precipitating factor but for a minimum of 3 months as compared with no further therapy (Grade 2C).

Chest 2012

Multicenter randomized controlled trial on Duration of Therapy for Thrombosis in Children and Young Adults (the Kids-DOTT trial): pilot/feasibility phase findings

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W. R. HIATT,‡‡§§ C. M. KESSLER,¶¶ J. M. KITTELSON,¶ M. J. MANCO-JOHNSON,***
A. C. SPYROPOULOS,††† P. G. STEG,‡‡‡ N. V. STENCE,¶ A. G. G. TURPIE§§§¶¶¶ and
S. SCHULMAN§§§¶¶¶FOR THE KIDS-DOTT TRIAL INVESTIGATORS[1]

JTH 2015

studies are critical to future RCT success. *Methods:* The Kids-DOTT trial is a multicenter RCT investigating non-inferiority of a 6-week (shortened) versus 3-month (conventional) duration of anticoagulation in patients aged < 21 years with provoked venous thrombosis. Primary efficacy and safety endpoints are symptomatic recurrent VTE at 1 year and anticoagulant-related, clinically rele-

Kids-DOTT, a RCT to assess
the duration of anticoagulation therapy in children with a new VTE secondary to a transient or reversible risk factor, is underway.

Table 3 Anticoagulant agent use in the randomized population, by the acute (first week) and the subacute (after the first week) period after diagnosis of the index venous thrombotic event

Acute period, *N* (%)	
LMWH	43 (67.2)
UFH	20 (31.3)
Other*	1 (1.6)
Subacute period, *N* (%)	
LMWH	62 (95.4.9)
Warfarin	2 (3.1)
Other*	1 (1.5)

-VTE and CVC not required → removal after 3-5 days treatment

-VTE and CVC required and functioning → anticoagulation for 3 months + prophylactic VKA or LMWH

- If recurrent VTE → therapeutic until removal

2.22.6. In children with a CVAD in place who have a VTE, if a CVAD is no longer required or is nonfunctioning, we recommend it be removed (Grade 1B). We suggest at least 3 to 5 days of anticoagulation therapy prior to its removal rather than no anticoagulation prior to removal (Grade 2C). If CVAD access is required and the CVAD is still functioning, we suggest that the CVAD remain in situ and the patient be given anticoagulants (Grade 2C). For children with a first CVAD-related VTE, we suggest initial management as for secondary VTE as previously described.

2.22.7. In children with CVAD in place who have a VTE and in whom the CVAD remains necessary, we suggest, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5-1.9) or LMWH (anti-Xa level range, 0.1-0.3 units/mL) be given until the CVAD is removed (Grade 2C). If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, we suggest continuing therapeutic doses until the CVAD is removed and for a minimum of 3 months following the VTE (Grade 2C).

Chest 2012

Acquired and congenital thrombophilia

2.26. For children with VTE in the setting of antiphospholipid antibodies (APLAs), we suggest management as per general recommendations for VTE management in children.

2.27. For children with VTE, independent of the presence or absence of inherited thrombophilic risk factors, we suggest that the duration and intensity of anticoagulant therapy as per Recommendation 2.22.

Chest 2012

Thrombophilia testing in symptomatic children

Universal thrombophilia testing after a first episode of DVT in children is not cost-effective

However

Some inherited thrombophilias have been associated with increased VTE recurrance → anticoagulation duration

Therapeutic discussions and decision-making with patients/parents → Thromboprophylaxis for adolescents in high-risk situations or counseling for females considering contraception

Thrombophilia testing in symptomatic children

Results should be interpreted by an experienced physician

Adolescent females are most likely to benefit from this information

Thrombolysis

In children with VTE, we suggest that thrombolysis therapy be used only for life- or limb-threatening thrombosis (Grade 2C).

If thrombolysis is used in the presence of physiologically low levels or pathologic deficiencies of plasminogen, we suggest supplementation with plasminogen (Grade 2C).

In children with VTE in whom thrombolysis is used, we suggest systemic thrombolysis or catheter-directed thrombolysis, depending on institutional experience and, in the latter case, technical feasibility.

Seminars in Fetal & Neonatal Medicine 16 (2011) 349–354

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Old and new antithrombotic drugs in neonates and infants

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Table 1
Historical context of new anticoagulants in children.

Anticoagulant	Discovery	First clinical use in adults	First use in children	First prospective study in children
Heparin	1916	1934	1954	1994[48]
Warfarin	1929	1954	1976	1994[18]
LMWH	1970s	1980s	1993	1996[9]
Direct thrombin inhibitors	1884	1997	1999	2007[31]
Fondaparinux	1985	2001	2004	2010[38]
New oral agents	2005	2010	NA	Studies began in 2010

LMWH, low molecular weight heparin; NA, not applicable.

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	–	–

Phase I PK/PD as well as phase II studies have been completed for rivaroxaban and dabigatran.
PK/PD studies for apixaban and edoxaban continue to recruit patients.

Pediatric phase III trials comparing each DOAC to standard anticoagulation (LMWH, fondaparinux, or VKAs) are open and recruiting for rivaroxaban, edoxaban, and dabigatran

A phase III randomized study is evaluating the safety and efficacy of apixaban to prevent thrombosis in children with newly diagnosed ALL treated with asparaginase

J Thromb Haemost 2018; **16**: 196–208.

The exposures were well tolerated

2 studies reported a combined total of 76 NOA exposures to poison control centers (rivaroxaban and dabigatran)

3 children experienced coagulopathies

Long-term sequelae

1. Local recurrence or second thrombotic episodes in children range from 7-21% depending on patient age, presence of thrombophilia, or provoking agent

2. **PTS** → up to 63% of children with DVT, especially in those with multiple vein segments involved and lack of radiographic DVT resolution

Patients with upper extremity DVT due to overuse (sports, weight lifting, musical
instrument playing) are more likely to develop PTS versus CVC-related DVTs

Techniques to prevent PTS have not been established in adult or pediatric patients

Avila ML et al, Blood 2014; Kumar R et al, Thromb Res 2015; Jaffray and Young Pediatr Blood Cancer 2018

PRIMARY THROMBOPROPHYLAXIS IN CHILDREN

Development of a New Risk Score for Hospital-Associated Venous Thromboembolism in Noncritically Ill Children: Findings from a Large Single-Institutional Case-Control Study

Christie M. Atchison, BS[1], Shilpa Arlikar, MD[2], Ernest Amankwah, PhD[2], Irmel Ayala, MD[3], Laurie Barrett, RN[2,3], Brian R. Branchford, MD[4], Michael Streiff, MD[5], Clifford Takemoto, MD[3,6], and Neil A. Goldenberg, MD, PhD[2,3,5,6]

Table II. Unadjusted OR and aOR for putative risk factors for development of HA-VTE in noncritically ill children from univariate and multiple logistic regression

	Unadjusted				Adjusted			
Putative risk factors	OR	95% LCL	95% UCL	*P* value	OR	95% LCL	95% UCL	*P* value
Age, y								
1-5	0.28	0.07	1.12	.07	0.38	0.05	2.75	.34
6-10	1.57	0.58	4.23	.37	2.54	0.48	13.42	.27
11-15	2.43	0.90	6.54	.08	2.21	0.40	12.32	.37
16-21	1.99	0.76	5.19	.16	2.32	0.45	11.87	.31
CVC	31.49	13.97	71.02	<.001	**27.67**	**8.40**	**91.22**	**<.0001**
Infection	7.95	4.18	15.09	<.001	**10.40**	**3.46**	**31.25**	**<.0001**
Major surgery	0.20	0.06	0.66	.008	0.34	0.07	1.62	.17
Malignancy	5.06	2.58	9.94	<.001	0.90	0.31	2.62	.85
Obesity	4.40	1.02	19.03	.047	1.95	0.21	18.20	.56
Dehydration	1.51	0.59	3.84	.39				
Chronic inflammatory disease (non-lupus)	7.67	2.14	27.52	.002	1.00	0.16	6.32	1.00
Hospital days (<4 vs ≥4)	15.38	6.37	37.14	<.001	**5.26**	**1.74**	**15.88**	**.003**
Previous hospitalization within 30 d	3.88	1.99	7.59	<.001	1.41	0.52	3.85	.50
Cardiac catheterization	14.54	1.29	163.41	.03	9.17	0.34	249.81	.19
History of prematurity	0.48	0.14	1.62	.24				
Congenital heart disease	0.49	0.06	3.81	.5				
Diabetes mellitus	1.17	0.14	9.93	.89				
Cystic fibrosis	3.66	0.89	15.13	.07	0.92	0.12	6.93	.93

(J Pediatr 2014;165:793-8).

Effectiveness of clinical guidelines for deep vein thrombosis prophylaxis in reducing the incidence of venous thromboembolism in critically ill children after trauma

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VTE Prophylaxis Guidelines

For patients at **high risk of VTE**[1] with **low risk of bleeding**[2]:

- anticoagulate with low molecular weight heparin at 0.5mg/kg subcutaneous, twi daily until hospital discharge

For patients at **high risk of VTE**[1] with **high risk of bleeding**[3]:

- apply sequential compression devices
- on PICU day 7 obtain screening ultrasound of bilateral lower extremities, and upper extremity if CVL is present

For patients at **low risk of VTE**[4]:

- no anticoagulation or other clinical intervention indicated

Risk Factors for VTE:

- projected immobility > 5 days
- Glasgow Coma Scale less than 9
- presence of CVL
- spinal cord injury
- complex lower extremity fracture
- operative pelvic fracture
- use of inotropes
- CPR during resuscitation
- exogenous estrogen
- chronic inflammatory state
- history of previous clot
- known thrombophilia
- current malignancy

Risk Factors for Bleeding:

- intracranial bleed
- solid organ injury
- planned surgical intervention or invasive procedure in the next 24 hours
- heparin allergy
- high risk of severe bleeding
- renal failure

[1]High risk of VTE defined as age greater than 13 years OR age less than 13 years with four or more risk factors for VTE.
[2]Low risk of bleeding defined as no risk factors for bleeding.
[3]High risk of bleeding defined as one or more risk factors for bleeding.
[4]Low risk of VTE defined as age less than 13 years AND three or fewer risk factors for VTE.

65% decrease in incidence of VTE in patients who were divided into low-and high-risk categories based on thrombotic and bleeding risk.

(*J Trauma.* 2012;72: 1292–1297.

ORIGINAL ARTICLE

Risk-prediction tool for identifying hospitalized children with a predisposition for development of venous thromboembolism: Peds-Clot clinical Decision Rule

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J Thromb Haemost 2012;

Table 3 Multivariate logistic analysis comparing the cases and controls

Descriptor	Estimate	Standard error	*P*-value (Wald χ^2)	Odds ratio (OR)	95% CI for OR	Risk score assignment
Length of stay (LOS) (ref: < 7)	2.257	0.376	< 0.0001	9.552	4.572–19.955	2
Direct admission to ICU/NICU (Admit_ICU) (ref: No)	0.552	0.267	0.0385	1.736	1.030–2.926	0.5
Central venous catheter (CVC) (ref: No)	1.036	0.260	< 0.0001	2.818	1.693–4.690	1
Positive blood stream infections (BSI_Pos) (ref: No)	1.391	0.407	0.0006	4.019	1.809–8.930	1
Immobilization (Immo) (ref: No)	3.034	0.852	0.0004	20.769	3.910–110.322	3
Birth control pills (BCP) (ref: No)	2.201	0.632	0.0005	9.038	2.617–31.212	2

A risk score of 3 or more identified high-risk children at a sensitivity of 70% and specificity of 80% and AUC of 0.852 (95% confidence interval, 0.814–0.890).

Journal of Thrombosis and Haemostasis, **12**: 1096–1109 DOI: 10.1111/jth.12598

ORIGINAL ARTICLE

Central venous catheter-related thrombosis and thromboprophylaxis in children: a systematic review and meta-analysis

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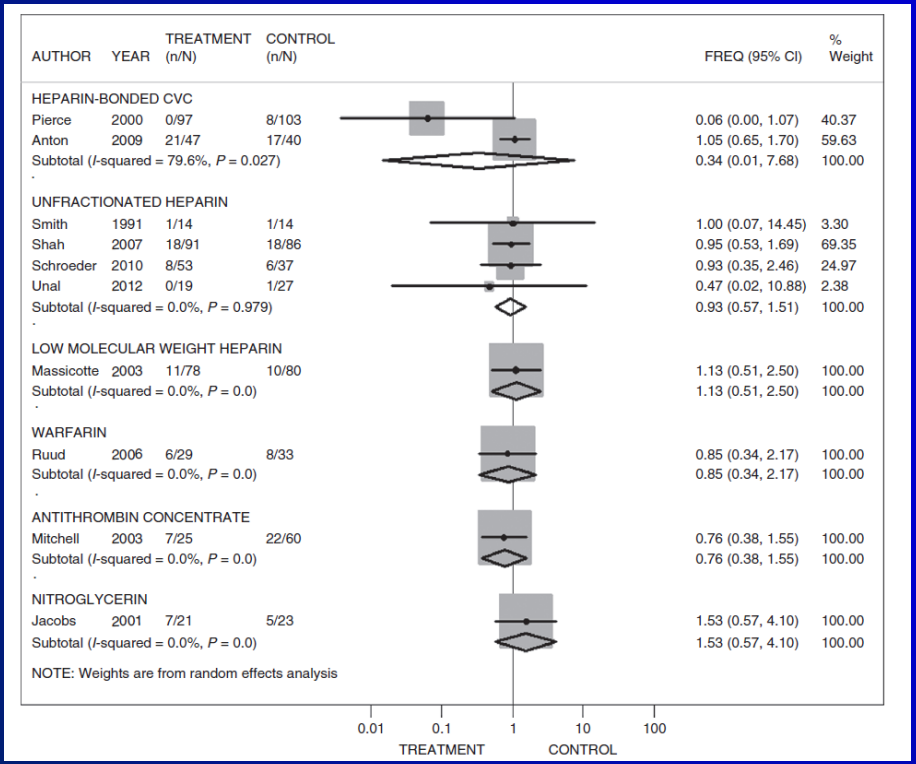

"We did not find evidence that thromboprophylaxis reduced the risk of CVC-related DVT in children".

"An adequately powered RCT that can detect a modest, clinically significant reduction in the frequency of DVT is needed to determine the efficacy of thromboprophylaxis against CVC-related DVT in children"

Table 2 Suggested thromboprophylactic interventions by venous thromboembolism (VTE) risk category

	VTE low (0–1 RFs)*	VTE medium (2 RFs)*	VTE high (≥ 3 RFs)*
Bleed low (unlikely to bleed)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical Pharmacological
Bleed medium (moderate bleeding potential)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical ± Pharmacological
Bleed high (current bleeding or high bleeding potential)	Early mobilization	Early mobilization Mechanical	Early mobilization Mechanical

RF, risk factor. *Defined by number of RFs from Table 1.

J Thromb Haemost 2018; **16**: 196–208.

Primary prophylaxis in children: open questions

Increase request for prophylaxis

Protocols like adults after puberty? (BMI?)

Candidates to heparin prophylaxis:

- Neonates with diseases and CVC?
- Thrombophylic children who undergo major or orthopedic surgery?

Increased use of non-pharmacological thromboprophylaxis (elastic stockings? Intermittent pneumatic compression?)

Role for new drugs in the prophylaxis of VTE

Needs for Pediatrics Thrombosis/Hemostasis Centers in Hospitals

Need for a Registry for the identification of children at risk **(RITI)**

Conclusions

- ✓ DVT ha become an increasingly recognised complication in children
- ✓ Increased efforts should be made to evaluate for DVT in all children with a CVC in place
- ✓ the consideration of DVT should be made for any child who presents with a painful and swollen limb, especially in high-risk populations, such as those with cancer or CHD, or an adolescent female recently started on oral contraception

Conclusions

- ✓ Most of the reccomandation for diagnosis and management are based on extrapolations from adults
- ✓ Anticoagulation is the standard of care and risk stratification algorithms for thromboprophylaxis have been proposed
- ✓ Much work is needed in the pediatric thrombosis community

Grazie per l'attenzione!

Clinical staff:
Luca Spiezia
Daniele Tormene
Fabio Dalla Valle
Elena Campello
Sara Maggiolo

The Anatomical Theatre
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