Pediatric thrombosis: Diagnosis and Management

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Financial Disclosure

- None

Objectives

- Discuss and compare thrombotic disorders in children and adults
- Indications for thrombolysis and anticoagulation
- Type of anticoagulation/duration treatment
- Cases, diagnosis, management

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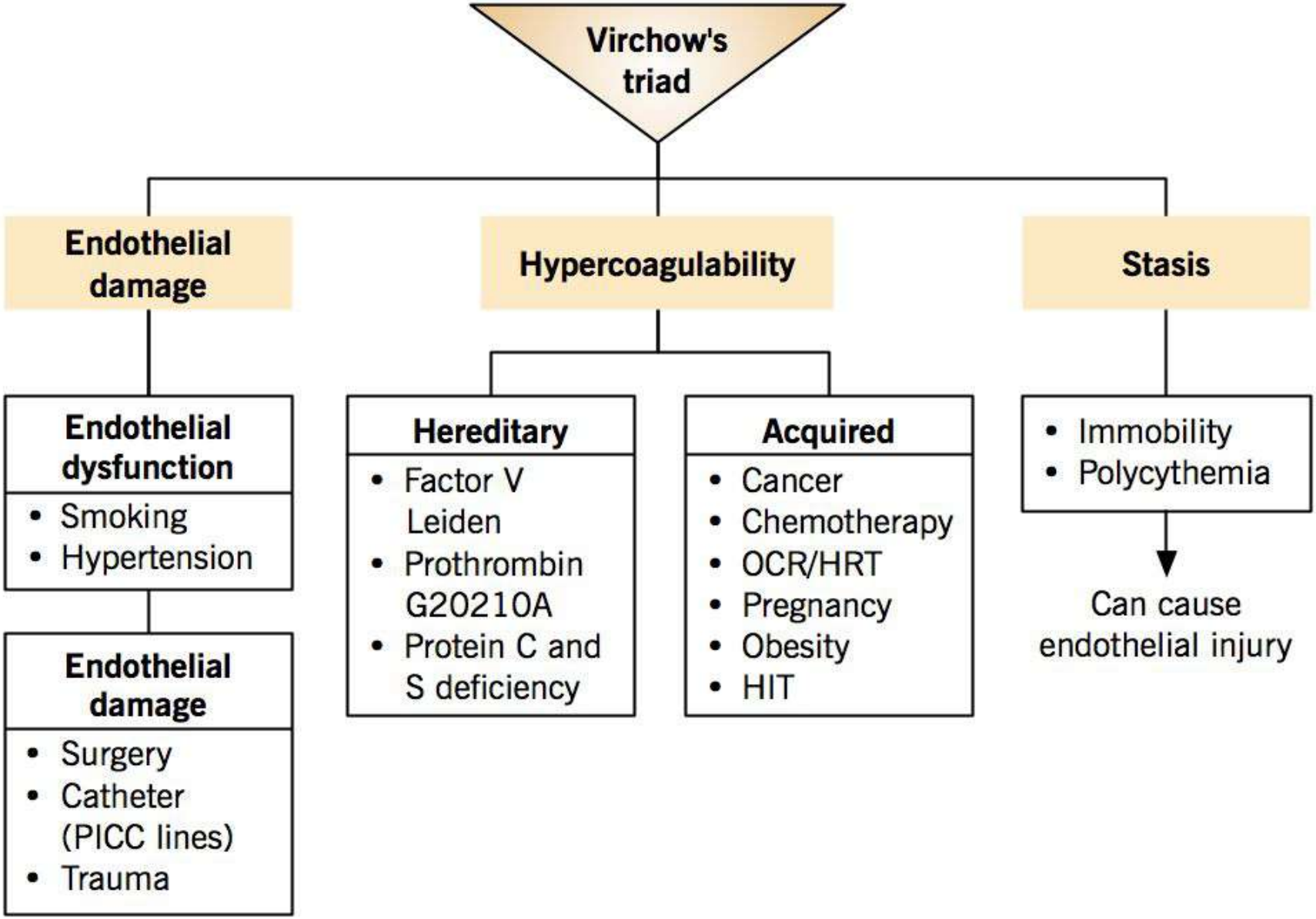
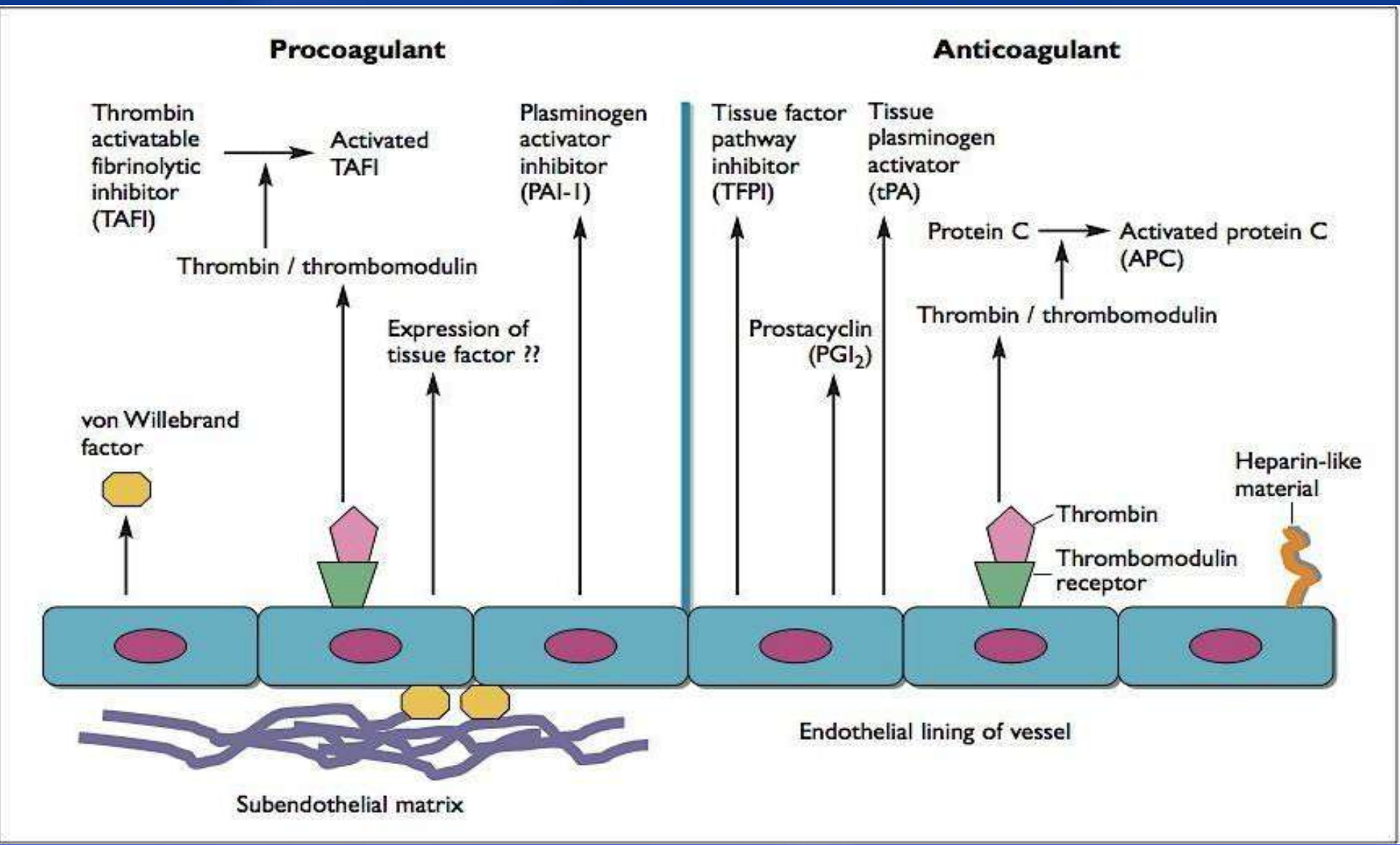
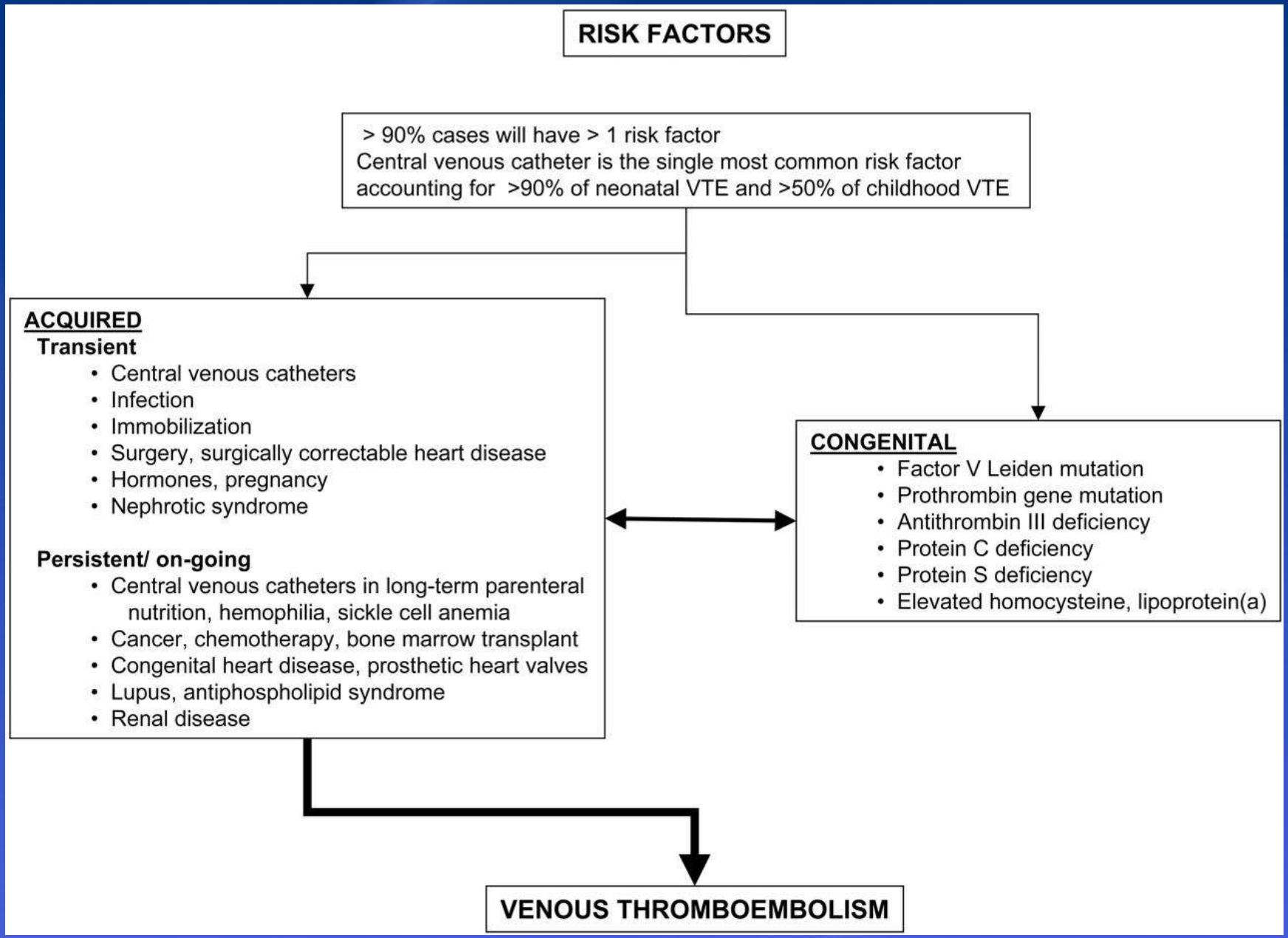

Virchow's triad
Endothelial damage
Hypercoagulability
Stasis
Endothelial dysfunction
• Smoking
• Hypertension
Endothelial damage
• Surgery
• Catheter (PICC lines)
• Trauma
Hereditary
• Factor V Leiden
• Prothrombin G20210A
• Protein C and S deficiency
Acquired
• Cancer
• Chemotherapy
• OCR/HRT
• Pregnancy
• Obesity
• HIT
• Immobility
• Polycythemia
Can cause endothelial injury

Endothelium





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Sudha Parasuraman, and Samuel Z. Goldhaber Circulation. 2006;113:e12-e16

Thrombosis in children

- Less than adults
- Intact vascular endothelium
- Lower capacity to generate thrombin
- Elevated levels α-2-macroglobulin
- Two peaks: neonatal and adolescent period (higher in females)

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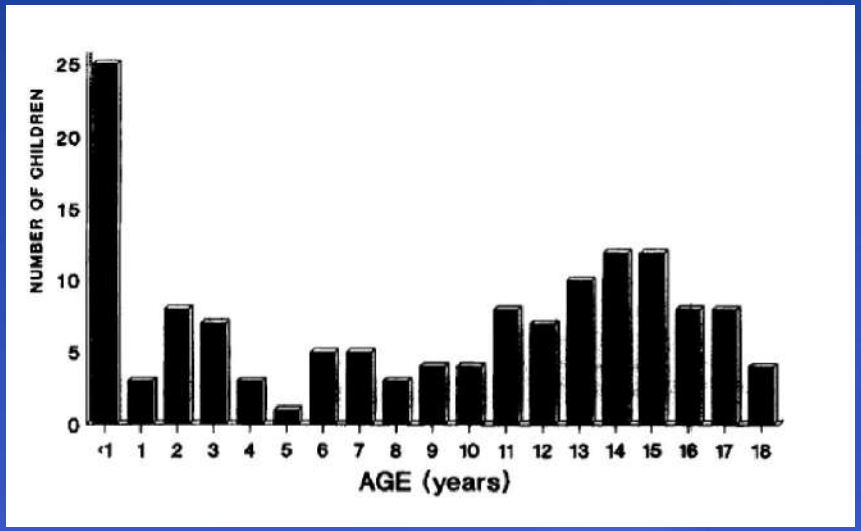
Canadian Registry of Venous Thrombo-embolism

- 137 cases entered in the registry.
- Incidence: 5.3/10,000 hospital admissions.
- Incidence: 0.07/10,000 population/year (1mo-18yrs).

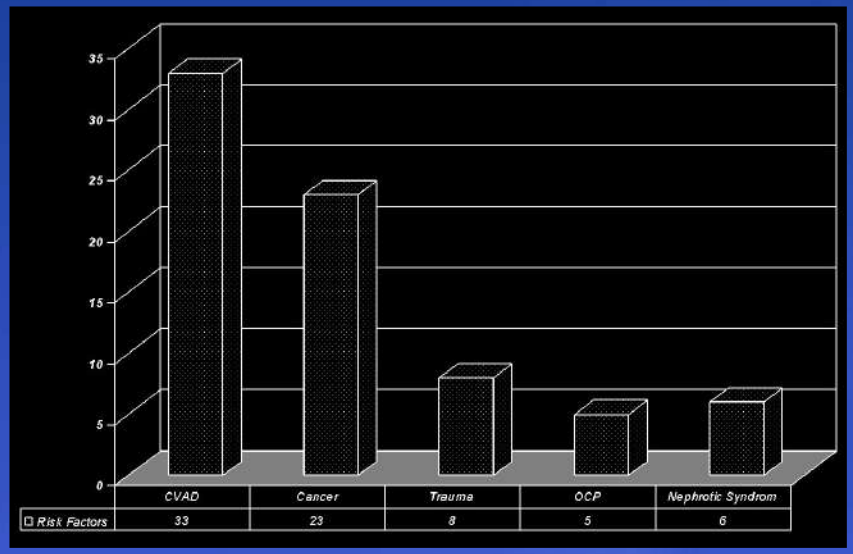
[Compare to 20-30/10,000/year in adults]



Andrew M et al Blood 1994

Canadian Registry of Venous Thrombo-embolism

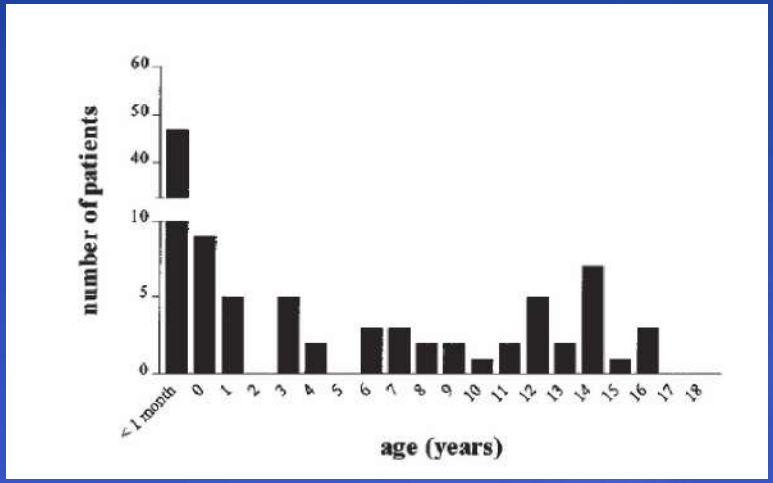
- 132/137 (96%): predisposing risk factor.
- Most children had more than one risk factor.
- CVADs were the most common risk factor.
- 12/45 (27%) had inherited thrombophilia.



Andrew M et al. Blood; 1994

Data from the Netherlands

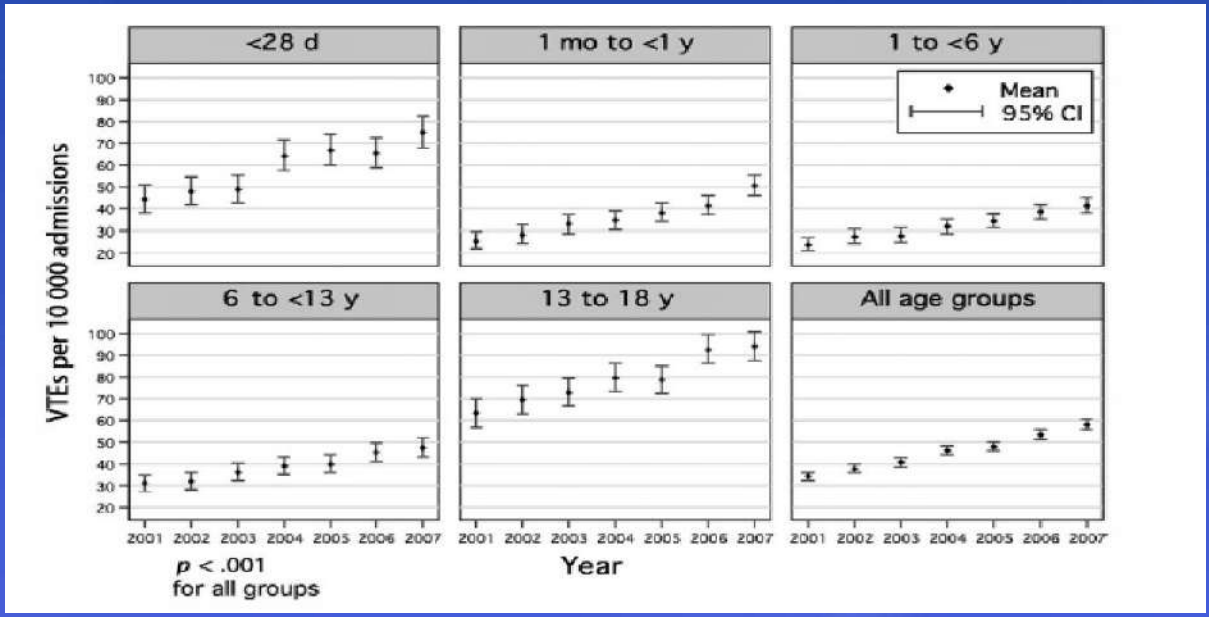
- Incidence was 0.14/10,000 population.
- Nearly 50% in neonates.
- CVADs were the most common risk factor.
- 85% of all VTE: hospitalized patients.



Van Ommen CH et al. The Journal of Pediatrics; 2001

VTE: New epidemic of tertiary care pediatric centers

- Retrospective cohort study.
- Discharge data from 41 tertiary care children's hospitals.
- 70% increase in the incidence of VTE from 2001 – 2007 (p< 0.001).



Raffini L et al. Pediatrics; 2009

Impact of Inherited Thrombophilia on Pediatric Thrombosis – *Canadian Experience*

- 171 patients evaluated for VTE.
- Median age 2.3 months.
- Underlying medical condition (heart condition, cancer etc) in 91% of the patients.
- CVADs in 77% of the patients.
- 107 evaluated for prothrombotic conditions – 13% positive.

"Inherited thrombophilia is not a significant risk factor for thrombosis in pediatric patients"

Revel-Vilk S et al. Journal of Thrombosis and Hemostasis; 2003

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Impact of Inherited Thrombophilia on Pediatric Thrombosis – *German Multicenter Registry*

- 285 patients with VTE were studied.
- Median age was 6 yrs.
- 18% of the patients had CVADs.
- A genetic pre-disposition to thrombosis was identified in 78% of the patients.

Ehrenforth S. et al. Eur J Pediatrics; 1999

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Venous thromboembolism

- Bimodal – neonates and adolescence
- Excluding extremity and malignancy -
  - Neonates – RVTs
  - Adolescents – Portal, splenic, mesenteric, and pulmonary
- Etiologies (acquired) –
  - Prematurity, asphyxia
  - CVCs – 2/3 of cases
  - Infections
  - Congenital heart disease
  - Trauma (low in peds)
  - Nephrotic syndrome
  - GI – IBD
  - Malignancy

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To test or not to test?

WE WIN!

- **Identify patients who benefit from lifelong anticoagulation.**
- **Pathogenesis.**
- **Thromboprophylaxis.**
- **Family members.**
- **PTS!!**

- **CVAD, CVAD, CVAD**
- **No change in acute management.**
- **Duration of therapy.**
- **Insurance costs.**

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Current Recommendations

Neonates with asymptomatic catheter related VTE	Testing not recommended
Neonates/children with symptomatic catheter related VTE	Insufficient Data
Neonates/children with non catheter related venous thrombosis or stroke	Consider testing
Adolescents with spontaneous thrombosis	Strongly consider testing
Asymptomatic children with positive family history	Decision made on individual basis after counseling
Asymptomatic children – routine screening (leukemia, OCPs, CVAD placement)	Testing not recommended **Family History!!!**
Neonates/children participating in thrombosis research	Testing recommended

Raffini L. et al: Hematology; 2008.

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Diagnosis: signs and symptoms

- Pain, swelling, discoloration: DVT
- IVC thrombosis: liver or renal dysfunction
- Renal vein thrombosis: hematuria
- Acute chest pain and dyspnea: PE
- Headache, visual impairment, seizures: sinus venous thrombosis
- CVC thrombosis: malfunctioning, collateral circulation

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Diagnosis

- History (risk factors) and physical exam
- Neonatal purpura fulminans - Homozygous protein C and S
  - rapidly progressive purpura and ecchymosis, often developing into large areas of skin necrosis with bulla formation
- Compression ultrasonography - both sensitive and specific for DVTs.
- D-dimer level can be done to rule-out DVT in individuals with low pretest probability
- Contrast venography - gold standard
  - rarely done because it is invasive, expensive, and not readily available. Contrast is injected into the dorsal foot vein, and the leg is imaged with CT scan or MRI.

Laboratory parameters

- D-dimers detected
- Specificity low
- Elevated D-dimer and FVIII 67% children TE (persistence correlated recurrence of TE and/or post-thrombotic syndrome)

Wells et al, N Engl J Med 2003; 349, 1227-1235
Goldenberg et al, N Engl J Med 2004; 351, 1081-1088

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Diagnosis and Management-Cases

Case 1

- You are called to evaluate a 6 year old boy, previously healthy, who underwent surgery for appendicitis. Left leg is swollen. He is 48 hr post-surgery. He had a femoral line placed for fluids/antibiotics administration. Ultrasound showed a femoral vein thrombosis.

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Case 1-femoral DVT

Management?

a. Remove central line after unfractionated anticoagulation 3-5 days

b. Remove central line and monitor ultrasound, if evidence of extension, anticoagulate with UFH

c. Anticoagulate using the central line

d. Thrombolysis

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Duration of anticoagulation?

- Individualized
- Risk factors?
- Identified acquired etiology 3 months
- Extensive thrombosis, inherited thrombophilia, 6 months-1 year
- Life-long (recurrent, life-threatening with inherited predisposition, LAC)

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Choice anticoagulation

- Lack of randomized trials in children
- Most recommendations derived from adult trials
- Hemostatic system infant different adult
- Pharmacokinetics
- Compliance
- Monitoring
- Drug interactions/diet

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Antithrombotic Therapy in Children (Chest 2004; 126; 645-687)

- Evidenced based guidelines for anticoagulation/thrombolysis in children
- Neonates VTE: tx UFH vs LMWH, or radiographic monitoring and anticoagulation if extension occurs.
- Thrombolysis neonate: only if critical compromise organs or limbs

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Low Molecular Weight Heparin

- Easy to monitor
- Lack of drug interactions
- Heparin assay=factor Xa activity level
- Caution renal insufficiency

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Duration?

- Individualized
- Risk factors?
- Identified acquired etiology 3 months
- Extensive thrombosis, inherited thrombophilia, 6 months-1 year
- Life-long (recurrent, life-threatening with inherited predisposition)

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Thrombolysis contraindications

Strong contraindication:

- Within 10 days surgery or bleeding
- Within 7 days severe asphyxia
- Within 3 days invasive procedure
- Within 48 hrs seizure

Soft contraindication:

- Prematurity less 32 weeks GA
- Sepsis
- Refractory thrombocytopenia and/or hypofibrinogenemia

Schoppenheim and Greiner, ASH 2006

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New anticoagulants?

- Dabigatran (inhibitor II), Rivaroxaban, Apixaban (inhibit Xa)
- Minimal drug interactions, reliable monitoring, compliance
- High cost, lack specific antidotes, lack long-term safety data
- Emerging pediatric data

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Chest Guidelines

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.

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Case 2

- 18 year old male with T cell ALL
- CVAD (port-a-cath)
- Four drug induction (PEG-asparaginase)
- Acute abdominal pain
- Swelling and pain right forearm

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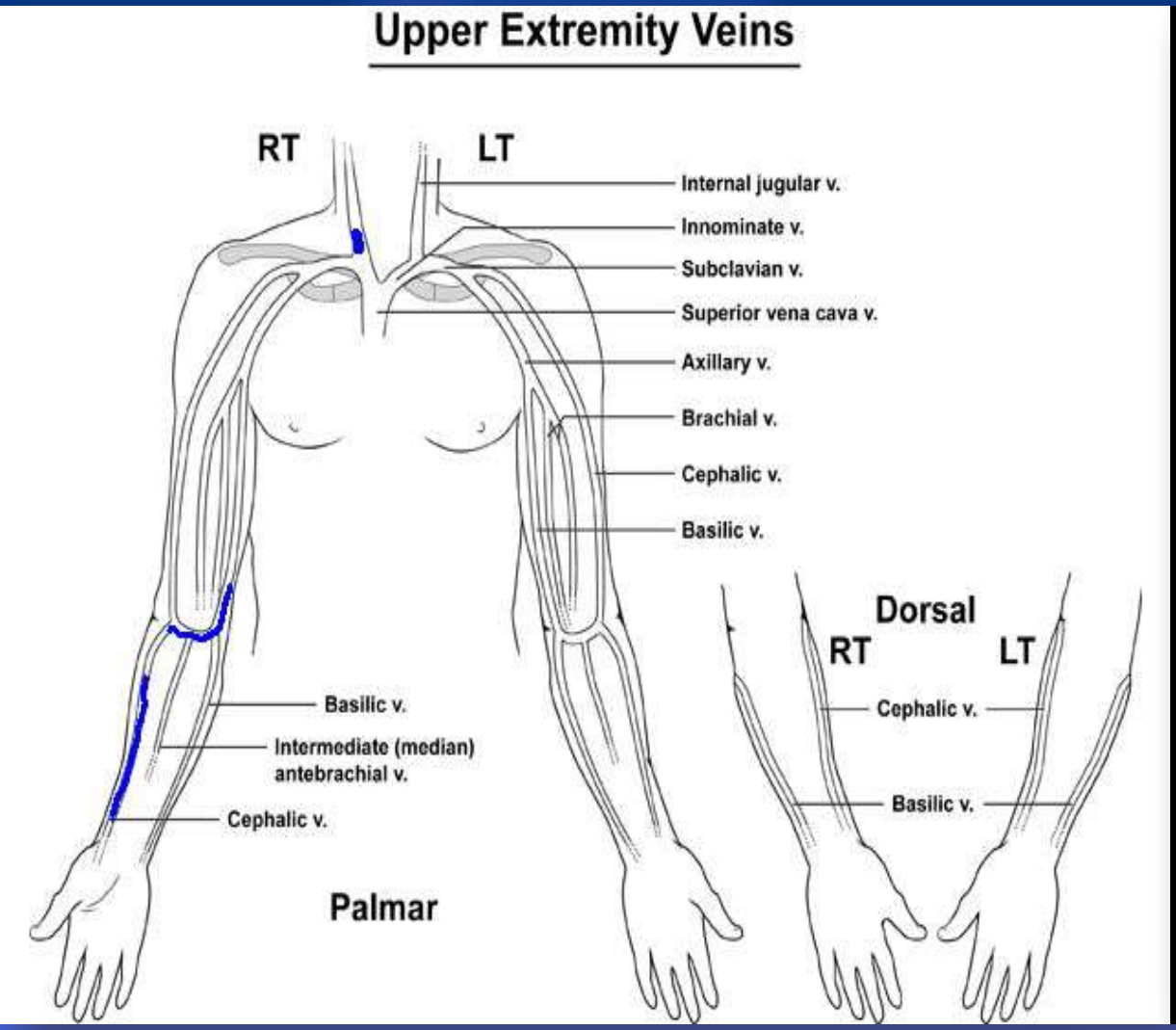
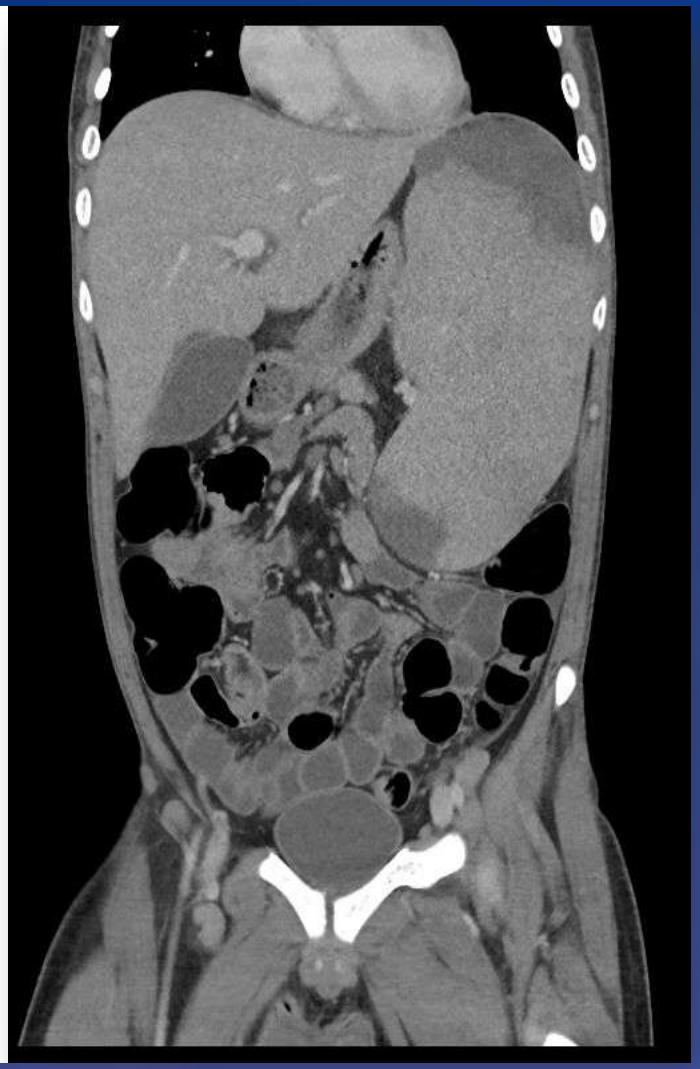

Upper Extremity Veins
RT
LT
Internal jugular v.
Innominate v.
Subclavian v.
Superior vena cava v.
Axillary v.
Brachial v.
Cephalic v.
Basilic v.
Basilic v.
Intermediate (median) antebrachial v.
Cephalic v.
Palmar
Dorsal
RT
LT
Cephalic v.
Basilic v.



Case 2

18 year old with acute splenic infarct, right upper extremity superficial thrombophlebitis and right internal jugular vein non-occlusive thrombus.

Recommendations for management of thrombotic event:

a. Observation only
b. Low molecular heparin and consider AT replacement
c. AT replacement only
d. Thrombolytic therapy followed by anticoagulation

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Thrombosis in children with malignancy

Laszlo Bajzar[a], Anthony K. Chan[b], Mary Patricia Massicotte[c] and Lesley G. Mitchell[c]

Table 1 Thrombosis in the general pediatric oncology population

	Study type	Study population	Overall prevalence *N* (%)	Prevalence based on diagnosis *N* (%)	Location of VTE	Diagnostic tests
Ruud *et al.* [38]	Prospective cohort	Cancer ($n=41$) ALL, AML, non-Hodgkins lymphoma, brain tumors	18/41 (44%)	N/A	18/18, Jugular veins	Screened with ultrasound
Knoffler *et al.* [39]	Prospective cohort	Cancer ($n=77$) 25 ALL 18 non-Hodgkins lymphoma 29 Solid tumors 5 AML	11/77 (14.2%)	ALL 4/25 (16%) AML 1/5 (20%) Non-Hodgkins lymphoma 3/18 (16.7%) Solid tumors 3/29 (10.3%)	11/11 central venous system	Clinical symptoms confirmed with ultrasound and all patients with prothrombotic risk factors were screened with U/S
Glaser *et al.* [40]	Prospective cohort	Cancer ($n=24$) Leukemia/ lymphoma, solid tumors, histiocytosis	12/24 (50%) Asymptomatic 9/24 (37.5%) Symptomatic 3/24 (12.5%)	Leukemia 4/10 (40%) Solid tumors 6/12 (50%) Histiocytosis 2/2	12/12 central venous system	Asymptomatic screened and symptomatic confirmed with venography
Wilimas [41]	Prospective cohort	Cancer ($n=25$) ALL and solid tumors	3/25 (12%)	Solid tumors 3/23 (13%) ALL 0/2 (0%)	6/6 central venous system	Asymptomatic screened with CT scan a minimum of 2 months after catheter removal
Wermes *et al.* [42]	Prospective cohort	Cancer ($n=137$) 73 ALL 11 AML 10 non-Hodgkins lymphoma 2 Hodgkins lymphoma 41 solid tumors	10/137 (7.3%)	ALL 6/73 (8.2%) Non ALL 4/64 (6.3%)	9/10 central venous system 1/10 central nervous system	Clinical symptoms confirmed by venography, magnetic resonance imaging (MRI) and ventilation perfusion scans
Sifontes *et al.* [43]	Case – control	Cancer ($n=32$) 19 ALL 8 lymphomas 4 solid tumors 1 brain tumor	Not reported	N/A	26/31 central venous system 5/31 central nervous system 1/31 both	Not stated

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia

Current Opinion Ped 2008; 18:1

Journal of Thrombosis and Haemostasis, 14: 485–494 DOI: 10.1111/jth.13236

ORIGINAL ARTICLE

Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study

R. TUCKUVIENE,* S. RANTA,† B. K. ALBERTSEN,‡ N. G. ANDERSSON,§ M. D. BENDTSEN,¶ T. FRISK,† M. W. GUNNES,** J. HELGESTAD,* M. M. HEYMAN,† O. G. JONSSON,†† A. MÄKIPERNAA,‡‡ K. PRUUNSILD,§§ U. TEDGÄRD,§ S. S. TRAKYMIENE¶¶ and E. RUUD***

- 1038 pediatric patients (less than 18 years of age); 2008-2013
- TE events n=63 (52/63 due Asp)
- Cumulative incidence TE 6.1%
- Older age (15-17 years) associated increased risk (HR 4.0)
- TE-associated 30 day case fatality of 6.4%
- TE-related truncation of Asp in 36.2% (21/58)
- Major hemorrhage 3.5% (2/58) anticoagulated patients (none in those LMWH)

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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

- Rate of thrombosis in 1752 studies 5.2% (95% CI: 4.2-6.4)
- Most events induction phase
- Lower doses of asp for long-periods of time, anthracyclines and prednisone: highest incidence

Table 2. Sites of thrombosis

Site of thrombosis, N = 91	No. of events (%)
Central nervous system	49 (53.8)
Cerebral venous thrombosis	26 (28.6)
Cerebral thrombosis (nonspecified)	5 (5.5)
Cerebral infarction	9 (9.9)
Stroke	9 (9.9)
Non-CNS venous thrombosis	39 (42.8)
Nonspecified DVT	3 (3.3)
DVT-lower limbs	7 (7.7)
DVT-upper limbs + CVC-associated thrombosis	25 (27.5)
Pulmonary embolism	1 (1.1)
Right atrium	1 (1.1)
Portal thrombosis	0
Superficial thrombosis	2 (2.2)
Nonspecified site of thrombosis	3 (3.3)

Blood 2006; 108: 2217

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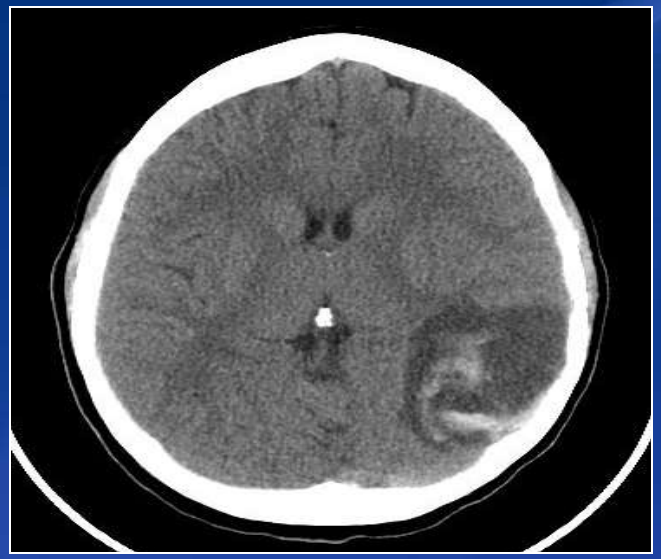

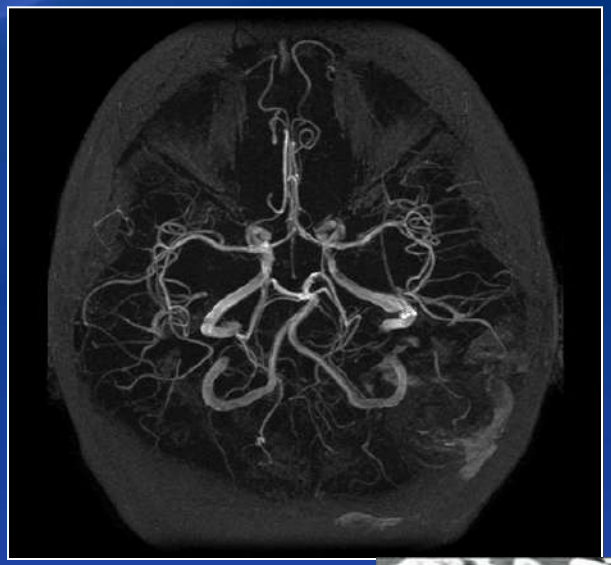

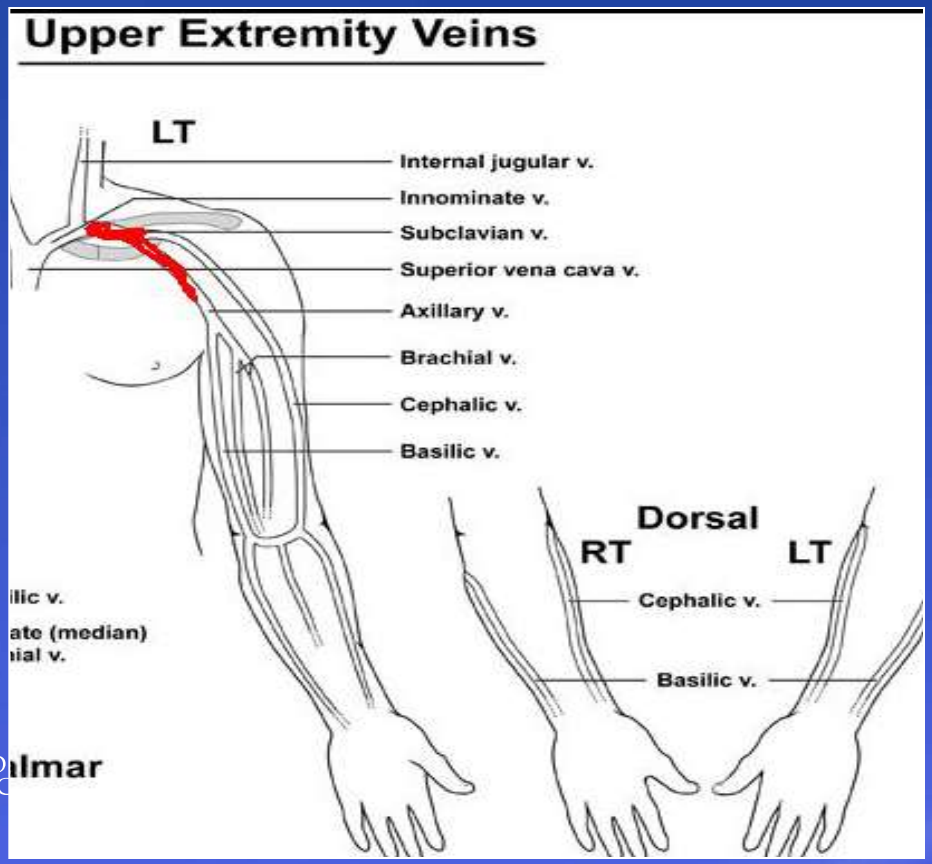
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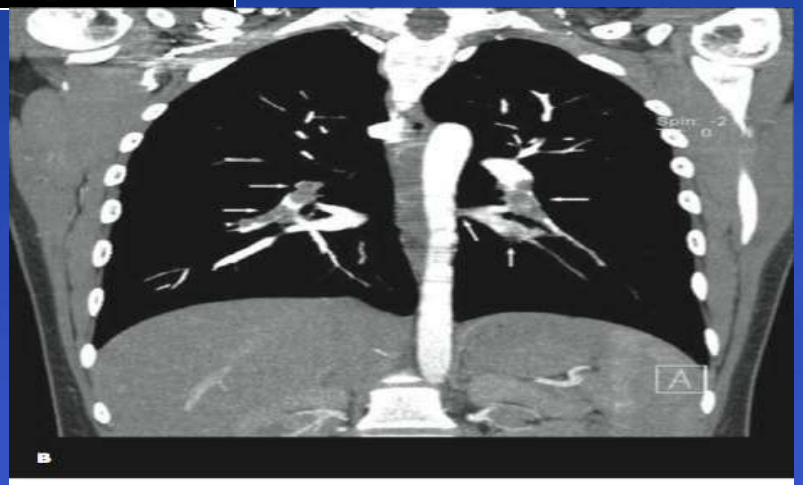
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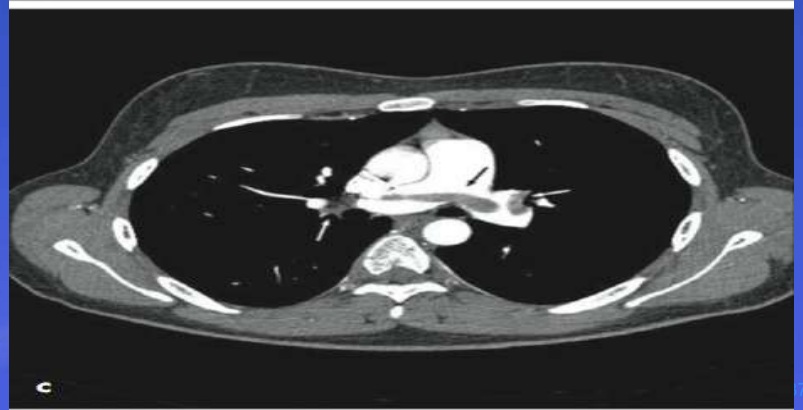
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Pediatr Blood Cancer 2010;55:153–156

Post-Thrombotic Syndrome After Central Venous Catheter Removal in Childhood Cancer Survivors Is Associated With a History of Obstruction

Shoshana Revel-Vilk, MD, MSc,* Motti Menahem, MD, Chanie Stoffer, RN, and Michael Weintraub, MD

TABLE II. Summary of Studies on Post-Thrombotic Syndrome (PTS) Post-Central Venous Catheter (CVC) Removal in Childhood Cancer Survivors

Refs.	Main cancer diagnosis	Age, median	Main CVC type	Time from CVC removal, mean ± SD	Diagnosed with PTS/ cohort	Mean PTS score	Type of PTS signs and symptoms (number)
Ruud et al. [13]	Leukemia + lymphoma (77%)	11 years	Hickman catheters (91%)	3 years (4 month to 15 years)[c]	4/71 (5.6%)	NA	Collateral (4)
Journeycake et al. [12]	Leukemia + lymphoma (68%)	13.8 ± 4.8 years[b]	Port-a-Caths (86%)	7.5 ± 2.8 years	8/50 (16%)	0.16	Pain (2), collaterals (1), arm differences (5)
Kuhle et al. [6][a]	Leukemia (100%)	I. 4.4 years	NA	I. 7.3 ± 0.6 years[d]	7/13 (53%)	1.9	Pain (1), collateral (7), arm differences (3)
		II. 3 years		II. 9.5 ± 4 years[d]	10/41 (24%)	1.8	Collateral (10), arm differences (5)
Revel-Vilk (This study)	Leukemia + lymphoma (53%)	10.5 years	Hickman catheters (84%)	2.3 ± 1.4 years	20/51 (39%)	0.43	Pain (5), collaterals (5), arm differences (10)

CVC, central venous catheter; PTS, post-thrombotic syndrome. [a]This study included two cohorts; [b]Presented as mean ± SD; [c]Presented as median (range); [d]Time from entry to the PARKAA study.

Case 2

18 year old with acute splenic infarct, right upper extremity superficial thrombophlebitis and right internal non-occlusive thrombus. Recommendations for management of thrombotic event:

b. Low molecular heparin and consider AT replacement

Prevention and management of asparaginase/pegasparaginase associated toxicities in adults and older adolescents: recommendations of an expert panel

- "It is also difficult to recommend prophylaxis in adult patients when the risk of thrombosis and bleeding has been inadequately characterized."

- "If prophylaxis is desired it is best applied during the induction phase of therapy when the majority of events take place, rather than for subsequent administrations."

- "Potential prophylaxis modalities include: AT supplementation, and anticoagulation with either low-molecular-weight heparin or heparin alone or in conjunction with AT and/or with cryoprecipitate administration.."

Stock W et al Leuk and Lymph 2011; 52: 2237-2253

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Studies	Design	Results	Limitations
Ruud E. et al. Low-dose warfarin for prevention of CVL-associated thromboses in children with malignancies	A randomized, controlled study for prevention of CVL-associated VTE using low dose warfarin (INR 1.3-1.9) in children with newly diagnosed cancer, a CVL in a jugular vein. # of subjects: warfain 31; control (SOC) 42.	CVL-related VTE was equally frequent among children on warfarin as compared to controls. Study terminated early due to lack of benefit with warfarin compared with control in the prevention of VTE (48% versus 36%).	Only a few patients achieved therapeutic INR levels at all times, indicating ineffective anticoagulation.
Massicotte P. et al. PROTEKT (REVIparin in Venous ThromboEmbolism).	Open-label, multi-center, randomized, prevention of CVL-associated VTE with reviparin in children. Blinded central outcome adjudication. # of subjects: SOC 80; reviparin 78	Was safe but its efficacy remains unclear. Enrolled only 31% 186/600) of the required number of patients. Closed earlier due to slow accrual.	Study under-powered to demonstrate either safety or efficacy due to premature closure.
Mitchell L, et al. PARKAA (Prophylactic Antithrombin Replacement in Kids with ALL treated with L-Asparaginase). Thromb Haemost. 2003.	Open-label, randomized, controlled, VTE prevention study in children with ALL who were receiving asparaginase. # of subjects: AT 25, no AT 60.	A statistically non-significant trend towards a protective effect of ATIII concentrate in prevention of asymptomatic thrombosis compared to placebo.	-No demonstrable positive laboratory effect on plasma markers of endogenous thrombin formation. -22% of the patients were not evaluated. - Study not powered to determine whether prophylactic AT was clinically beneficial.
Elhasid R. VTE prevention with enoxaparin during L-asparaginase treatment in ALL. Blood Coagul Fibrinolysis 2001;12:367.	A non-randomized ALL cohort study, compared with historical control ALL children who had not received prophylactic enoxaparin during l-asparaginase treatment. # of subjects: enoxaparin cohort 41; control cohort 50.	No symptomatic VTE or bleeding complications in enoxaparin cohort; 1 DVT, 1 PE in historical cohort.	Non-randomized cohort study; historical control.
REVIVE (REVIparin in Venous ThromboEmbolism)	Multicenter, open-label, randomized patients with objectively confirmed VTE to receive either reviparin or heparin+coumadin for VTE treatment in children. # of subjects: reviparin 36; heparin+coumadin 40	Enrolled only 20% (76/352) of the targeted population. Closed earlier due to slow accrual.	Study under-powered to demonstrate either safety or efficacy due to premature closure.

Case 3

- 15 year old female, previously healthy, developed abdominal pain. She also presents with high blood pressures and seizures. Further evaluation showed CT abdomen IVC clot at the level of renal veins. Due to chest pain, Chest CT revealed PE.
- Consult weekend: Prolonged PT and aPTT
- Evidence renal dysfunction

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Some hints coagulation studies

- Prolongation clotting times failed to correct with normal plasma mixing (inhibitor to factor or lupus anticoagulant).
- Further inhibition clotting assays using phospholipids (PNP, DRVVT, Staclot): think lupus anticoagulant

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Thrombophilia evaluation

PT 17.3 (8.3-10.8 s)

INR 1.9

PT Eq Mix 10.9

aPTT 94 (21-33s)

APTT eq vol mix 55

TT 24

PNP 77 (PNP buffer control 84)

- DRVVT screen ratio <1.2 4.7
- 1:1 mix 2.9
- Confirm ratio 3.3
- Fibrinogen >800
- D-dimer 6350 (<250 ng/ml)
- Mildly decreased II, VII, IX, X
- Neg antiphospholipid antibodies

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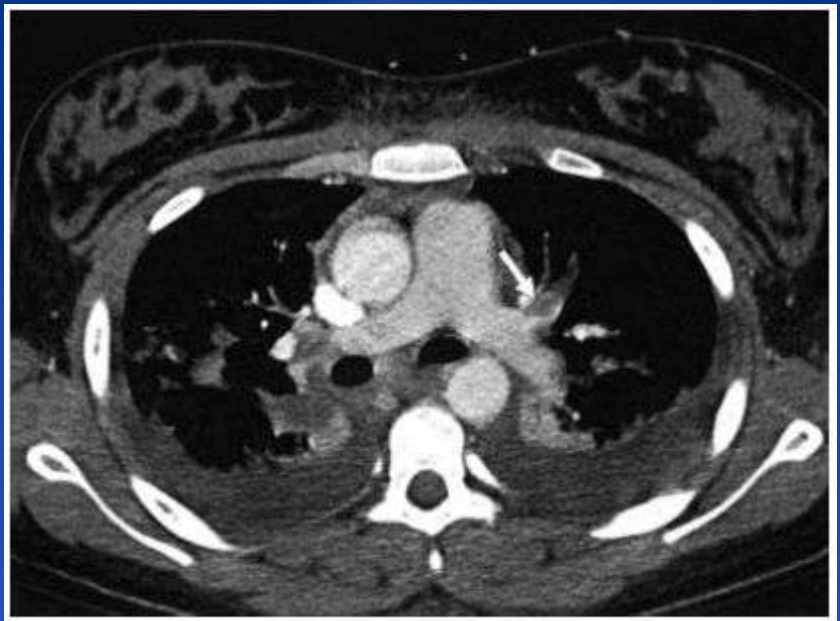

Fig. 1. Computed tomography of the chest showing pulmonary arterial thrombosis (arrow).

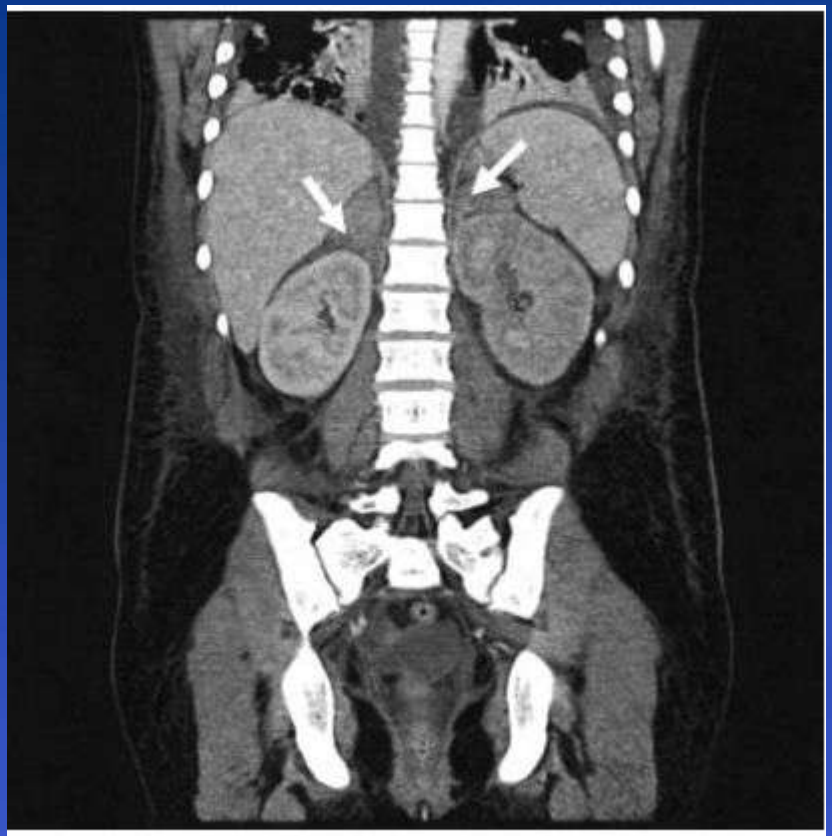

Fig. 2. Computed tomography of the abdomen showing bilateral adrenal hemorrhages (arrows).

Case 3…

- What are your recommendations?

a. Anticoagulation UFH (anti-Xa 0.5-1.0) and later switch to Coumadin to keep INR (2-3).

b. Do not start anticoagulation due to adrenal hemorrhages.

c. Thrombolysis followed by anticoagulation

d. Anticoagulation with LMWH

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Multidisciplinary approach

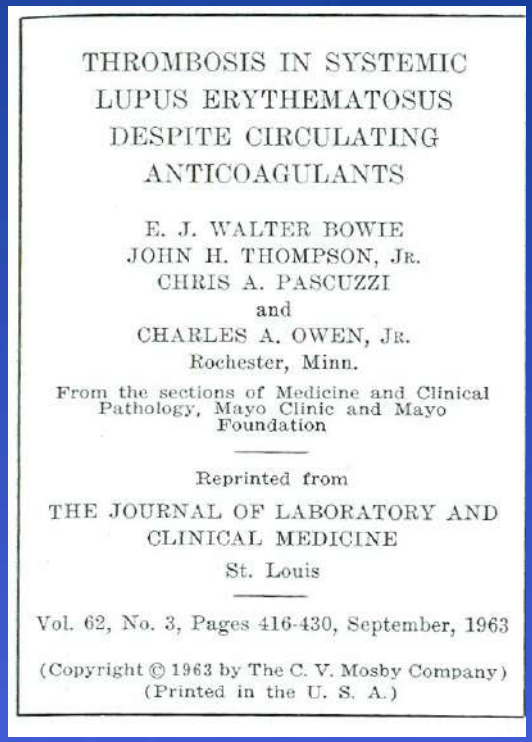
Rituximab for Successful Management of Probable Pediatric Catastrophic Antiphospholipid Syndrome

Amulya A. Nageswara Rao, MD,[1]* Grace M. Arteaga, MD,[2] Ann M. Reed, MD,[3] James M. Gloor, MD,[4] and Vilmarie Rodriguez, MD[1]

Catastrophic antiphospholipid syndrome (CAPS) is a life-threatening condition characterized by small-vessel thrombi and a rapid onset of multiorgan system failure associated with systemic inflammatory response syndrome. Current treatment options include anticoagulants, corticosteroids, plasma exchange, and intravenous immunoglobulin, but these are not always effective. Rituximab, a chimeric anti-CD20 monoclonal antibody, may help eliminate autoreactive B cells and thus limit the rapid inflammatory process involved in CAPS. We describe the use of rituximab in the successful initial management of a probable case of pediatric CAPS. Pediatr Blood Cancer 2009;52:536–538.

Key words: catastrophic antiphospholipid syndrome; lupus anticoagulant; rituximab; thrombosis

LAC



THROMBOSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS DESPITE CIRCULATING ANTICOAGULANTS

E. J. WALTER BOWIE
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and
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From the sections of Medicine and Clinical Pathology, Mayo Clinic and Mayo Foundation

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St. Louis

Vol. 62, No. 3, Pages 416-430, September, 1963

Lupus Anticoagulant (LA) Definition

- LA are antiphospholipids antibodies (IgG, IgM & IgA)
- Directed against antigens comprised of a combination of anionic (neg charged) phospholipids and a protein cofactor (eg prothrombin or βGPI)
- Inhibit *in vitro* phospholipid-dependent clotting time tests (eg, aPTT, dRVVT).

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Antiphospholipid antibodies classification (APL)

- Lupus anticoagulant (LA)
- Identified by functional coagulation testing
- Qualitative, interpretive
- Anticardiolipin Antibodies (ACL)
- Identified by immunoassays (eg ELISA)
- IgG, IgM, IgA
- β2GPI component

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APL Classification

- Autoantibodies (persistent)
  - Primary APL/APS
  - Secondary APL/APS (eg SLE)
- Alloantibodies (transient)
  - Infection
  - Inflammation
- Drug induced
  - Procainamide, Quinidine, Quinine
  - Hydralazine
  - Phenothiazines
  - Antibiotics

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APL Significance

- Thrombosis risk
  - LA ≥ ACL IgG > ACL IgM
- Pregnancy loss or complications
  - ACL IgG = LA (?)
- Bleeding risk (uncommon)
  - LA / hypoprothrombinemia (or F X def.)
  - Thrombocytopenia (AITP)
  - Anticoagulation -related bleeding

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LA ISTH Diagnostic Criteria

1. Prolongation of at least 1 phospholipid-dependent clotting time assay.
2. Inhibition shown by mixing patient and normal pooled plasma.
3. Phospholipid-dependent inhibition demonstrated.
4. Evaluate for other coagulopathies

Brandt JT, Triplett DA, Alving B, Scharrer I. *Thromb Haemost* 1995;74(4):1185-1190

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LA & APL Antibodies Pathophysiology

- Inhibition of natural anticoagulant pathways (PL dependent assembly)-Protein C & S
- Platelet activation
- Endothelial cell activation or injury
- Disruption of Annexin V binding to anionic phospholipids
- Dysregulation of fibrinolysis
- Others

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Pediatric APS Syndrome

- Registry 12/1/2007 121 cases in 14 countries
- Mean age 10.7 years
- 60 (49.5%) underlying autoimmune disease
- Venous thrombosis 72 (60%), arterial 39 (32%), small vessel 7 (6%) and mixed 3 (2%).

Avcin T et al Pediatrics 2008; 122: e1100-1107

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Pediatric APS …

- Non-thrombotic manifestations (hematologic 38%, skin 18%, neurologic 16%).
- Laboratory: + aCL 81%, anti-βGPI 67%, LA 72%
- Primary APS: younger, higher frequency arterial events
- Secondary APS: older, venous events associated hematologic and skin manifestations

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A retrospective review of pediatric antiphospholipid syndrome and thrombosis outcomes

Amulya A. Nageswara Rao[a,b], Kendra Elwood[a], Dominder Kaur[a,b], Deepti M. Warad[a,b] and Vilmarie Rodriguez[a,b]

- 20 year retrospective review
- 17 patients (10 males; 7 females)
- Median age thrombosis 15.3 years
- Venous thrombosis 64.7% (11)
- Arterial events 35.3% (6)
- 53% (9) primary APS
- Recurrent/progression thrombosis 58.8% (10)
- Median time progression 1.4 years
- At time progression only 2 (20%) were therapeutic anticoagulation

Blood Coag Fib 2017; 28: 205

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Catastrophic Antiphospholipid Syndrome

- Incidence <1% of all APS
- High mortality (50%) due to multiorgan failure
- Criteria: thromboses three or more organs, histologic confirmation small vessel occlusion at least one organ, rapid development clinical manifestation and confirmation APLas

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Catastrophic APS

- Plasmapheresis
- Prednisone/Rituximab
- UFH (monitor heparin levels instead aPTT)
- Lifelong anticoagulation (Coumadin INR 2.5-3.5)

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Mortality

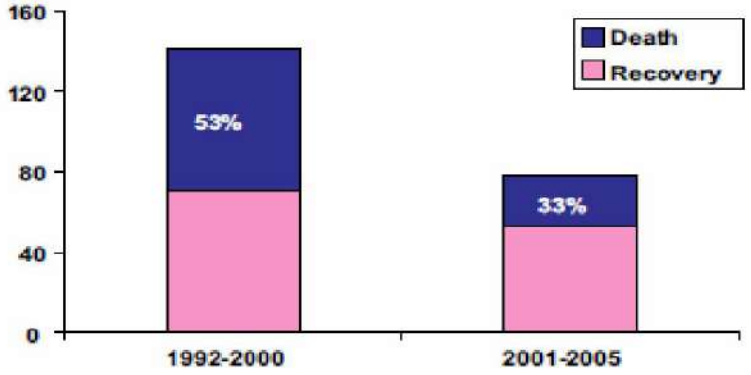

Figure 1 Influence of the time of diagnosis on evolution in patients with catastrophic APS. The mortality decreased from 53% in the first period (1992–2000) to 33% in the second period (2001–2005). The patients with catastrophic APS diagnosed after 2001 had a higher recovery rate with a statistically significant reduction on mortality of 20%.[13] $P = 0.005$.

Case 4

- 16 year old female, previously healthy except for morbid obesity and sedentary life style, developed shortness of breath. Treated with bronchodilators: no improvement. Developed chest pain and hypoxia.

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What is your next evaluation?

a. High resolution computed tomography chest
b. Add corticosteroids to bronchodilator therapy
c. Pulmonology consult
d. Put her on a diet and physical training to improve exercise tolerance

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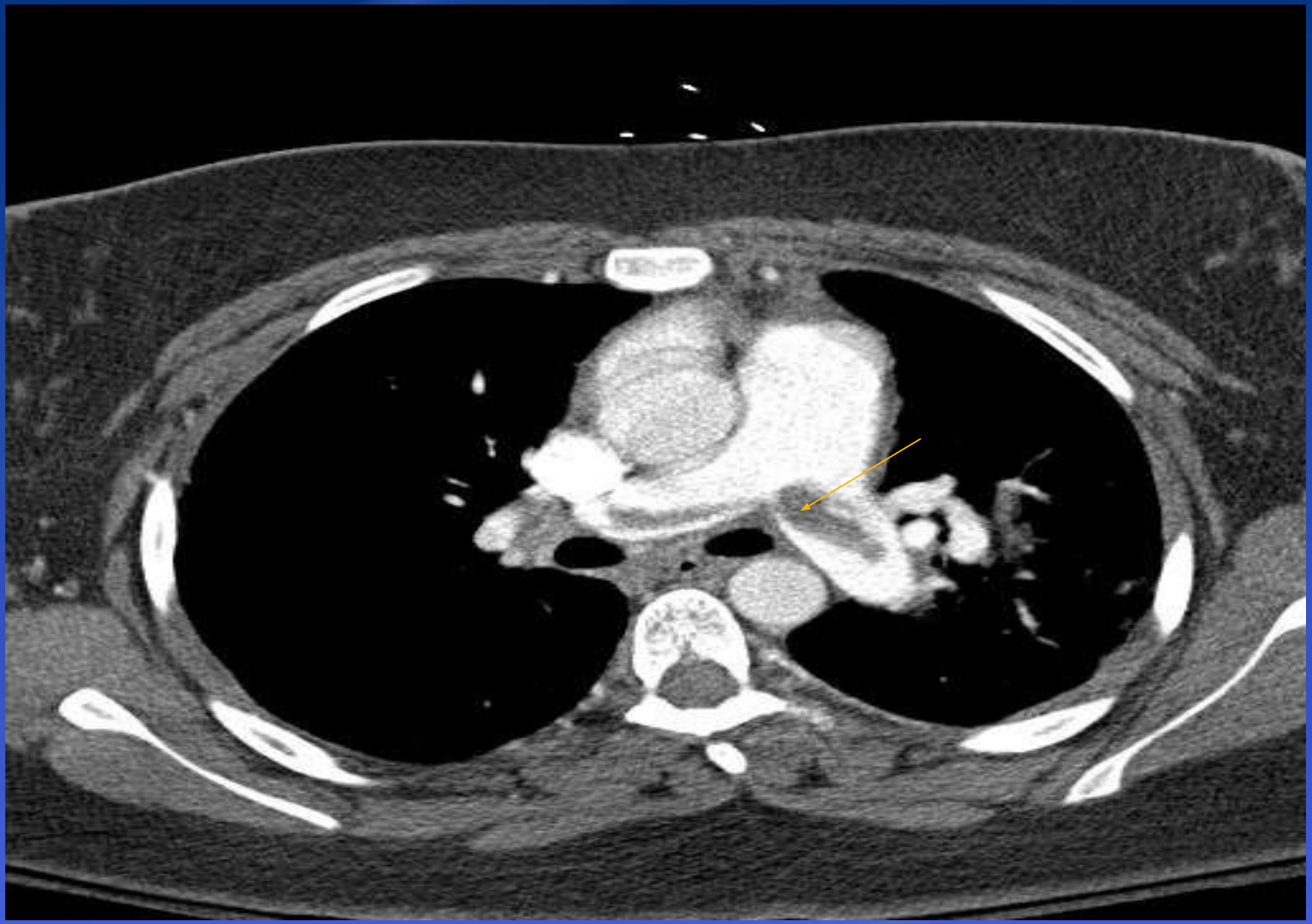

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Case 4-PE

- Obesity and sedentary life risk factors
- Thrombophilia work up negative
- UFH and Coumadin

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DOI: 10.1002/pbc.27041

BRIEF REPORT

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

Obesity, sedentary lifestyle, and video games: The new thrombophilia cocktail in adolescents

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Funding information
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Abstract

Rates of venous thromboembolism have increased in the adolescent population over the last two decades, likely due to advanced diagnostics, increased use of central venous catheters, chronic medical conditions, obesity, and oral contraceptive use. Of these factors, a modifiable risk factor for adolescents is obesity. Sedentary lifestyle and prolonged immobilization are additional pro-thrombotic risk factors that are often associated with obesity. With ever-increasing screen time, sedentary behavior has risen accordingly, especially among gamers. We present four cases of adolescents who developed life-threatening venous thromboembolic events in the setting of obesity, sedentary lifestyle and/or immobilization, and prolonged video game use.

KEYWORDS

adolescents, electronics, obesity, sedentary, thrombosis, video games

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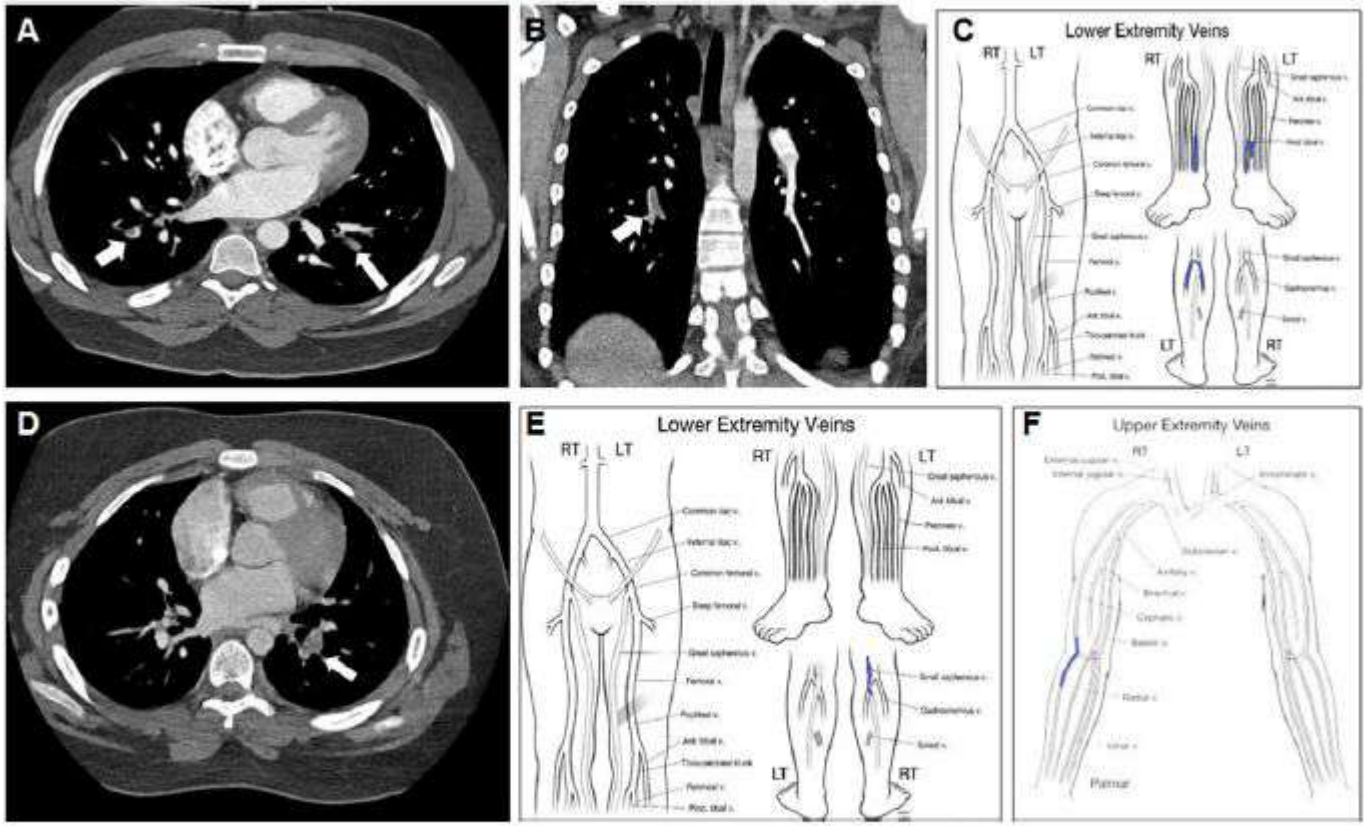

FIGURE 1 (A) Chest CT, axial view, revealing a pulmonary embolism (arrows) in case 2.1. (B) Chest CT scan, coronal view, revealing an acute right pulmonary artery embolism (arrow) in case 2.2. (C) Lower extremity mapping computed from ultrasound revealing thromboses in bilateral posterior tibial veins and left upper calf gastrocnemius vein (case 2.2). (D) Pulmonary embolism on chest CT scan in case 2.3 (arrow). (E) Lower extremity mapping computed from ultrasound revealing a right saphenous vein thrombus in case 2.3. (F) Upper extremity mapping demonstrating bilateral cephalic vein thromboses in case 2.3

Case 5-arterial thrombosis

- 12 mo old girl with RSV pneumonia. Various attempts to place a line without success. After right femoral line is placed, leg turns cold, “dusky” with no pulses. Central line is removed and she is being transferred management of right femoral artery thrombosis

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Indications thrombolysis

- Arterial thrombosis with tissue ischemia
- Phlegmasia alba/cerulea dolens: extensive thrombosis with total venous occlusion with compartment syndrome
- Pulmonary embolism with hypotension/shock, right ventricular strain or myocardial ischemia
- Superior vena cava syndrome
- Bilateral renal vein thrombosis
- Congenital heart disease with shunt thrombosis
- Large (>2 cm) mobile right atrial thrombosis
- Kawasaki disease with coronary artery thrombosis
- Cerebral sinovenous thrombosis with neurologic impairment and no improvement on anticoagulation

Front Pediatrics 2017; 5: 260

Contraindications

- Active bleeding
- Concurrent bleeding diathesis and inability to keep plts >100,000/μL and fibrinogen >100 mg/dL
- Recent major surgery or trauma within previous 10 days
- Intracranial bleeding, infarction, intracranial or spinal surgery within last 2 months
- Known right to left cardiac shunt
- CPR or asphyxia within 7 days therapy
- Extreme prematurity

Front Pediatrics 2017; 5: 260

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Pediatric thrombolysis

TABLE 1 | Published results of thrombolysis in children.

Author	Method	*N*	Age, range and site of thrombosis	Lysis*	Major hemorrhage	SAEs, other	Recurrent VTE	PTS
Manco-Johnson (28)	Systemic UK/UH	32	6 weeks to 17 years and UE, LE, SVC, IVC, PE, atrial	50%	0	Death 1; PE 1; progress 1	9%	11.1% MJ
Wang (29)	Systemic TPA	12 HD 17 LD	1 day to 17 years and LE, UE, PE, CSVT, renal, hepatic, arterial, and venous	92% 100%	0 1 ICH, PT infant	1 embolic stroke with left atrial thrombus	0	8% 0% MJ
Goldenberg (38)	Systemic/PPMT	9	1–21 years and LE	89%	1 pulmonary	0	0%	11.1% MJ
Goldenberg (33)	CDT/PMT/PPMT	16	11–19 years and LE and UE	88%	0	PE 1	27%	13% MJ
Derbari (39)	CDT/PMT/PPMT	34	13 days to 21 years and LE and UE	17%(52%) 50 (99%)	1 2 required prbcs	0%	NA	NA
Dandoy (31)	CDT/PMT/PPMT	41	3 months to 21 years and LE, UE, SVC, and IVC	90% (> 50%)	1 Required prbcs	PE 1	NA	14% (V or mV)
Gaballah (55)	CDT/PMT/PPMT	57	1–17 years and LE	33% (93.7%) >50%	1.8%		12%	2.1%V 59.3% mV

Front Pediatrics 2017; 5: 260

Thrombolysis

TABLE 2 | Dosing of alteplase and heparin during thrombolysis.

Mode of thrombolysis	Alteplase dosing		Duration of thrombolysis	Concomitant UFH therapy	Laboratory monitoring
	Bolus	Infusion			
Systemic thrombolysis	None None	Low-dose: 0.01–0.06 mg/kg/h (max 2 mg/h) High-dose: 0.1–0.5	6–72 h 2–6 h, may repeat if indicated	Prophylactic UFH with goal UFH anti-Xa level of 0.1–0.3 or UFH at 10 U/kg/h	Every 6–12 h: fibrinogen, CBC, FDPs, PT, aPTT, UFH anti-Xa
Site-directed thrombolysis	0.1–0.3 mg/kg (max dose 10 mg)	0.01–0.03 mg/kg/h or max 1–2 mg/h	Up to 72—96 h	Therapeutic UFH with goal UFH anti-Xa level of 0.3–0.7 or ufh at 10 U/kg/h	Every 6–12 h: fibrinogen, CBC, FDPs, PT, aPTT, UFH anti-Xa, renal profile, urinalysis

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Case 5

- Anticoagulated UFH later transitioned LMWH
- No need thrombolysis (perfusion improved-not complete occlusion)

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Summary

- Thrombosis increasingly recognized in pediatrics
- Congenital vs Acquired
- Early intervention
- Long term sequelae

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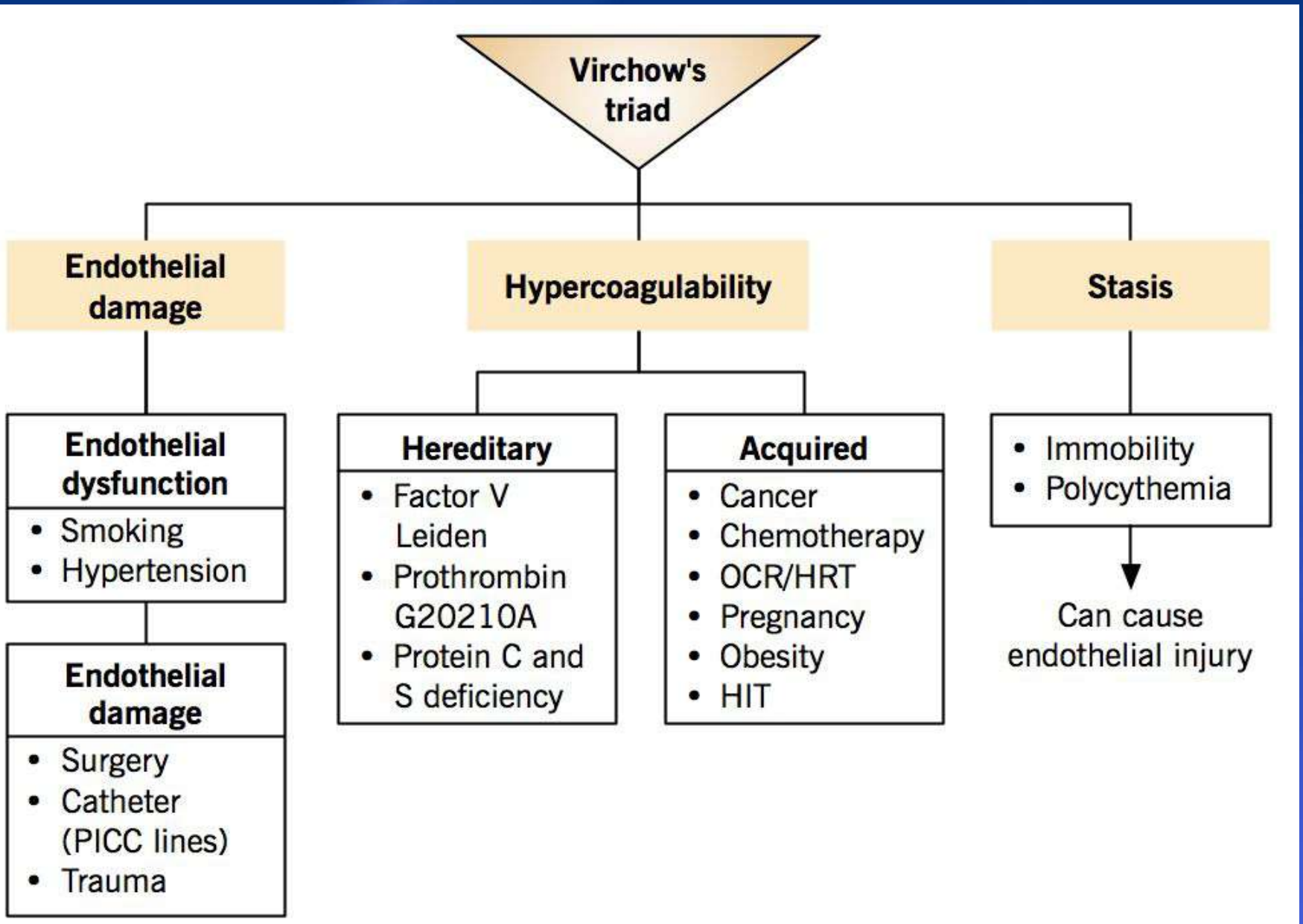
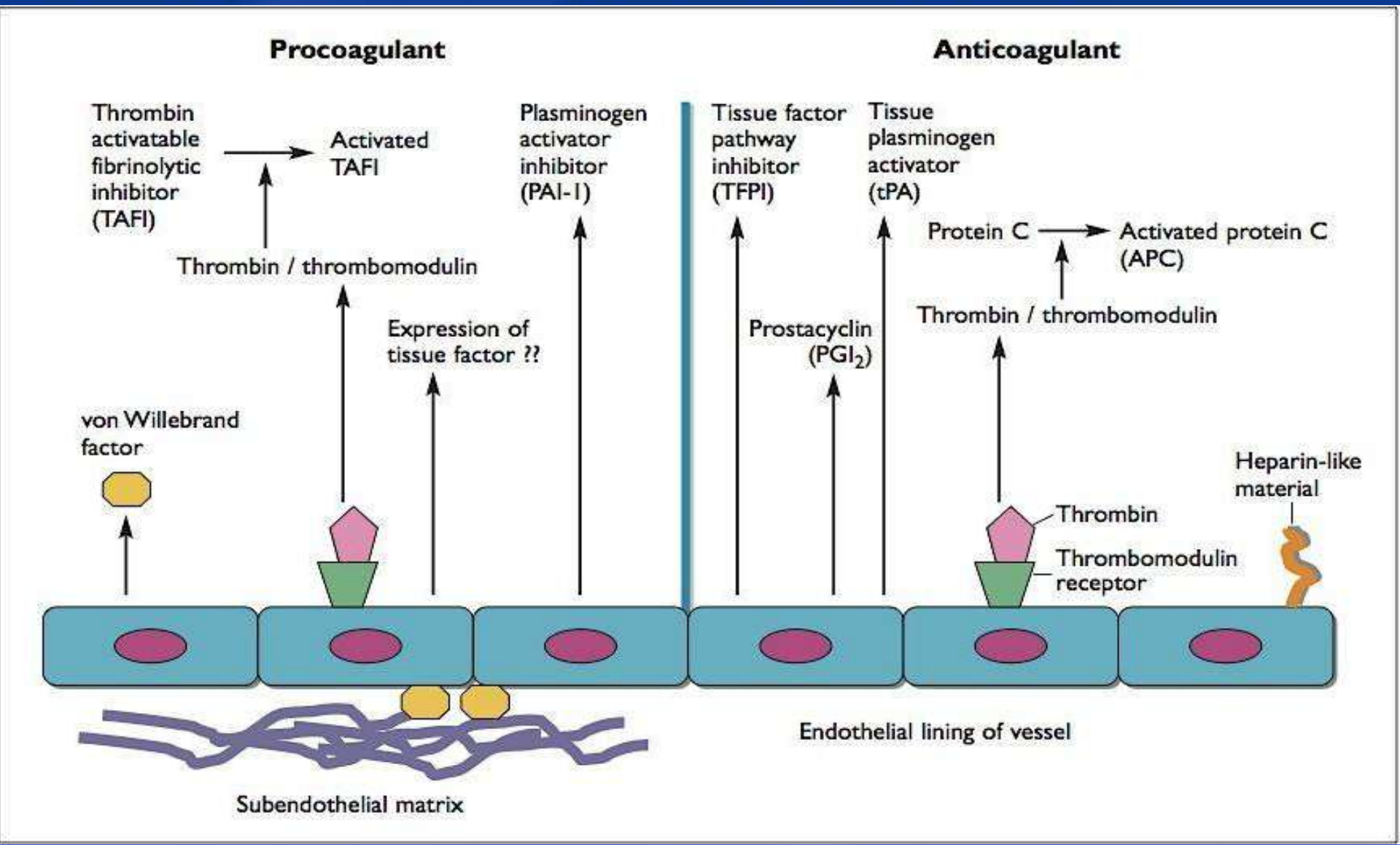
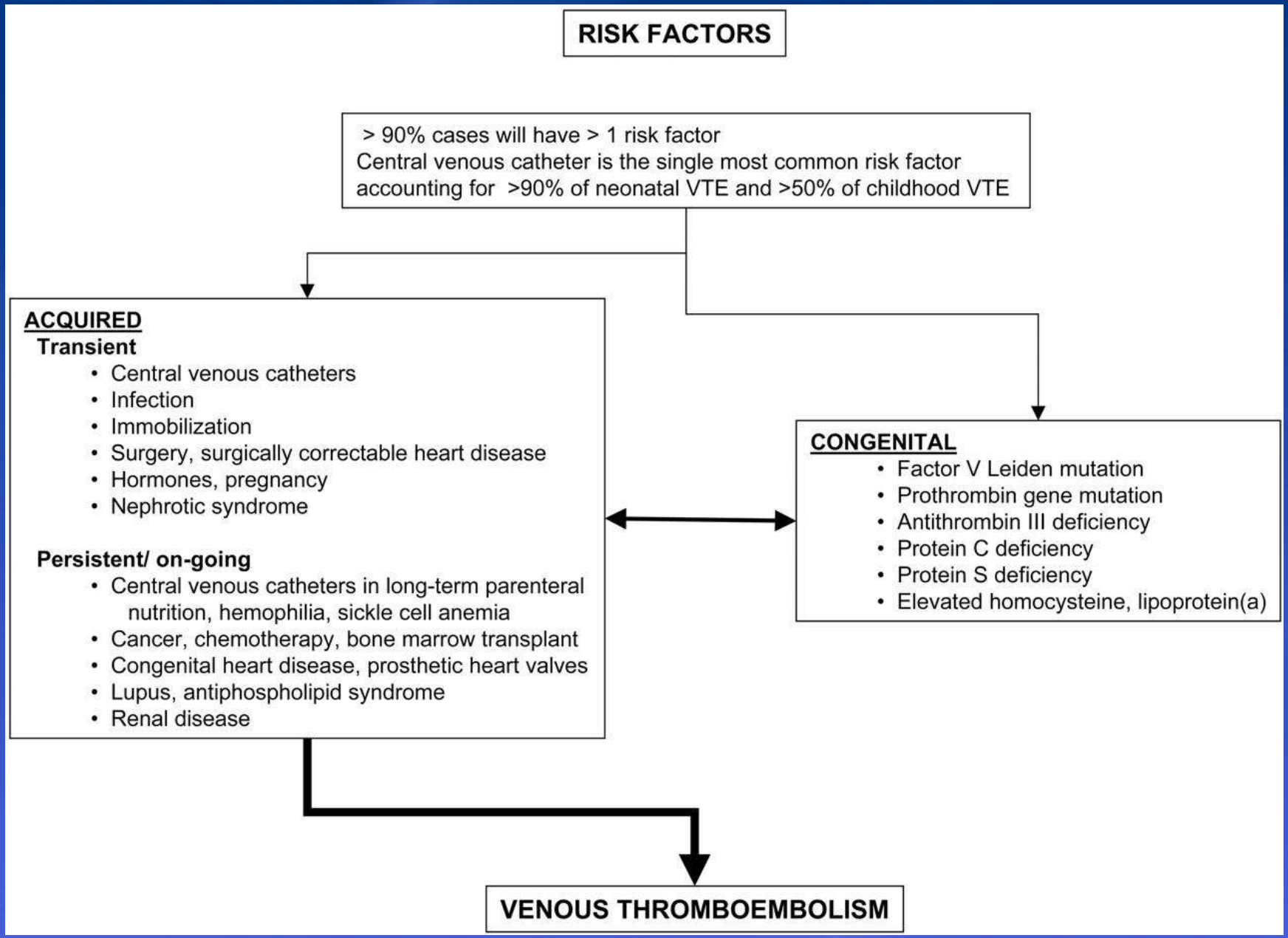

Virchow's triad
Endothelial damage
Hypercoagulability
Stasis
Endothelial dysfunction
• Smoking
• Hypertension
Endothelial damage
• Surgery
• Catheter (PICC lines)
• Trauma
Hereditary
• Factor V Leiden
• Prothrombin G20210A
• Protein C and S deficiency
Acquired
• Cancer
• Chemotherapy
• OCR/HRT
• Pregnancy
• Obesity
• HIT
• Immobility
• Polycythemia
Can cause endothelial injury

Endothelium





Sudha Parasuraman, and Samuel Z. Goldhaber Circulation. 2006;113:e12-e16

Thrombosis in children

- Less than adults
- Intact vascular endothelium
- Lower capacity to generate thrombin
- Elevated levels α-2-macroglobulin
- Two peaks: neonatal and adolescent period (higher in females)

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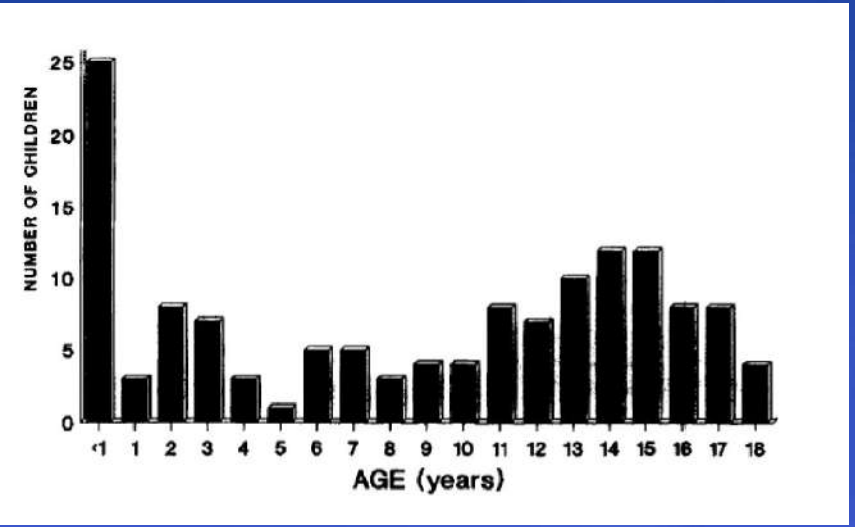
Canadian Registry of Venous Thrombo-embolism

- 137 cases entered in the registry.
- Incidence: 5.3/10,000 hospital admissions.
- Incidence: 0.07/10,000 population/year (1mo-18yrs).

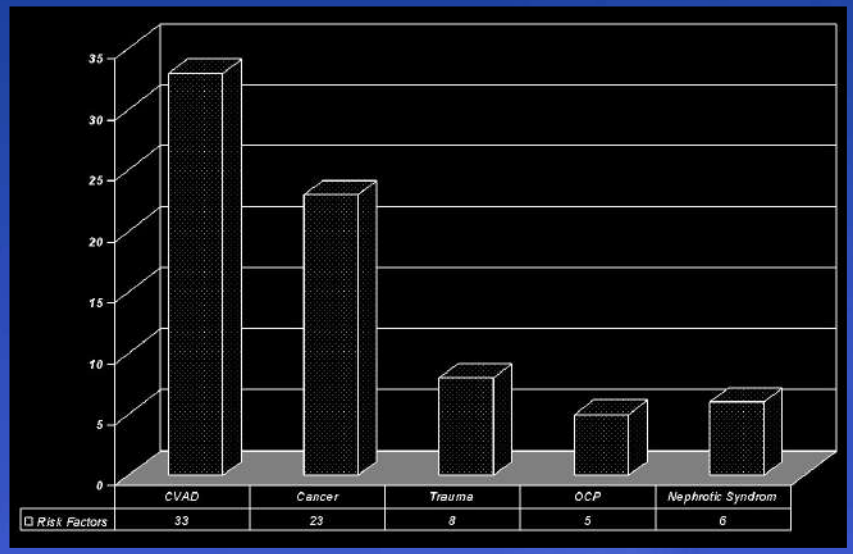
[Compare to 20-30/10,000/year in adults]



Andrew M et al Blood 1994

Canadian Registry of Venous Thrombo-embolism

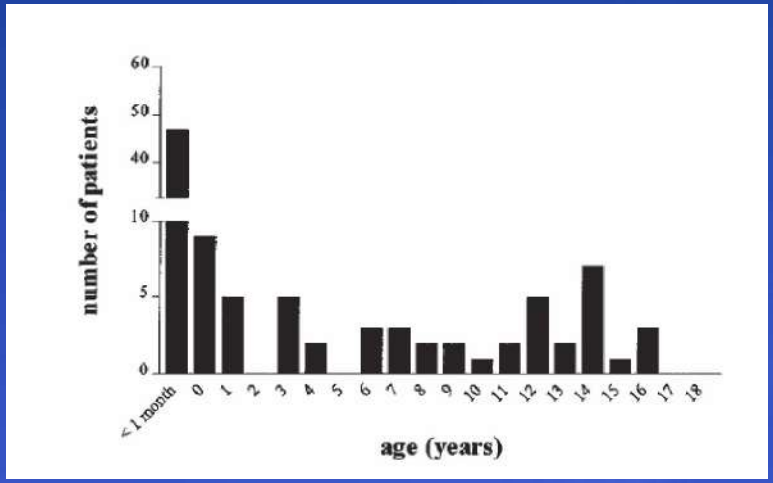
- 132/137 (96%): predisposing risk factor.
- Most children had more than one risk factor.
- CVADs were the most common risk factor.
- 12/45 (27%) had inherited thrombophilia.



Andrew M et al. Blood; 1994

Data from the Netherlands

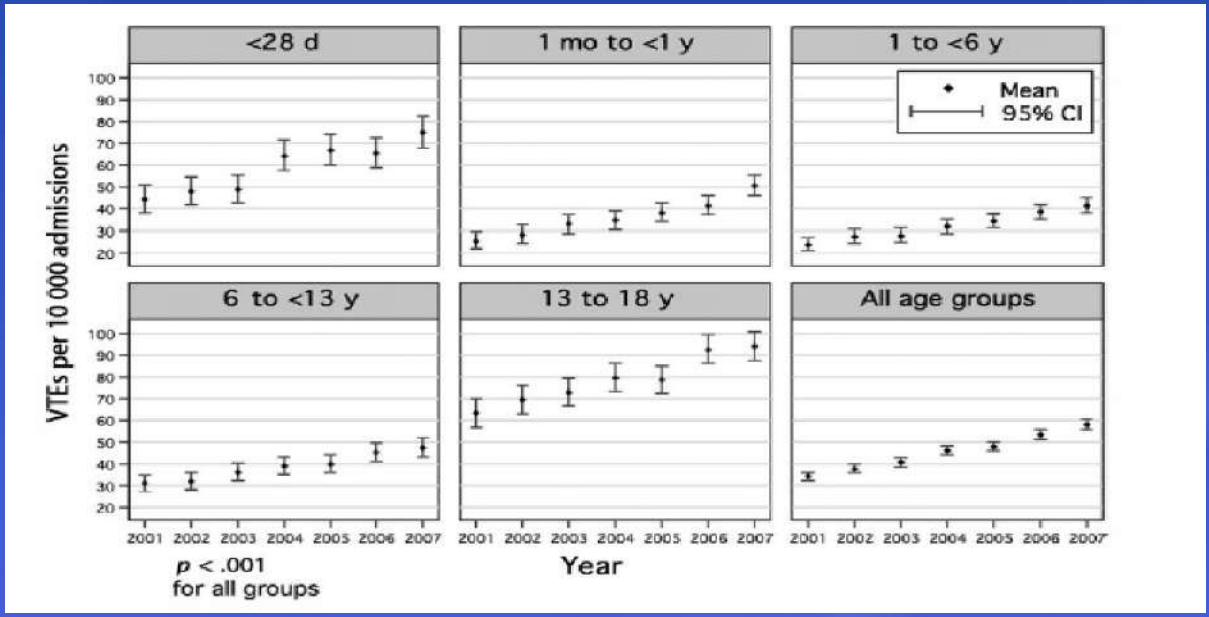
- Incidence was 0.14/10,000 population.
- Nearly 50% in neonates.
- CVADs were the most common risk factor.
- 85% of all VTE: hospitalized patients.



Van Ommen CH et al. The Journal of Pediatrics; 2001

VTE: New epidemic of tertiary care pediatric centers

- Retrospective cohort study.
- Discharge data from 41 tertiary care children's hospitals.
- 70% increase in the incidence of VTE from 2001 – 2007 (p< 0.001).



Raffini L et al. Pediatrics; 2009

Impact of Inherited Thrombophilia on Pediatric Thrombosis – *Canadian Experience*

- 171 patients evaluated for VTE.
- Median age 2.3 months.
- Underlying medical condition (heart condition, cancer etc) in 91% of the patients.
- CVADs in 77% of the patients.
- 107 evaluated for prothrombotic conditions – 13% positive.

"Inherited thrombophilia is not a significant risk factor for thrombosis in pediatric patients"

Revel-Vilk S et al. Journal of Thrombosis and Hemostasis; 2003

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Impact of Inherited Thrombophilia on Pediatric Thrombosis – *German Multicenter Registry*

- 285 patients with VTE were studied.
- Median age was 6 yrs.
- 18% of the patients had CVADs.
- A genetic pre-disposition to thrombosis was identified in 78% of the patients.

Ehrenforth S. et al. Eur J Pediatrics; 1999

Venous thromboembolism

- Bimodal – neonates and adolescence
- Excluding extremity and malignancy -
  - Neonates – RVTs
  - Adolescents – Portal, splenic, mesenteric, and pulmonary
- Etiologies (acquired) –
  - Prematurity, asphyxia
  - CVCs – 2/3 of cases
  - Infections
  - Congenital heart disease
  - Trauma (low in peds)
  - Nephrotic syndrome
  - GI – IBD
  - Malignancy

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To test or not to test?

WE WIN!

- **Identify patients who benefit from lifelong anticoagulation.**
- **Pathogenesis.**
- **Thromboprophylaxis.**
- **Family members.**
- **PTS!!**

- **CVAD, CVAD, CVAD**
- **No change in acute management.**
- **Duration of therapy.**
- **Insurance costs.**

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Current Recommendations

Neonates with asymptomatic catheter related VTE	Testing not recommended
Neonates/children with symptomatic catheter related VTE	Insufficient Data
Neonates/children with non catheter related venous thrombosis or stroke	Consider testing
Adolescents with spontaneous thrombosis	Strongly consider testing
Asymptomatic children with positive family history	Decision made on individual basis after counseling
Asymptomatic children – routine screening (leukemia, OCPs, CVAD placement)	Testing not recommended **Family History!!!**
Neonates/children participating in thrombosis research	Testing recommended

Raffini L. et al: Hematology; 2008.

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Diagnosis: signs and symptoms

- Pain, swelling, discoloration: DVT
- IVC thrombosis: liver or renal dysfunction
- Renal vein thrombosis: hematuria
- Acute chest pain and dyspnea: PE
- Headache, visual impairment, seizures: sinus venous thrombosis
- CVC thrombosis: malfunctioning, collateral circulation

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Diagnosis

- History (risk factors) and physical exam
- Neonatal purpura fulminans - Homozygous protein C and S
  - rapidly progressive purpura and ecchymosis, often developing into large areas of skin necrosis with bulla formation
- Compression ultrasonography - both sensitive and specific for DVTs.
- D-dimer level can be done to rule-out DVT in individuals with low pretest probability
- Contrast venography - gold standard
  - rarely done because it is invasive, expensive, and not readily available. Contrast is injected into the dorsal foot vein, and the leg is imaged with CT scan or MRI.

Laboratory parameters

- D-dimers detected
- Specificity low
- Elevated D-dimer and FVIII 67% children TE (persistence correlated recurrence of TE and/or post-thrombotic syndrome)

Wells et al, N Engl J Med 2003; 349, 1227-1235
Goldenberg et al, N Engl J Med 2004; 351, 1081-1088

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Diagnosis and Management-Cases

Case 1

- You are called to evaluate a 6 year old boy, previously healthy, who underwent surgery for appendicitis. Left leg is swollen. He is 48 hr post-surgery. He had a femoral line placed for fluids/antibiotics administration. Ultrasound showed a femoral vein thrombosis.

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Case 1-femoral DVT

Management?

a. Remove central line after unfractionated anticoagulation 3-5 days

b. Remove central line and monitor ultrasound, if evidence of extension, anticoagulate with UFH

c. Anticoagulate using the central line

d. Thrombolysis

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Duration of anticoagulation?

- Individualized
- Risk factors?
- Identified acquired etiology 3 months
- Extensive thrombosis, inherited thrombophilia, 6 months-1 year
- Life-long (recurrent, life-threatening with inherited predisposition, LAC)

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Choice anticoagulation

- Lack of randomized trials in children
- Most recommendations derived from adult trials
- Hemostatic system infant different adult
- Pharmacokinetics
- Compliance
- Monitoring
- Drug interactions/diet

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Antithrombotic Therapy in Children (Chest 2004; 126; 645-687)

- Evidenced based guidelines for anticoagulation/thrombolysis in children
- Neonates VTE: tx UFH vs LMWH, or radiographic monitoring and anticoagulation if extension occurs.
- Thrombolysis neonate: only if critical compromise organs or limbs

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Low Molecular Weight Heparin

- Easy to monitor
- Lack of drug interactions
- Heparin assay=factor Xa activity level
- Caution renal insufficiency

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Duration?

- Individualized
- Risk factors?
- Identified acquired etiology 3 months
- Extensive thrombosis, inherited thrombophilia, 6 months-1 year
- Life-long (recurrent, life-threatening with inherited predisposition)

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Thrombolysis contraindications

Strong contraindication:

- Within 10 days surgery or bleeding
- Within 7 days severe asphyxia
- Within 3 days invasive procedure
- Within 48 hrs seizure

Soft contraindication:

- Prematurity less 32 weeks GA
- Sepsis
- Refractory thrombocytopenia and/or hypofibrinogenemia

Schoppenheim and Greiner, ASH 2006

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New anticoagulants?

- Dabigatran (inhibitor II), Rivaroxaban, Apixaban (inhibit Xa)
- Minimal drug interactions, reliable monitoring, compliance
- High cost, lack specific antidotes, lack long-term safety data
- Emerging pediatric data

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Chest Guidelines

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.

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Case 2

- 18 year old male with T cell ALL
- CVAD (port-a-cath)
- Four drug induction (PEG-asparaginase)
- Acute abdominal pain
- Swelling and pain right forearm

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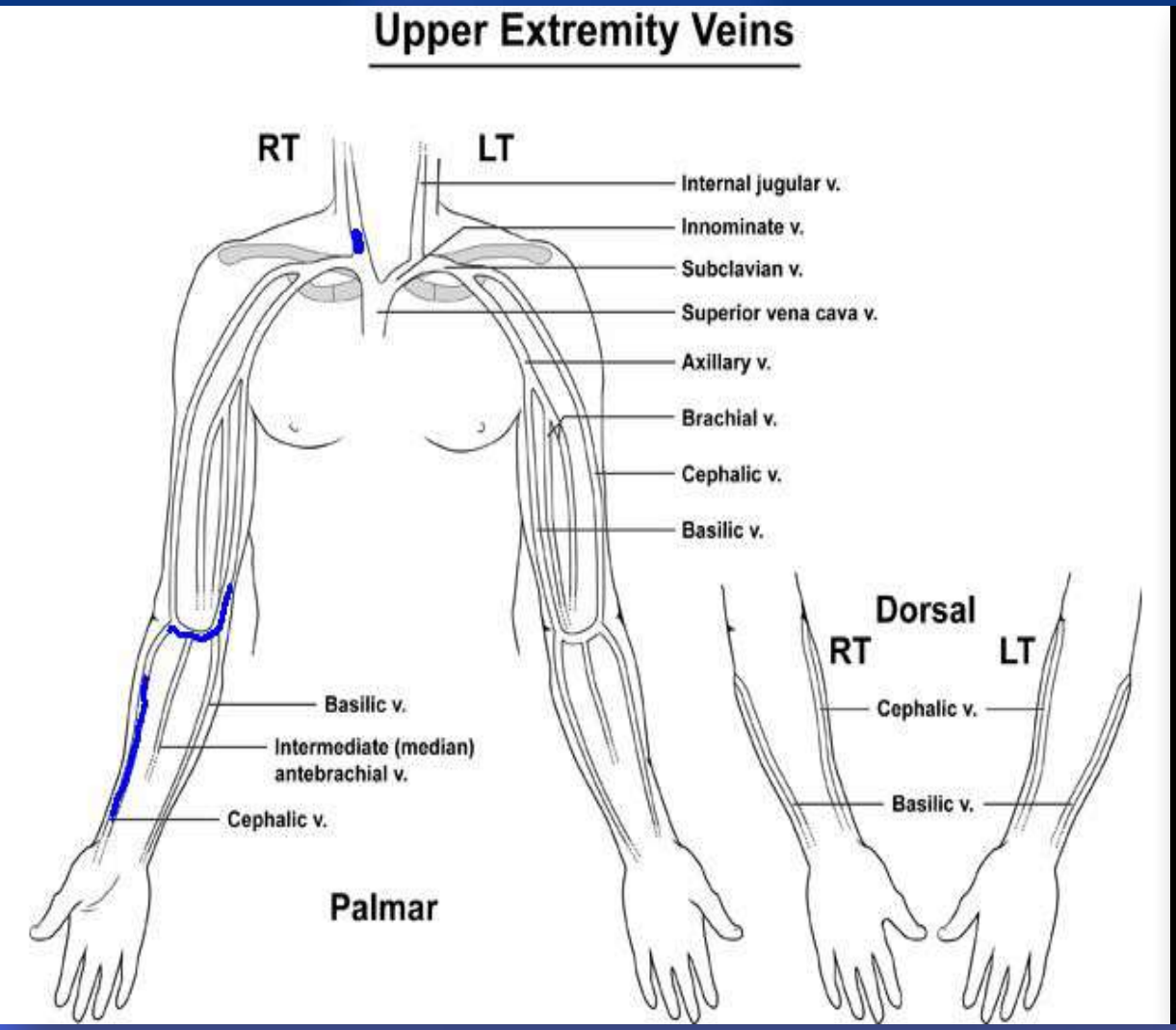
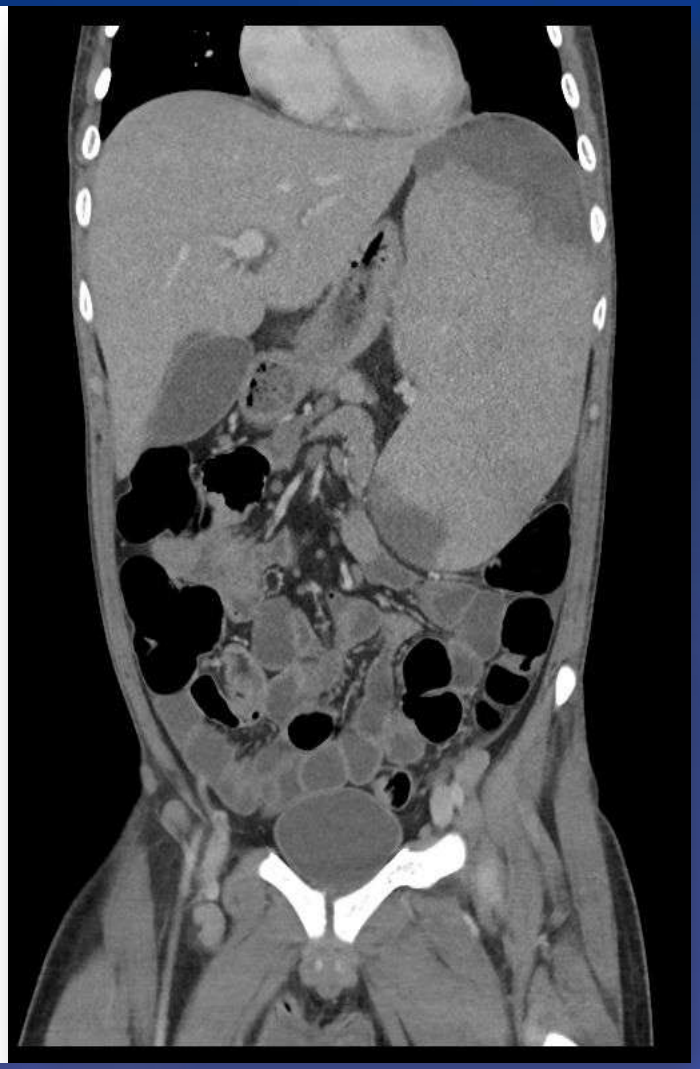

Upper Extremity Veins
RT
LT
Internal jugular v.
Innominate v.
Subclavian v.
Superior vena cava v.
Axillary v.
Brachial v.
Cephalic v.
Basilic v.
Basilic v.
Intermediate (median) antebrachial v.
Cephalic v.
Palmar
Dorsal
RT
LT
Cephalic v.
Basilic v.



Case 2

18 year old with acute splenic infarct, right upper extremity superficial thrombophlebitis and right internal jugular vein non-occlusive thrombus.

Recommendations for management of thrombotic event:

a. Observation only
b. Low molecular heparin and consider AT replacement
c. AT replacement only
d. Thrombolytic therapy followed by anticoagulation

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Thrombosis in children with malignancy

Laszlo Bajzar[a], Anthony K. Chan[b], Mary Patricia Massicotte[c] and Lesley G. Mitchell[c]

Table 1 Thrombosis in the general pediatric oncology population

	Study type	Study population	Overall prevalence *N* (%)	Prevalence based on diagnosis *N* (%)	Location of VTE	Diagnostic tests
Ruud *et al.* [38]	Prospective cohort	Cancer ($n=41$) ALL, AML, non-Hodgkins lymphoma, brain tumors	18/41 (44%)	N/A	18/18, Jugular veins	Screened with ultrasound
Knoffler *et al.* [39]	Prospective cohort	Cancer ($n=77$) 25 ALL 18 non-Hodgkins lymphoma 29 Solid tumors 5 AML	11/77 (14.2%)	ALL 4/25 (16%) AML 1/5 (20%) Non-Hodgkins lymphoma 3/18 (16.7%) Solid tumors 3/29 (10.3%)	11/11 central venous system	Clinical symptoms confirmed with ultrasound and all patients with prothrombotic risk factors were screened with U/S
Glaser *et al.* [40]	Prospective cohort	Cancer ($n=24$) Leukemia/ lymphoma, solid tumors, histiocytosis	12/24 (50%) Asymptomatic 9/24 (37.5%) Symptomatic 3/24 (12.5%)	Leukemia 4/10 (40%) Solid tumors 6/12 (50%) Histiocytosis 2/2	12/12 central venous system	Asymptomatic screened and symptomatic confirmed with venography
Wilimas [41]	Prospective cohort	Cancer ($n=25$) ALL and solid tumors	3/25 (12%)	Solid tumors 3/23 (13%) ALL 0/2 (0%)	6/6 central venous system	Asymptomatic screened with CT scan a minimum of 2 months after catheter removal
Wermes *et al.* [42]	Prospective cohort	Cancer ($n=137$) 73 ALL 11 AML 10 non-Hodgkins lymphoma 2 Hodgkins lymphoma 41 solid tumors	10/137 (7.3%)	ALL 6/73 (8.2%) Non ALL 4/64 (6.3%)	9/10 central venous system 1/10 central nervous system	Clinical symptoms confirmed by venography, magnetic resonance imaging (MRI) and ventilation perfusion scans
Sifontes *et al.* [43]	Case – control	Cancer ($n=32$) 19 ALL 8 lymphomas 4 solid tumors 1 brain tumor	Not reported	N/A	26/31 central venous system 5/31 central nervous system 1/31 both	Not stated

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia

Current Opinion Ped 2008; 18:1

Journal of Thrombosis and Haemostasis, 14: 485–494 DOI: 10.1111/jth.13236

ORIGINAL ARTICLE

Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study

R. TUCKUVIENE,* S. RANTA,† B. K. ALBERTSEN,‡ N. G. ANDERSSON,§ M. D. BENDTSEN,¶ T. FRISK,† M. W. GUNNES,** J. HELGESTAD,* M. M. HEYMAN,† O. G. JONSSON,†† A. MÄKIPERNAA,‡‡ K. PRUUNSILD,§§ U. TEDGÄRD,§ S. S. TRAKYMIENE¶¶ and E. RUUD***

- 1038 pediatric patients (less than 18 years of age); 2008-2013
- TE events n=63 (52/63 due Asp)
- Cumulative incidence TE 6.1%
- Older age (15-17 years) associated increased risk (HR 4.0)
- TE-associated 30 day case fatality of 6.4%
- TE-related truncation of Asp in 36.2% (21/58)
- Major hemorrhage 3.5% (2/58) anticoagulated patients (none in those LMWH)

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

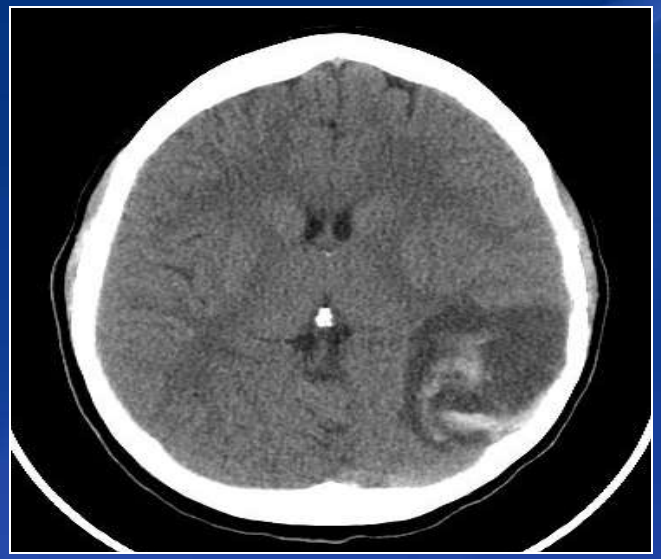
Vanesa Caruso, Licia Iacoviello, Augusto Di Castelnuovo, Sergio Storti, Guglielmo Mariani, Giovanni de Gaetano, and Maria Benedetta Donati

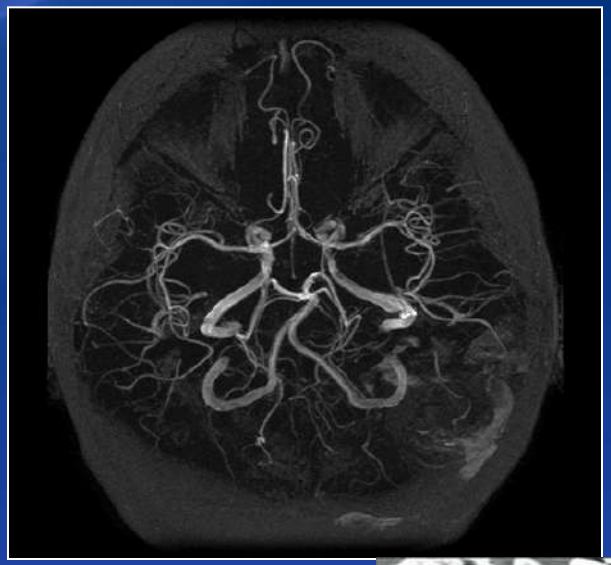
- Rate of thrombosis in 1752 studies 5.2% (95% CI: 4.2-6.4)
- Most events induction phase
- Lower doses of asp for long-periods of time, anthracyclines and prednisone: highest incidence

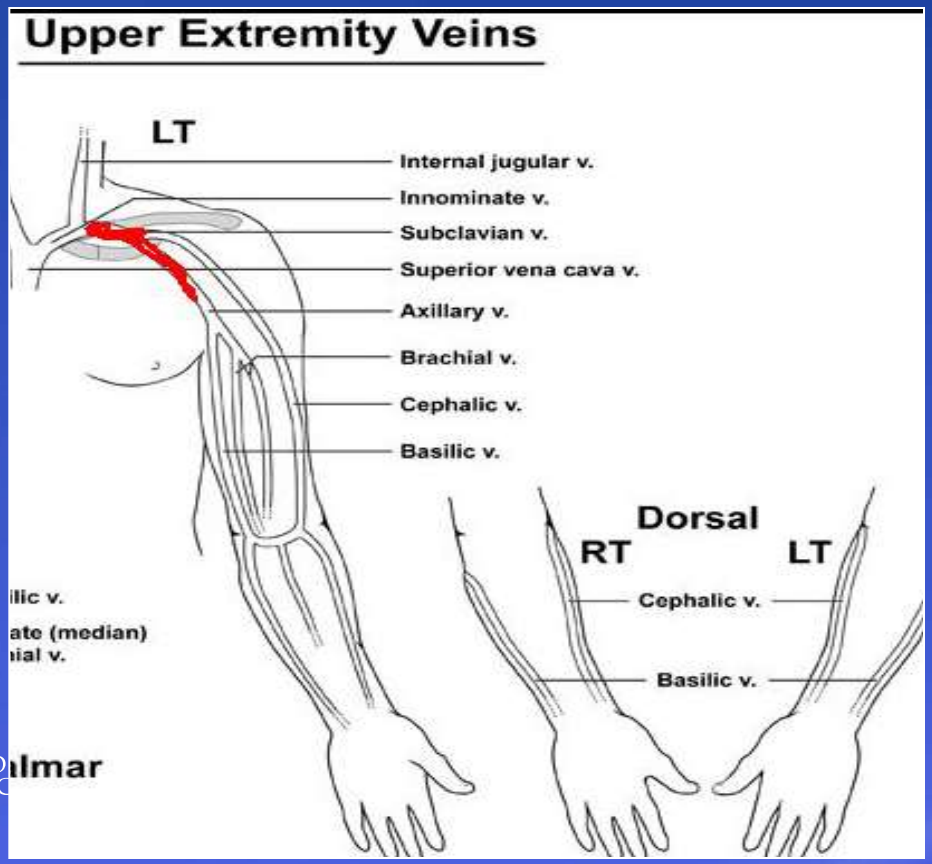
Table 2. Sites of thrombosis

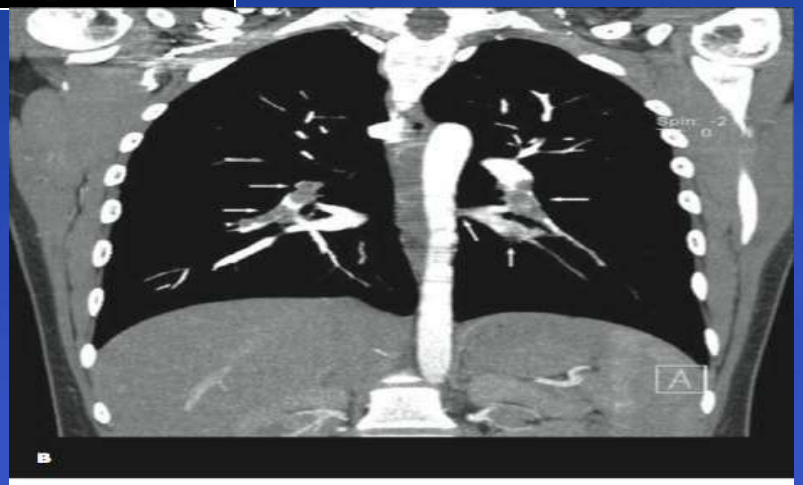
Site of thrombosis, N = 91	No. of events (%)
Central nervous system	49 (53.8)
Cerebral venous thrombosis	26 (28.6)
Cerebral thrombosis (nonspecified)	5 (5.5)
Cerebral infarction	9 (9.9)
Stroke	9 (9.9)
Non-CNS venous thrombosis	39 (42.8)
Nonspecified DVT	3 (3.3)
DVT-lower limbs	7 (7.7)
DVT-upper limbs + CVC-associated thrombosis	25 (27.5)
Pulmonary embolism	1 (1.1)
Right atrium	1 (1.1)
Portal thrombosis	0
Superficial thrombosis	2 (2.2)
Nonspecified site of thrombosis	3 (3.3)

Blood 2006; 108: 2217






Upper Extremity Veins
LT
Internal jugular v.
Innominate v.
Subclavian v.
Superior vena cava v.
Axillary v.
Brachial v.
Cephalic v.
Basilic v.
Dorsal
RT
LT
Cephalic v.
Basilic v.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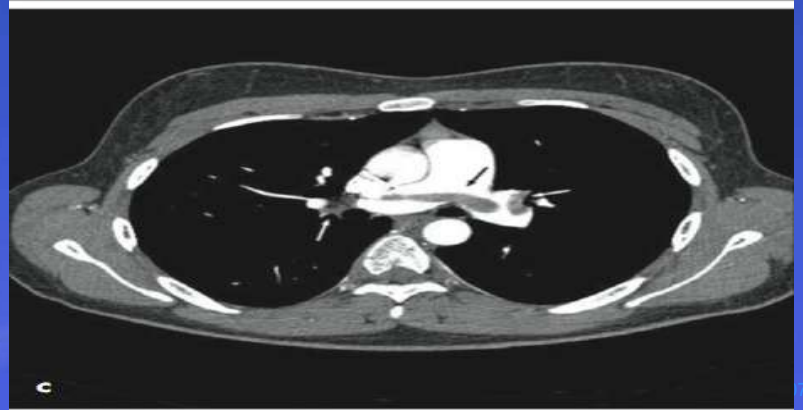
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Pediatr Blood Cancer 2010;55:153–156

Post-Thrombotic Syndrome After Central Venous Catheter Removal in Childhood Cancer Survivors Is Associated With a History of Obstruction

Shoshana Revel-Vilk, MD, MSc,* Motti Menahem, MD, Chanie Stoffer, RN, and Michael Weintraub, MD

TABLE II. Summary of Studies on Post-Thrombotic Syndrome (PTS) Post-Central Venous Catheter (CVC) Removal in Childhood Cancer Survivors

Refs.	Main cancer diagnosis	Age, median	Main CVC type	Time from CVC removal, mean ± SD	Diagnosed with PTS/ cohort	Mean PTS score	Type of PTS signs and symptoms (number)
Ruud et al. [13]	Leukemia + lymphoma (77%)	11 years	Hickman catheters (91%)	3 years (4 month to 15 years)[c]	4/71 (5.6%)	NA	Collateral (4)
Journeycake et al. [12]	Leukemia + lymphoma (68%)	13.8 ± 4.8 years[b]	Port-a-Caths (86%)	7.5 ± 2.8 years	8/50 (16%)	0.16	Pain (2), collaterals (1), arm differences (5)
Kuhle et al. [6][a]	Leukemia (100%)	I. 4.4 years	NA	I. 7.3 ± 0.6 years[d]	7/13 (53%)	1.9	Pain (1), collateral (7), arm differences (3)
		II. 3 years		II. 9.5 ± 4 years[d]	10/41 (24%)	1.8	Collateral (10), arm differences (5)
Revel-Vilk (This study)	Leukemia + lymphoma (53%)	10.5 years	Hickman catheters (84%)	2.3 ± 1.4 years	20/51 (39%)	0.43	Pain (5), collaterals (5), arm differences (10)

CVC, central venous catheter; PTS, post-thrombotic syndrome. [a]This study included two cohorts; [b]Presented as mean ± SD; [c]Presented as median (range); [d]Time from entry to the PARKAA study.

Case 2

18 year old with acute splenic infarct, right upper extremity superficial thrombophlebitis and right internal non-occlusive thrombus. Recommendations for management of thrombotic event:

b. Low molecular heparin and consider AT replacement

Prevention and management of asparaginase/pegasparaginase associated toxicities in adults and older adolescents: recommendations of an expert panel

- "It is also difficult to recommend prophylaxis in adult patients when the risk of thrombosis and bleeding has been inadequately characterized."

- "If prophylaxis is desired it is best applied during the induction phase of therapy when the majority of events take place, rather than for subsequent administrations."

- "Potential prophylaxis modalities include: AT supplementation, and anticoagulation with either low-molecular-weight heparin or heparin alone or in conjunction with AT and/or with cryoprecipitate administration.."

Stock W et al Leuk and Lymph 2011; 52: 2237-2253

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Studies	Design	Results	Limitations
Ruud E. et al. Low-dose warfarin for prevention of CVL-associated thromboses in children with malignancies	A randomized, controlled study for prevention of CVL-associated VTE using low dose warfarin (INR 1.3-1.9) in children with newly diagnosed cancer, a CVL in a jugular vein. # of subjects: warfain 31; control (SOC) 42.	CVL-related VTE was equally frequent among children on warfarin as compared to controls. Study terminated early due to lack of benefit with warfarin compared with control in the prevention of VTE (48% versus 36%).	Only a few patients achieved therapeutic INR levels at all times, indicating ineffective anticoagulation.
Massicotte P. et al. PROTEKT (REVIparin in Venous ThromboEmbolism).	Open-label, multi-center, randomized, prevention of CVL-associated VTE with reviparin in children. Blinded central outcome adjudication. # of subjects: SOC 80; reviparin 78	Was safe but its efficacy remains unclear. Enrolled only 31% 186/600) of the required number of patients. Closed earlier due to slow accrual.	Study under-powered to demonstrate either safety or efficacy due to premature closure.
Mitchell L, et al. PARKAA (Prophylactic Antithrombin Replacement in Kids with ALL treated with L-Asparaginase). Thromb Haemost. 2003.	Open-label, randomized, controlled, VTE prevention study in children with ALL who were receiving asparaginase. # of subjects: AT 25, no AT 60.	A statistically non-significant trend towards a protective effect of ATIII concentrate in prevention of asymptomatic thrombosis compared to placebo.	-No demonstrable positive laboratory effect on plasma markers of endogenous thrombin formation. -22% of the patients were not evaluated. - Study not powered to determine whether prophylactic AT was clinically beneficial.
Elhasid R. VTE prevention with enoxaparin during L-asparaginase treatment in ALL. Blood Coagul Fibrinolysis 2001;12:367.	A non-randomized ALL cohort study, compared with historical control ALL children who had not received prophylactic enoxaparin during l-asparaginase treatment. # of subjects: enoxaparin cohort 41; control cohort 50.	No symptomatic VTE or bleeding complications in enoxaparin cohort; 1 DVT, 1 PE in historical cohort.	Non-randomized cohort study; historical control.
REVIVE (REVIparin in Venous ThromboEmbolism)	Multicenter, open-label, randomized patients with objectively confirmed VTE to receive either reviparin or heparin+coumadin for VTE treatment in children. # of subjects: reviparin 36; heparin+coumadin 40	Enrolled only 20% (76/352) of the targeted population. Closed earlier due to slow accrual.	Study under-powered to demonstrate either safety or efficacy due to premature closure.

Case 3

- 15 year old female, previously healthy, developed abdominal pain. She also presents with high blood pressures and seizures. Further evaluation showed CT abdomen IVC clot at the level of renal veins. Due to chest pain, Chest CT revealed PE.
- Consult weekend: Prolonged PT and aPTT
- Evidence renal dysfunction

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Some hints coagulation studies

- Prolongation clotting times failed to correct with normal plasma mixing (inhibitor to factor or lupus anticoagulant).
- Further inhibition clotting assays using phospholipids (PNP, DRVVT, Staclot): think lupus anticoagulant

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Thrombophilia evaluation

PT 17.3 (8.3-10.8 s)

INR 1.9

PT Eq Mix 10.9

aPTT 94 (21-33s)

APTT eq vol mix 55

TT 24

PNP 77 (PNP buffer control 84)

- DRVVT screen ratio <1.2 4.7
- 1:1 mix 2.9
- Confirm ratio 3.3
- Fibrinogen >800
- D-dimer 6350 (<250 ng/ml)
- Mildly decreased II, VII, IX, X
- Neg antiphospholipid antibodies

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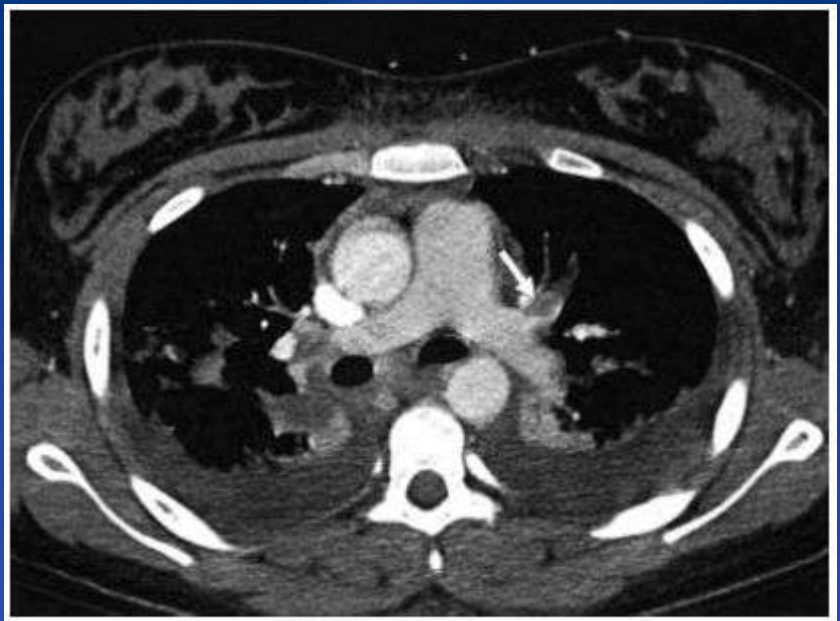

Fig. 1. Computed tomography of the chest showing pulmonary arterial thrombosis (arrow).

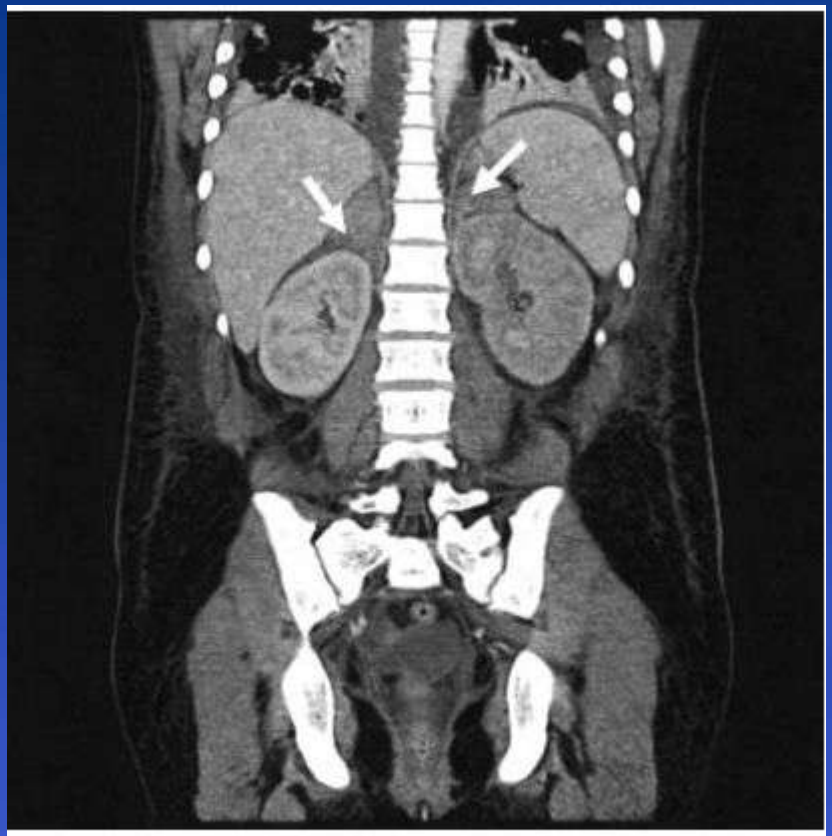

Fig. 2. Computed tomography of the abdomen showing bilateral adrenal hemorrhages (arrows).

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Case 3…

- What are your recommendations?

a. Anticoagulation UFH (anti-Xa 0.5-1.0) and later switch to Coumadin to keep INR (2-3).

b. Do not start anticoagulation due to adrenal hemorrhages.

c. Thrombolysis followed by anticoagulation

d. Anticoagulation with LMWH

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Multidisciplinary approach

Rituximab for Successful Management of Probable Pediatric Catastrophic Antiphospholipid Syndrome

Amulya A. Nageswara Rao, MD,[1]* Grace M. Arteaga, MD,[2] Ann M. Reed, MD,[3] James M. Gloor, MD,[4] and Vilmarie Rodriguez, MD[1]

Catastrophic antiphospholipid syndrome (CAPS) is a life-threatening condition characterized by small-vessel thrombi and a rapid onset of multiorgan system failure associated with systemic inflammatory response syndrome. Current treatment options include anticoagulants, corticosteroids, plasma exchange, and intravenous immunoglobulin, but these are not always effective. Rituximab, a chimeric anti-CD20 monoclonal antibody, may help eliminate autoreactive B cells and thus limit the rapid inflammatory process involved in CAPS. We describe the use of rituximab in the successful initial management of a probable case of pediatric CAPS. Pediatr Blood Cancer 2009;52:536–538.

Key words: catastrophic antiphospholipid syndrome; lupus anticoagulant; rituximab; thrombosis

LAC

THROMBOSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS DESPITE CIRCULATING ANTICOAGULANTS

E. J. WALTER BOWIE
JOHN H. THOMPSON, JR.
CHRIS A. PASCUZZI
and
CHARLES A. OWEN, JR.
Rochester, Minn.

From the sections of Medicine and Clinical Pathology, Mayo Clinic and Mayo Foundation

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St. Louis

Vol. 62, No. 3, Pages 416-430, September, 1963

Lupus Anticoagulant (LA) Definition

- LA are antiphospholipids antibodies (IgG, IgM & IgA)
- Directed against antigens comprised of a combination of anionic (neg charged) phospholipids and a protein cofactor (eg prothrombin or βGPI)
- Inhibit *in vitro* phospholipid-dependent clotting time tests (eg, aPTT, dRVVT).

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Antiphospholipid antibodies classification (APL)

- Lupus anticoagulant (LA)
- Identified by functional coagulation testing
- Qualitative, interpretive
- Anticardiolipin Antibodies (ACL)
- Identified by immunoassays (eg ELISA)
- IgG, IgM, IgA
- β2GPI component

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APL Classification

- Autoantibodies (persistent)
  - Primary APL/APS
  - Secondary APL/APS (eg SLE)
- Alloantibodies (transient)
  - Infection
  - Inflammation
- Drug induced
  - Procainamide, Quinidine, Quinine
  - Hydralazine
  - Phenothiazines
  - Antibiotics

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APL Significance

- Thrombosis risk
  - LA ≥ ACL IgG > ACL IgM
- Pregnancy loss or complications
  - ACL IgG = LA (?)
- Bleeding risk (uncommon)
  - LA / hypoprothrombinemia (or F X def.)
  - Thrombocytopenia (AITP)
  - Anticoagulation -related bleeding

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LA ISTH Diagnostic Criteria

1. Prolongation of at least 1 phospholipid-dependent clotting time assay.
2. Inhibition shown by mixing patient and normal pooled plasma.
3. Phospholipid-dependent inhibition demonstrated.
4. Evaluate for other coagulopathies

Brandt JT, Triplett DA, Alving B, Scharrer I. *Thromb Haemost* 1995;74(4):1185-1190

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LA & APL Antibodies Pathophysiology

- Inhibition of natural anticoagulant pathways (PL dependent assembly)-Protein C & S
- Platelet activation
- Endothelial cell activation or injury
- Disruption of Annexin V binding to anionic phospholipids
- Dysregulation of fibrinolysis
- Others

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Pediatric APS Syndrome

- Registry 12/1/2007 121 cases in 14 countries
- Mean age 10.7 years
- 60 (49.5%) underlying autoimmune disease
- Venous thrombosis 72 (60%), arterial 39 (32%), small vessel 7 (6%) and mixed 3 (2%).

Avcin T et al Pediatrics 2008; 122: e1100-1107

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Pediatric APS …

- Non-thrombotic manifestations (hematologic 38%, skin 18%, neurologic 16%).
- Laboratory: + aCL 81%, anti-βGPI 67%, LA 72%
- Primary APS: younger, higher frequency arterial events
- Secondary APS: older, venous events associated hematologic and skin manifestations

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A retrospective review of pediatric antiphospholipid syndrome and thrombosis outcomes

Amulya A. Nageswara Rao[a,b], Kendra Elwood[a], Dominder Kaur[a,b], Deepti M. Warad[a,b] and Vilmarie Rodriguez[a,b]

- 20 year retrospective review
- 17 patients (10 males; 7 females)
- Median age thrombosis 15.3 years
- Venous thrombosis 64.7% (11)
- Arterial events 35.3% (6)
- 53% (9) primary APS
- Recurrent/progression thrombosis 58.8% (10)
- Median time progression 1.4 years
- At time progression only 2 (20%) were therapeutic anticoagulation

Blood Coag Fib 2017; 28: 205

Catastrophic Antiphospholipid Syndrome

- Incidence <1% of all APS
- High mortality (50%) due to multiorgan failure
- Criteria: thromboses three or more organs, histologic confirmation small vessel occlusion at least one organ, rapid development clinical manifestation and confirmation APLas

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Catastrophic APS

- Plasmapheresis
- Prednisone/Rituximab
- UFH (monitor heparin levels instead aPTT)
- Lifelong anticoagulation (Coumadin INR 2.5-3.5)

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Mortality

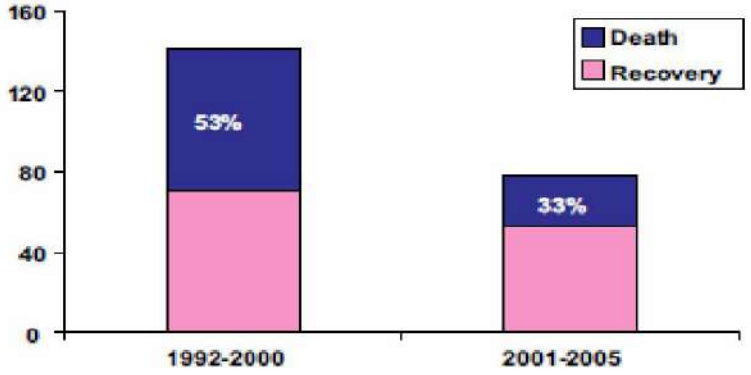

Figure 1 Influence of the time of diagnosis on evolution in patients with catastrophic APS. The mortality decreased from 53% in the first period (1992–2000) to 33% in the second period (2001–2005). The patients with catastrophic APS diagnosed after 2001 had a higher recovery rate with a statistically significant reduction on mortality of 20%.[13] $P = 0.005$.

Case 4

- 16 year old female, previously healthy except for morbid obesity and sedentary life style, developed shortness of breath. Treated with bronchodilators: no improvement. Developed chest pain and hypoxia.

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What is your next evaluation?

a. High resolution computed tomography chest
b. Add corticosteroids to bronchodilator therapy
c. Pulmonology consult
d. Put her on a diet and physical training to improve exercise tolerance

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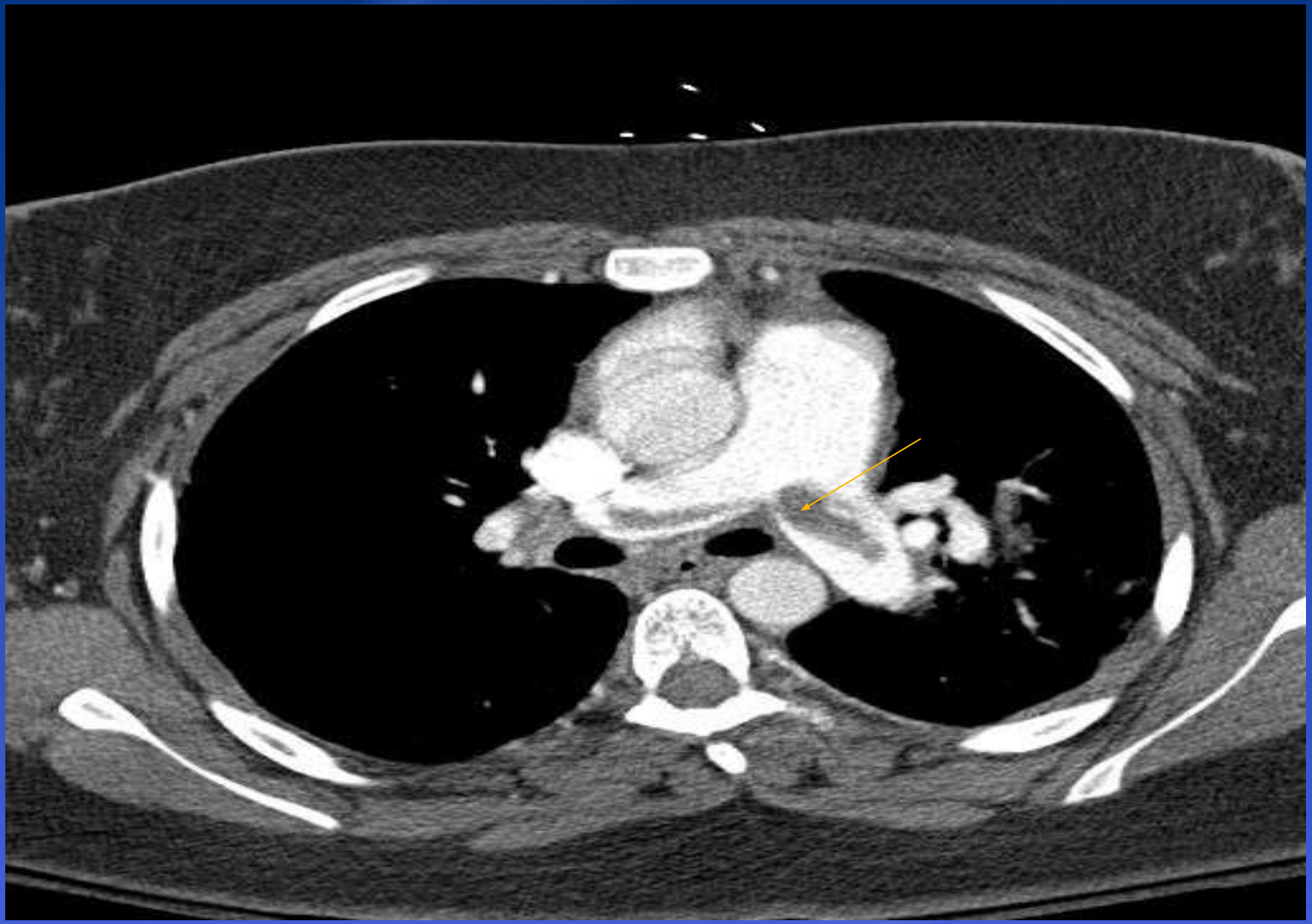

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Case 4-PE

- Obesity and sedentary life risk factors
- Thrombophilia work up negative
- UFH and Coumadin

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DOI: 10.1002/pbc.27041

BRIEF REPORT

WILEY Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

Obesity, sedentary lifestyle, and video games: The new thrombophilia cocktail in adolescents

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Abstract

Rates of venous thromboembolism have increased in the adolescent population over the last two decades, likely due to advanced diagnostics, increased use of central venous catheters, chronic medical conditions, obesity, and oral contraceptive use. Of these factors, a modifiable risk factor for adolescents is obesity. Sedentary lifestyle and prolonged immobilization are additional pro-thrombotic risk factors that are often associated with obesity. With ever-increasing screen time, sedentary behavior has risen accordingly, especially among gamers. We present four cases of adolescents who developed life-threatening venous thromboembolic events in the setting of obesity, sedentary lifestyle and/or immobilization, and prolonged video game use.

KEYWORDS

adolescents, electronics, obesity, sedentary, thrombosis, video games

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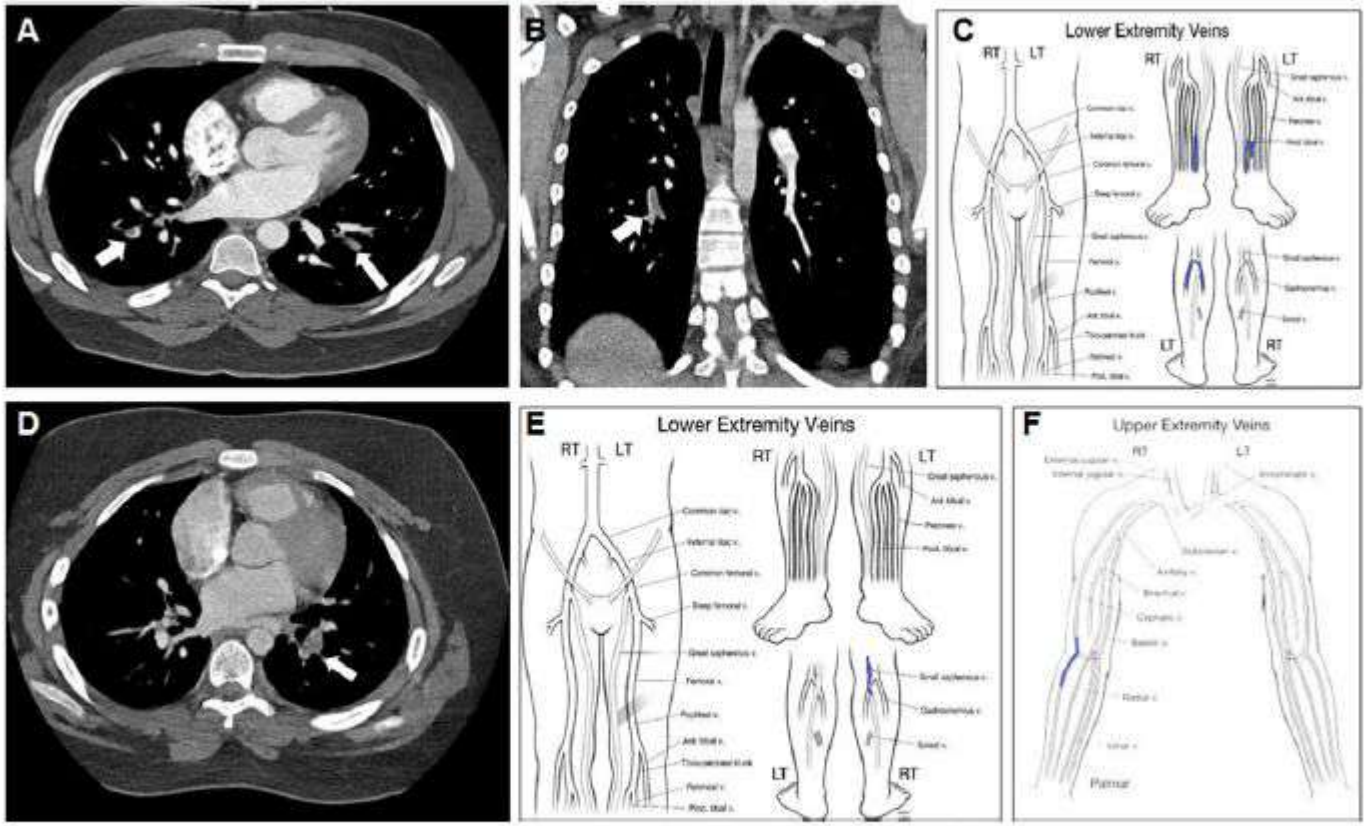

FIGURE 1 (A) Chest CT, axial view, revealing a pulmonary embolism (arrows) in case 2.1. (B) Chest CT scan, coronal view, revealing an acute right pulmonary artery embolism (arrow) in case 2.2. (C) Lower extremity mapping computed from ultrasound revealing thromboses in bilateral posterior tibial veins and left upper calf gastrocnemius vein (case 2.2). (D) Pulmonary embolism on chest CT scan in case 2.3 (arrow). (E) Lower extremity mapping computed from ultrasound revealing a right saphenous vein thrombus in case 2.3. (F) Upper extremity mapping demonstrating bilateral cephalic vein thromboses in case 2.3

Case 5-arterial thrombosis

- 12 mo old girl with RSV pneumonia. Various attempts to place a line without success. After right femoral line is placed, leg turns cold, “dusky” with no pulses. Central line is removed and she is being transferred management of right femoral artery thrombosis

Indications thrombolysis

- Arterial thrombosis with tissue ischemia
- Phlegmasia alba/cerulea dolens: extensive thrombosis with total venous occlusion with compartment syndrome
- Pulmonary embolism with hypotension/shock, right ventricular strain or myocardial ischemia
- Superior vena cava syndrome
- Bilateral renal vein thrombosis
- Congenital heart disease with shunt thrombosis
- Large (>2 cm) mobile right atrial thrombosis
- Kawasaki disease with coronary artery thrombosis
- Cerebral sinovenous thrombosis with neurologic impairment and no improvement on anticoagulation

Front Pediatrics 2017; 5: 260

Contraindications

- Active bleeding
- Concurrent bleeding diathesis and inability to keep plts >100,000/μL and fibrinogen >100 mg/dL
- Recent major surgery or trauma within previous 10 days
- Intracranial bleeding, infarction, intracranial or spinal surgery within last 2 months
- Known right to left cardiac shunt
- CPR or asphyxia within 7 days therapy
- Extreme prematurity

Front Pediatrics 2017; 5: 260

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Pediatric thrombolysis

TABLE 1 | Published results of thrombolysis in children.

Author	Method	*N*	Age, range and site of thrombosis	Lysis*	Major hemorrhage	SAEs, other	Recurrent VTE	PTS
Manco-Johnson (28)	Systemic UK/UH	32	6 weeks to 17 years and UE, LE, SVC, IVC, PE, atrial	50%	0	Death 1; PE 1; progress 1	9%	11.1% MJ
Wang (29)	Systemic TPA	12 HD 17 LD	1 day to 17 years and LE, UE, PE, CSVT, renal, hepatic, arterial, and venous	92% 100%	0 1 ICH, PT infant	1 embolic stroke with left atrial thrombus	0	8% 0% MJ
Goldenberg (38)	Systemic/PPMT	9	1–21 years and LE	89%	1 pulmonary	0	0%	11.1% MJ
Goldenberg (33)	CDT/PMT/PPMT	16	11–19 years and LE and UE	88%	0	PE 1	27%	13% MJ
Derbari (39)	CDT/PMT/PPMT	34	13 days to 21 years and LE and UE	17%(52%) 50 (99%)	1 2 required prbcs	0%	NA	NA
Dandoy (31)	CDT/PMT/PPMT	41	3 months to 21 years and LE, UE, SVC, and IVC	90% (> 50%)	1 Required prbcs	PE 1	NA	14% (V or mV)
Gaballah (55)	CDT/PMT/PPMT	57	1–17 years and LE	33% (93.7%) >50%	1.8%		12%	2.1%V 59.3% mV

Front Pediatrics 2017; 5: 260

Thrombolysis

TABLE 2 | Dosing of alteplase and heparin during thrombolysis.

Mode of thrombolysis	Alteplase dosing		Duration of thrombolysis	Concomitant UFH therapy	Laboratory monitoring
	Bolus	Infusion			
Systemic thrombolysis	None None	Low-dose: 0.01–0.06 mg/kg/h (max 2 mg/h) High-dose: 0.1–0.5	6–72 h 2–6 h, may repeat if indicated	Prophylactic UFH with goal UFH anti-Xa level of 0.1–0.3 or UFH at 10 U/kg/h	Every 6–12 h: fibrinogen, CBC, FDPs, PT, aPTT, UFH anti-Xa
Site-directed thrombolysis	0.1–0.3 mg/kg (max dose 10 mg)	0.01–0.03 mg/kg/h or max 1–2 mg/h	Up to 72—96 h	Therapeutic UFH with goal UFH anti-Xa level of 0.3–0.7 or ufh at 10 U/kg/h	Every 6–12 h: fibrinogen, CBC, FDPs, PT, aPTT, UFH anti-Xa, renal profile, urinalysis

Case 5

- Anticoagulated UFH later transitioned LMWH
- No need thrombolysis (perfusion improved-not complete occlusion)

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Summary

- Thrombosis increasingly recognized in pediatrics
- Congenital vs Acquired
- Early intervention
- Long term sequelae

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