Deep Vein Thrombosis: Thrombolysis in the Pediatric Population

Lindsey A. Greene, M.D.¹ Neil A. Goldenberg, M.D., Ph.D.²⁻⁵

¹Department of Pediatrics, Weill Cornell Medical College, New York, New York

²Children's Hospital Colorado

³Section of Hematology/Oncology/Bone Marrow Transplant and Center for Cancer and Blood Disorders, Department of Pediatrics

⁴Mountain States Regional Hemophilia and Thrombosis Center

⁵Division of Hematology/Oncology, Department of Internal Medicine, University of Colorado School of Medicine, Aurora, Colorado

Address for correspondence and reprint requests Lindsey A. Greene, M.D., Department of Pediatrics, Weill Cornell Medical College, 525 East 68th Street, M-610, New York, NY 10065 (e-mail: lig2016@nyp.org).

Semin Intervent Radiol 2012;29:36-43

Abstract

Improved medical treatment options have advanced pediatric care but often necessitate both invasive vascular procedures and venous access predisposing these patients to venous thrombotic events. Although pediatric deep vein thrombosis (DVT) is an increasingly recognized phenomenon, high-quality evidence for its antithrombotic treatment in general remains limited, and even more so with respect to thrombolytic therapy. Correspondingly, current American College of Chest Physicians guidelines discourage the routine use of thrombolytic therapy for pediatric DVT; by contrast, American Heart Association guidelines suggest consideration for such therapy in young patients in whom the balance of benefit to risk may be most favorable. The developing hemostatic system and relative rarity of thrombotic events have historically posed impediments to the design and conduction of prospective clinical trials of thrombolysis in children. This narrative review summarizes available information regarding thrombolytic therapy for pediatric DVT.

Keywords

- ▶ thrombolysis
- ▶ deep vein thrombosis
- ▶ pediatric

Objectives: Upon completing this article, the reader should be able to explain the role of systemic and catheter directed therapies in the treatment of DVT in the pediatric population, as well as how treatment in the pediatric patient differs from the adult population.

Accreditation: Tufts University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit: Tufts University School of Medicine designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Pediatric Deep Vein Thrombosis

Epidemiology

Advances in the treatment and supportive care of critically ill children have led to improved pediatric survival. Such treatment options frequently necessitate invasive vascular procedures and devices, which has resulted in both an increased risk of deep vein thrombosis (DVT) and the recognition of vascular events among children.^{1,2} In particular, central venous catheters are associated with >50% of DVTs in children and >80% of cases in newborns.¹ Information from the National Hospital Discharge Survey indicates an overall pediatric venous thromboembolism (VTE) incidence of 0.05 per 1,000 per year; however, much higher rates of VTE are

Issue Theme Venous Thromboembolism; Guest Editors, Suresh Vedantham, M.D., F.S.I.R., and Nael Saad, M.D.

Copyright © 2012 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0032-1302450>.
ISSN 0739-9529.

observed among hospitalized pediatric patients with an estimated incidence of 4.2 per 1,000 pediatric hospitalizations.^{1,3,4} Nevertheless, given the often low index of suspicion, it is hypothesized that many thromboembolic events go unrecognized.^{1,5}

Within pediatrics, thrombosis is observed in a bimodal distribution most commonly seen in neonates (0 to 28 days) and adolescents (15 to 17 years).¹ As opposed to a 60% incidence in adults, >90% of pediatric thrombosis is associated with a clinical prothrombotic risk factor (e.g., venous catheters, exogenous estrogen, decreased mobility, obesity, oral contraception use) and/or an underlying hypercoagulable state (e.g., antiphospholipid antibodies, acquired or congenital anticoagulant deficiencies, factor V Leiden, or prothrombin G20210A mutations).^{1,6}

Conventional Therapy

Conventional DVT therapy includes anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH).^{1,2} The goal of therapy is to prevent thrombus progression, minimize embolic events, and prevent recurrence.¹ For pediatric patients the preferred initial anticoagulation treatment duration is 3 to 6 months, with subsequent continuation of therapy determined by the persistence of clinically significant prothrombotic risk factors.^{1,2} Complications of anticoagulation are namely bleeding; LMWH-associated major hemorrhage occurs in ~5% of pediatric patients undergoing treatment for VTE.^{7,8} A multicenter study reported higher rates (12.5%) of major hemorrhage with combined UFH and warfarin among pediatric patients on anticoagulation for VTE.⁸

Acute and Chronic Sequelae

Pediatric thrombosis has both acute and chronic manifestations. Acutely, VTE sequelae include confirmed pulmonary embolism (PE) in 16 to 20%, an estimated mortality rate of large vessel thrombosis of 1 to 4%, and an associated twofold increased risk of in-hospital mortality.^{3,9,10} Further acute problems include limb ischemia secondary to venous insufficiency and renal insufficiency particularly following renal vein thrombosis typically seen in neonates.¹

Chronic complications associated with DVT are primarily postthrombotic syndrome (PTS) and recurrent thrombosis.^{1,6,11–13} PTS is a clinical condition caused by venous obstruction and venous valvular reflux characterized by limb pain, edema, stasis dermatitis, ulceration, and limitation of activity.^{9,10,14,15} PTS occurs with comparable frequency in children as adults, with a mean weighted frequency reported at 26% in the pediatric population versus 25 to 50% in adults.^{5,6,9,15} This risk becomes particularly meaningful when thought is given to the duration children may be expected to live with DVT-related morbidity, making the anticipated medical and financial burden disproportionately high in children. Similarly, the implication of limited physical activity on normal childhood development further underscores the long-term impact on function. Unlike PTS, recurrent DVT appears to be half as frequent in children as adults, with incidences at 1 and 2 years of 6 to 11% versus 12 to 22% in adults.¹⁴

Predictors of long-term outcome following pediatric DVT are important for risk stratification and hence are potentially important for decisions regarding clinical management. In adults, predictors of poor outcome include complete thrombus occlusion of the vessel and lack of clot resolution following anticoagulation. Such predictors are frequently extrapolated to pediatric DVT.^{5,6,16} Like adults, cohort study evidence in 2004 indicated that elevated levels of factor (F) VIII (>150 U/dL), D-dimer (>500 ng/mL), or both at diagnosis and persistent elevation following 3 to 6 months of anticoagulation therapy are associated with poor outcome (i.e., composite of PTS, recurrent thrombosis, and failed thrombus resolution) in children with thrombosis.¹⁷ Subsequently, two studies have reported high risks of PTS in patients with occlusive proximal limb DVT in whom plasma FVIII and D-dimer levels are both elevated, and who did not receive thrombolytic therapy.^{5,18} Advances in the prediction of post-thrombotic outcomes in pediatric patients have led to the opportunity for a risk-stratified approach to thrombosis management, including consideration of a role for thrombolytic therapy.^{1,6,18}

Thrombolysis in Pediatric Deep Vein Thrombosis

Rationale

Although approximately half of venous thrombotic events treated with traditional anticoagulant therapy resolve during a 3- to 6-month conventional duration of routine anticoagulation, the risk of PTS persists, likely due to acute valvular damage from complete venous obstruction, as well as venous inflammatory changes resulting in valvular insufficiency.^{2,6,15} Traditional anticoagulation attenuates coagulation, whereas thrombolytic therapy augments fibrinolysis by catalyzing the activation of plasminogen to plasmin, the key enzyme in fibrin dissolution.¹ When administered within 2 weeks of symptomatic onset, the use of thrombolytic agents has been shown to be highly effective in achieving thrombus resolution or restored venous patency in most cases of pediatric DVT.^{11,19,20} Experience in the use of thrombolytic therapy for pediatric acute DVT is rapidly evolving, and recent small controlled single-institutional studies have suggested the potential for the efficacy and safety of specific thrombolytic approaches.¹⁸

Although increasingly used, thrombolytic therapies in children do not have well-established indications.²¹ The American College of Chest Physicians (ACCP) 2008 consensus-based recommendations for DVT antithrombotic therapy in children reserve thrombolytic therapy for life-, organ-, or limb-threatening thrombosis with particular reference made that thrombolysis should not be routinely used in children with DVT.²² American Heart Association (AHA) guidelines suggest consideration for such therapy in young patients, in whom the balance of benefit to risk may be most favorable.²³ Analogous adult AHA and ACCP clinical practice guidelines recommend consideration of thrombolysis in young patients with extensive and/or occlusive DVT of recent onset with an anticipated long lifespan.^{18,23,24} For both adults and children,

Table 1 Published Suggested Contraindications to Thrombolytic Therapy in Infants and Children^{2,18,20,29–31}

Surgery or invasive procedure within 7–14 days of therapy
CNS hemorrhage/trauma/surgery within the preceding 2 months
Severe asphyxia event within 7 days of therapy
Current CNS pathology (i.e., aneurysm, neoplasm, vascular malformation)
Seizures
Severe bleeding
Uncontrolled or uncorrectable coagulopathy (inability to maintain fibrinogen >100 mg/dL or platelets >75,000–100,000 × 10 ⁹ /L)
Systemic septicemia
Contrast allergy
Serum creatinine >2 mg/dL

CNS, central nervous system.

controversy exists regarding the use of thrombolytic therapy in non-limb-threatening DVT to prevent PTS, recurrent thrombosis, and thromboembolic events.^{11,15} A Cochrane review of adult DVT concluded that there is a lower incidence of PTS following fibrinolytic therapy than standard therapy, with the caveat of increased acute bleeding complications.^{2,25} In 2008, the American Academy of Chest Physicians guidelines for antithrombotic treatment in adult VTE, in an effort to decrease PTS, recommended thrombolysis may be used in DVT <14 days duration and in patients with a low bleeding risk.²⁴ This has already been adapted into adult practice with increasing percutaneous procedures, including mechanical thrombectomy and pharmacological thrombolysis, in the treatment of adult acute proximal lower extremity DVT.¹⁰

The CaVent Study, a randomized controlled clinical trial, is currently underway to determine the safety and efficacy of percutaneous pharmacomechanical thrombolysis in adults with acute proximal DVT; however, this therapy is only available at select centers that have sufficient expertise for children.^{5,10,26} A recent commentary highlights the importance of extending evidence-based PTS preventive measures for pediatric DVT and urges further study of PTS prevention in children.²⁷ A recent survey of members of the American Society of Pediatric Hematology/Oncology members' approach to the treatment of pediatric VTE indicated no prevailing consensus regarding thrombolytic therapy indication, dosing, duration, mode of delivery, or desirability of concurrent anticoagulation administration.²⁸

Contraindications To Thrombolytic Therapy

Most contraindications to thrombolytic therapy in pediatric patients are relative and must be weighed against the anticipated benefits of such aggressive treatment (►Table 1).

Agents

Age-dependent alterations in the neonatal and childhood fibrinolytic system may influence the response to thrombo-

lytic agents.^{2,21,32–35} Neonates exhibit ~50% of adult concentrations of plasminogen; children have decreased concentrations of tissue plasminogen activator (tPA) and plasminogen activator inhibitor.^{21,36,37} The net impact of these alterations on fibrinolytic capacity in neonates and children relative to adults remains unclear, with some investigations suggesting increased fibrinolysis and others suggesting decreased fibrinolysis.^{33,34}

The most commonly used thrombolytic agents are streptokinase, urokinase, and tPA, with the latter predominating current thrombolytic therapy in children.^{2,22,28} Thus far there is no consensus-based recommendation regarding thrombolytic treatment agent of choice in pediatric DVT.

- **Streptokinase** is derived from group C β-hemolytic streptococci. It is now rarely used in pediatrics due to the high incidence of allergic reaction and humoral or cellular antibodies resulting in a neutralizing effect that may persist for >2 years.^{2,38–40} The half-life of streptokinase is 18 to 30 minutes.³⁸
- **Urokinase** is isolated from human urine or neonatal kidney cell culture.^{2,38} In 1999, the U.S. Food and Drug Administration issued a warning regarding inadequate donor screening and the potential for risk of transmitted infections. This warning was repealed in 2003 following improvements in viral inactivation and donor screening. Intravascular urokinase is hepatically cleared with a half-life of 13 minutes.^{2,21,40}
- **tPA** is produced in the Chinese hamster cell line, hepatically cleared with an intravascular half-life of ~5 minutes. In vitro studies suggest that tPA more effectively stimulates fibrinolysis than urokinase, which has not been substantiated in vivo.^{2,21,41,42} Recent survey reports of pediatric hematologist-oncologists indicate tPA as the thrombolytic agent of choice.²⁸

In adults, adjuvant UFH during thrombolytic therapy has demonstrated improved outcomes with decreased mortality and pulmonary embolism but increased bleeding risk.^{10,43} Such studies have not been replicated in children. Manco-Johnson et al described the use of systemic urokinase with low-dose UFH (10 U/kg) for 48 hours in children with first-time venous thrombosis. They reported no progression of thrombus or increase in bleeding complications.¹⁹ Subsequent publications have similarly reported on the concurrent use of low-dose heparin with thrombolytic therapy in children (►Table 2).^{5,15,18,20,29,44} If there is no bleeding risk contraindication to thrombolytic therapy in children, adjuvant UFH or LMWH is generally recommended.^{11,19} Due to its short half-life, most experience with concurrent anticoagulation in children has been frequently dosed at 10 to 15 U/kg per hour.^{11,18,21}

Routes of Administration

Thrombolytic agents may be administered systemically or by local infusion. There are no randomized controlled trials comparing the two modalities in pediatric thrombolytic therapy. Trends from case series of combined pediatric venous and arterial thrombosis support higher efficacy and

Table 2 Published Thrombolytic and Adjuvant Anticoagulation Dosing in Children

Thrombolytic Medication	Loading Dose	Dose	Duration
Urokinase	4400 U/kg	4400 U/kg	6–12 hours
tPA (high dose)	–	0.5–0.6 mg/kg/hour	6 hours
tPA (low dose)	–	0.03–0.06 mg/kg/hour	24–96 hours
Adjuvant Anticoagulation	Loading dose	Dose	Duration
LMWH (enoxaparin)	–	0.5 mg/kg twice daily	3–6 months
UFH	–	5–15 U/kg	12–96 hours

tPA, tissue plasminogen activator; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

decreased bleeding risk with catheter-directed thrombolytic (CDT) therapy.²¹ Although there is a paucity of evidence regarding the mode of delivery, a survey of pediatric hematologist-oncologists identified CDT, including percutaneous mechanical thrombolysis (PMT) or percutaneous pharmacomechanical thrombolysis (PPMT), as the preferred method of thrombolysis in the treatment of pediatric DVT.²⁸

Retrospective studies of adult DVT thrombolysis suggest greater efficacy of CDT compared with systemic therapy and have influenced preference for this method of thrombolytic therapy administration.^{2,45} CDT achieves higher local intrathrombus drug concentration, facilitating successful clot lysis with reduced drug dose and theoretically decreasing bleeding risk.¹⁰ However, unlike systemic thrombolysis, CDT carries the potential for exacerbating endothelial damage (particularly problematic in neonates and small children) and requires significant expertise, which may be limited by the availability of a qualified interventional radiologist.^{2,30}

Systemic Thrombolysis

► **Table 2** summarizes the tPA and urokinase systemic dosing approaches. Currently, systemic therapy is typically composed of either high-dose tPA (0.5 to 1.0 mg/kg per hour) or low-dose tPA with a starting dose of 0.03 mg/kg per hour and 0.06 mg/kg per hour in neonates.^{2,20,21,29,44,46} The use of urokinase has also been reported but is a less frequently used modality than tPA.^{19,28,46} High-dose tPA is administered with assessment of clot 6 hours following therapy initiation. If no resolution is observed, a second 6-hour course of therapy may be delivered 24 hours later.^{2,47} This dosing strategy may be more beneficial in arterial thrombosis in which rapid clot resolution is required. In the venous system, low-dose tPA may be more safely delivered for a longer duration (48 to 96 hours), which has been hypothesized to aid in the slow lysis of venous thrombi.^{2,46}

Wang et al published the initial prospective findings of both efficacy and safety of low-dose tPA (0.01 to 0.06 mg/kg per hour) versus established high-dose therapy (0.1 to 0.5 mg/kg per hour) among 35 pediatric patients with arterial and venous thrombi. Both tPA dosing regimens were accompanied by concomitant antithrombotic therapy with UFH (5–10 U/kg per hour) or LMWH (enoxaparin 0.5 mg/kg twice

daily). Catheter-directed infusion of tPA was administered in 29% of cases (10 of 35); the remaining cases received systemic therapy. Complete clot lysis was observed in 97% of acute thrombi, and major hemorrhage occurred in one extremely premature patient. No difference in lytic result was observed with respect to route of administration. Although minimally effective dosing could not be concluded from the study, the authors recommended a tPA starting dose of 0.03 mg/kg per hour in children and 0.06 mg/kg per hour in neonates for both local and systemic thrombolysis.²⁰ Subsequently, increasing evidence has supported the use of low-dose systemic tPA with similar efficacy and greater safety margins when compared with high-dose therapy.^{20,21,44}

In 2007 Goldenberg et al retrospectively analyzed their cohort experience with thrombolytic therapy followed by standard anticoagulation versus standard anticoagulation alone in first-episode acute occlusive DVT of the proximal lower extremity in children with elevated FVIII activity (≥ 150 U/dL) and/or D-dimer levels (≥ 500 ng/mL). Among the 22 patients, 9 underwent thrombolytic therapy with tPA: seven received systemic tPA by low-dose continuous IV infusion (2 of whom underwent salvage mechanical thrombectomy with catheter-directed tPA); 2 subjects underwent local thrombolysis via mechanical thrombectomy and catheter-directed tPA. The prevalence of PTS at ~2 years, determined with the Manco-Johnson pediatric PTS instrument, was significantly lower among those who underwent thrombolytic therapy (22.2% versus 76.9%; $p = 0.02$) with an associated decreased risk of PTS (odds ratio: 0.086; 95% confidence interval, 0.011–0.655). This finding was also supported by a reduction in clinically important PTS. Major bleeding developed in one DVT patient with concomitant bilateral PE who received systemic tPA but, due to cardiorespiratory decompensation, underwent urgent percutaneous mechanical embolectomy, which was complicated by pulmonary hemorrhage. This report provided the first findings in support of the potential efficacy and safety of the use of thrombolytic therapy to diminish PTS risk in a subset of children with DVT perceived to be at high a priori risk for this complication based on prognostic clinical factors and biomarkers.⁵ However, given that two of seven children initially treated with systemic tPA required salvage local thrombolysis to establish venous patency, and the concurrent potential risks of systemic

administration of thrombolytic agents, important questions remained regarding whether local thrombolysis may be preferable in children of suitable size.

Local Catheter-Directed Thrombolytic Infusion

In the previously mentioned study, Wang et al reported on the use of low-dose tPA thrombolysis. Catheter-directed thrombolytic infusion (CDTI) with tPA (0.01 to 0.06 mg/kg per hour) was used in 29% of subjects (10 of 35). No difference in outcome was observed with respect to systemic versus local route of administration, with 97% complete clot lysis observed overall.²⁰ Goldenberg et al's findings published in 2007 and 2011 used a tPA dose (0.5 to 1.0 mg/hour) in CDTI that, in average-size teens, equated to a similar range as that prescribed by Wang et al.^{5,18,20} Major bleeding events were very rare in both reports, and complete clot lysis was observed most recently in 83% of acute proximal lower extremity DVT cases in which CDTI was used following mechanical thrombolysis.¹⁸

Percutaneous Mechanical and Pharmacomechanical Thrombolytic Interventions

PMT/PPMT has been performed in adolescents and large children with high-risk DVTs using the Amplatz ClotBuster thrombectomy device (EV3, Plymouth, MN), Angiojet (Medrad Interventional/Possis, Warrendale, PA), Trellis device (Bacchus Vascular, Santa Clara, CA), and the Arrow-Treotola device (Arrow International, Reading, PA).^{11,18,30} Device manufacturing and technical expertise limit the widespread eligibility for mechanical thrombectomy in neonates and small children.³⁰

Goldenberg et al recently published on the evidence of safety and efficacy of PMT/PPMT with or without adjunctive CDTI in children, via a prospective nonrandomized cohort of 16 children 11 to 21 years of age with an occlusive proximal limb DVT in whom D-dimer and FVIII:C were both elevated at diagnosis.¹⁸ In most cases (11 of 16), CDTI with tPA at a rate of 0.5 to 1 mg/hour was used for 12 to 24 hours following PMT/PPMT with adjuvant heparin (10 U/kg per hour) therapy. There were no major bleeding events, one symptomatic PE, and no deaths. Technical success (grade II/III lysis) was achieved in 15 of 16 cases (94%).¹⁸ Although comparable in number of subjects to adult studies, outcome estimates may be imprecise given the limitations of sample size. Nonetheless, the potential advantage of PMT/PPMT to reduce overall dose of thrombolytic agents and thereby concomitantly theoretically decrease bleeding risk, lend enthusiasm to further work confirming the safety of PMT/PPMT with CDTI and investigating the reduction in long-term sequelae (i.e., PTS, recurrent thrombosis) in the pediatric population.

Safety Considerations

Published suggested contraindications to thrombolysis in pediatric DVT (perhaps most applicable to systemic thrombolysis) are provided in **Table 1**. The most serious complication of thrombolytic therapy remains major bleeding events, commonly recognized as (1) intracranial hemorrhage

(ICH), (2) retroperitoneal hemorrhage, (3) bleeding requiring surgical intervention, and (4) drop in hemoglobin of ≥ 2 g/dL 24 hours following therapy.^{11,18,31,48} Prevalence of bleeding complications following thrombolytic therapy ranges from 0% to 40%.² In 1997, Zenz et al reported a retrospective review on 929 patients who received thrombolytic therapy, of whom 1.5% sustained ICH.⁴⁹ Upon subgroup analysis, ICH as a complication of therapy was observed in 25% of preterm neonates treated within the first week of life, thereby lending to the recommendation that thrombolytic therapy be used with extreme caution in premature neonates.^{2,29,49}

More recently, bleeding association with thrombolytic therapy appears to be decreasing in both the pediatric and adult populations. This is likely due to improved risk stratification and greater experience with thrombolytic dosing regimens and local approaches, including CDTI and PMT/PPMT.^{2,7,22,24,48} Among young patients, it has been recognized that when appropriate contraindications are observed, hemorrhagic complications of thrombolytic therapy are low.^{20,49} Standards of safety and efficacy in treatment of pediatric DVT with thrombolytic therapy remain to be determined.

Clinical and Laboratory Monitoring for Safety and Efficacy

Monitoring for thrombolytic therapy morbidity and mortality is best accomplished in an intensive care unit. To minimize bleeding, fibrinogen should be maintained at a level >100 mg/dL and platelets $>75,000$ to $100,000 \times 10^9/L$. Complete blood count should be monitored every 6 to 12 hours for evidence of bleeding.^{6,38} Alteration in the patient's neurological examination should prompt immediate evaluation for concern of central nervous system hemorrhage. If significant bleeding occurs, fibrinolytic therapy should be immediately discontinued with consideration for supplementation of fibrinogen with cryoprecipitate and antifibrinolytic therapy (aminocaproic acid).²

Due to plasminogen depletion, the effect of thrombolytic agents may be limited. As such, monitoring plasminogen concentrations and replacement with fresh frozen plasma (FFP) (10 mL/kg) when levels fall below 50% of baseline should be considered, particularly in the neonate.^{2,11,36} Some pediatric thrombosis experts suggest prophylactic FFP to support plasminogen, particularly in neonates; others express concern that such an approach may pose prothrombotic risks, and they advocate for replacement only in setting of documented deficient plasminogen levels.

To evaluate progress and provide information for consideration of dose escalation in the setting of systemic tPA, imaging of the DVT (typically ultrasound) is recommended at least every 24 hours.^{2,11,30} Clinical symptoms of improving tissue perfusion, pain, and edema similarly support the success of thrombolytic therapy. There are no specific goal laboratory parameters when monitoring thrombolytic therapy; however, increased fibrinogen degradation products (D-dimer) support a response to thrombolytic therapy.^{11,21}

Figure 1 Serial digital subtraction venograms in a pediatric patient with May-Thurner anomaly. (A) Preintervention: Complete occlusion of the common femoral and iliac veins, with extensive collateral vessels. (B) Post lysis: Patency of the iliac vein, with effacement of contrast in the most central portion of the common iliac vein, due to extrinsic compression by the right iliac artery (May-Thurner anomaly). (C) Post stent: Patency of the iliac vein, with extrinsic compression alleviated by an endovascular stent deployed at the site of the May-Thurner anomaly.

Conclusions

Although still rare in comparison with adults, pediatric DVT is being recognized with increasing frequency. Thrombolytic therapy presents an important treatment option in select circumstances of pediatric DVT, with the aim of minimizing morbidity and mortality. Incomplete understanding of risks and benefits of therapy limit widespread practice of thrombolysis in both adult and pediatric DVT. Published guidelines vary with respect to recommendations for thrombolytic therapy in pediatric patients with DVT: AHA guidelines suggest considering thrombolytic therapy in children in whom the benefit may outweigh risk, whereas ACCP guidelines discourage the routine use of thrombolytic therapy for pediatric DVT. Like ongoing studies in adults, randomized controlled clinical trials are needed to evaluate the safety and efficacy of thrombolytic approaches in pediatric patients with DVT.

Disclosures

Dr. Goldenberg is supported in part by a Career Development Award from the National Institutes of Health, National Heart, Lung, and Blood Institute.

Acknowledgments

The authors thank Dr. Charles Ray and Timothy Nelson for assistance with preparation of the venographic images shown in **Fig. 1**.

References

- 1 Goldenberg NA, Bernard TJ. Venous thromboembolism in children. *Hematol Oncol Clin North Am* 2010;24(1):151–166
- 2 Raffini L. Thrombolysis for intravascular thrombosis in neonates and children. *Curr Opin Pediatr* 2009;21(1):9–14

- 3 Vu LT, Nobuhara KK, Lee H, Farmer DL. Determination of risk factors for deep venous thrombosis in hospitalized children. *J Pediatr Surg* 2008;43(6):1095-1099
- 4 Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. *J Pediatr* 2004;145(4):563-565
- 5 Goldenberg NA, Durham JD, Knapp-Clevenger R, Manco-Johnson MJ. A thrombolytic regimen for high-risk deep venous thrombosis may substantially reduce the risk of postthrombotic syndrome in children. *Blood* 2007;110(1):45-53
- 6 Goldenberg NA. Long-term outcomes of venous thrombosis in children. *Curr Opin Hematol* 2005;12(5):370-376
- 7 Dix D, Andrew M, Marzinotto V, et al. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. *J Pediatr* 2000;136(4):439-445
- 8 Massicotte P, Julian JA, Gent M, et al; REVIVE Study Group. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and Coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thromb Res* 2003;109(2-3):85-92
- 9 Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125(1):1-7
- 10 Popuri RK, Vedantham S. The role of thrombolysis in the clinical management of deep vein thrombosis. *Arterioscler Thromb Vasc Biol* 2011;31(3):479-484
- 11 Manco-Johnson MJ. How I treat venous thrombosis in children. *Blood* 2006;107(1):21-29
- 12 Nowak-Göttl U, Junker R, Kreuz W, et al; Childhood Thrombophilia Study Group. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. *Blood* 2001;97(4):858-862
- 13 Young G, Albisetti M, Bonduel M, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. *Circulation* 2008;118(13):1373-1382
- 14 Manco-Johnson MJ. Postthrombotic syndrome in children. *Acta Haematol* 2006;115(3-4):207-213
- 15 Goldenberg NA, Donadini MP, Kahn SR, et al. Post-thrombotic syndrome in children: a systematic review of frequency of occurrence, validity of outcome measures, and prognostic factors. *Haematologica* 2010;95(11):1952-1959
- 16 Manco-Johnson MJ, Knapp-Clevenger R, Miller B, et al. Post thrombotic syndrome (PTS) in children: validation of a new pediatric outcome instrument and results in a comprehensive cohort of children with extremity deep vein thrombosis (DVT). *Blood* 2003;102:553a
- 17 Goldenberg NA, Knapp-Clevenger R, Manco-Johnson MJ; Mountain States Regional Thrombophilia Group. Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children. *N Engl J Med* 2004;351(11):1081-1088
- 18 Goldenberg NA, Branchford B, Wang M, Ray C Jr, Durham JD, Manco-Johnson MJ. Percutaneous mechanical and pharmacomechanical thrombolysis for occlusive deep vein thrombosis of the proximal limb in adolescent subjects: findings from an institution-based prospective inception cohort study of pediatric venous thromboembolism. *J Vasc Interv Radiol* 2011;22(2):121-132
- 19 Manco-Johnson MJ, Nuss R, Hays T, Krupski W, Drose J, Manco-Johnson ML. Combined thrombolytic and anticoagulant therapy for venous thrombosis in children. *J Pediatr* 2000;136(4):446-453
- 20 Wang M, Hays T, Balasa V, et al; Pediatric Coagulation Consortium. Low-dose tissue plasminogen activator thrombolysis in children. *J Pediatr Hematol Oncol* 2003;25(5):379-386
- 21 Albisetti M. Thrombolytic therapy in children. *Thromb Res* 2006;118(1):95-105
- 22 Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):887S-968S
- 23 Jaff MR, McMurtry MS, Archer SL, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;123(16):1788-1830
- 24 Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):454S-545S
- 25 Watson LJ, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev* 2004(4):CD002783
- 26 Enden T, Kløw NE, Sandvik L, et al; CaVenT study group. Catheter-directed thrombolysis vs. anticoagulant therapy alone in deep vein thrombosis: results of an open randomized, controlled trial reporting on short-term patency. *J Thromb Haemost* 2009;7(8):1268-1275
- 27 Vedantham S. Preventing pediatric postthrombotic syndrome: preparing the way. *J Vasc Interv Radiol* 2011;22(3):405-407
- 28 Yee DL, Chan AK, Williams S, Goldenberg NA, Massicotte MP, Raffini LJ. Varied opinions on thrombolysis for venous thromboembolism in infants and children: findings from a survey of pediatric hematology-oncology specialists. *Pediatr Blood Cancer* 2009;53(6):960-966
- 29 Gupta AA, Leaker M, Andrew M, et al. Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *J Pediatr* 2001;139(5):682-688
- 30 Kukreja K, Vaidya S. Venous interventions in children. *Tech Vasc Interv Radiol* 2011;14(1):16-21
- 31 Manco-Johnson MJ, Grabowski EF, Hellgreen M, et al. Recommendations for tPA thrombolysis in children. On behalf of the Scientific Subcommittee on Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis. *Thromb Haemost* 2002;88(1):157-158
- 32 Saxonhouse MA, Manco-Johnson MJ. The evaluation and management of neonatal coagulation disorders. *Semin Perinatol* 2009;33(1):52-65
- 33 Goldenberg NA, Hathaway WE, Jacobson L, Manco-Johnson MJ. A new global assay of coagulation and fibrinolysis. *Thromb Res* 2005;116(4):345-356
- 34 Simpson ML, Goldenberg NA, Jacobson LJ, Bombardier CG, Hathaway WE, Manco-Johnson MJ. Simultaneous thrombin and plasmin generation capacities in normal and abnormal states of coagulation and fibrinolysis in children and adults. *Thromb Res* 2011;127(4):317-323
- 35 Smith AA, Jacobson LJ, Miller BI, Hathaway WE, Manco-Johnson MJ. A new euglobulin clot lysis assay for global fibrinolysis. *Thromb Res* 2003;112(5-6):329-337
- 36 Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. *Am J Pediatr Hematol Oncol* 1990;12(1):95-104
- 37 Andrew M, Brooker L, Leaker M, Paes B, Weitz J. Fibrin clot lysis by thrombolytic agents is impaired in newborns due to a low plasminogen concentration. *Thromb Haemost* 1992;68(3):325-330
- 38 Col JJ, Col-De Beys CM, Renkin JP, Lavenne-Pardonge EM, Bachy JL, Moriau MH. Pharmacokinetics, thrombolytic efficacy and hemorrhagic risk of different streptokinase regimens in heparin-treated acute myocardial infarction. *Am J Cardiol* 1989;63(17):1185-1192
- 39 Lynch M, Pentecost BL, Littler WA, Stockley RA. The significance of anti-streptokinase antibodies. *Clin Exp Immunol* 1994;96(3):427-431

- 40 Köhler M, Sen S, Miyashita C, et al. Half-life of single-chain urokinase-type plasminogen activator (scu-PA) and two-chain urokinase-type plasminogen activator (tcu-PA) in patients with acute myocardial infarction. *Thromb Res* 1991;62(1-2):75-81
- 41 Pennica D, Holmes WE, Kohr WJ, et al. Cloning and expression of human tissue-type plasminogen activator cDNA in *E. coli*. *Nature* 1983;301(5897):214-221
- 42 Hoylaerts M, Rijken DC, Lijnen HR, Collen D. Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. *J Biol Chem* 1982;257(6):2912-2919
- 43 Hoffmeister HM, Szabo S, Helber U, Seipel L. The thrombolytic paradox. *Thromb Res* 2001;103(Suppl 1):S51-S55
- 44 Leary SE, Harrod VL, de Alarcon PA, Reiss UM. Low-dose systemic thrombolytic therapy for deep vein thrombosis in pediatric patients. *J Pediatr Hematol Oncol* 2010;32(2):97-102
- 45 Laiho MK, Oinonen A, Sugano N, et al. Preservation of venous valve function after catheter-directed and systemic thrombolysis for deep venous thrombosis. *Eur J Vasc Endovasc Surg* 2004;28(4):391-396
- 46 Williams MD. Thrombolysis in children. *Br J Haematol* 2010;148(1):26-36
- 47 Newall F, Browne M, Savoia H, Campbell J, Barnes C, Monagle P. Assessing the outcome of systemic tissue plasminogen activator for the management of venous and arterial thrombosis in pediatrics. *J Pediatr Hematol Oncol* 2007;29(4):269-273
- 48 Bush RL, Lin PH, Bates JT, Mureebe L, Zhou W, Lumsden AB. Pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis: safety and feasibility study. *J Vasc Surg* 2004;40(5):965-970
- 49 Zenz W, Arlt F, Sodja S, Berghold A. Intracerebral hemorrhage during fibrinolytic therapy in children: a review of the literature of the last thirty years. *Semin Thromb Hemost* 1997;23(3):321-332