

# The ABCs of Iliofemoral DVT

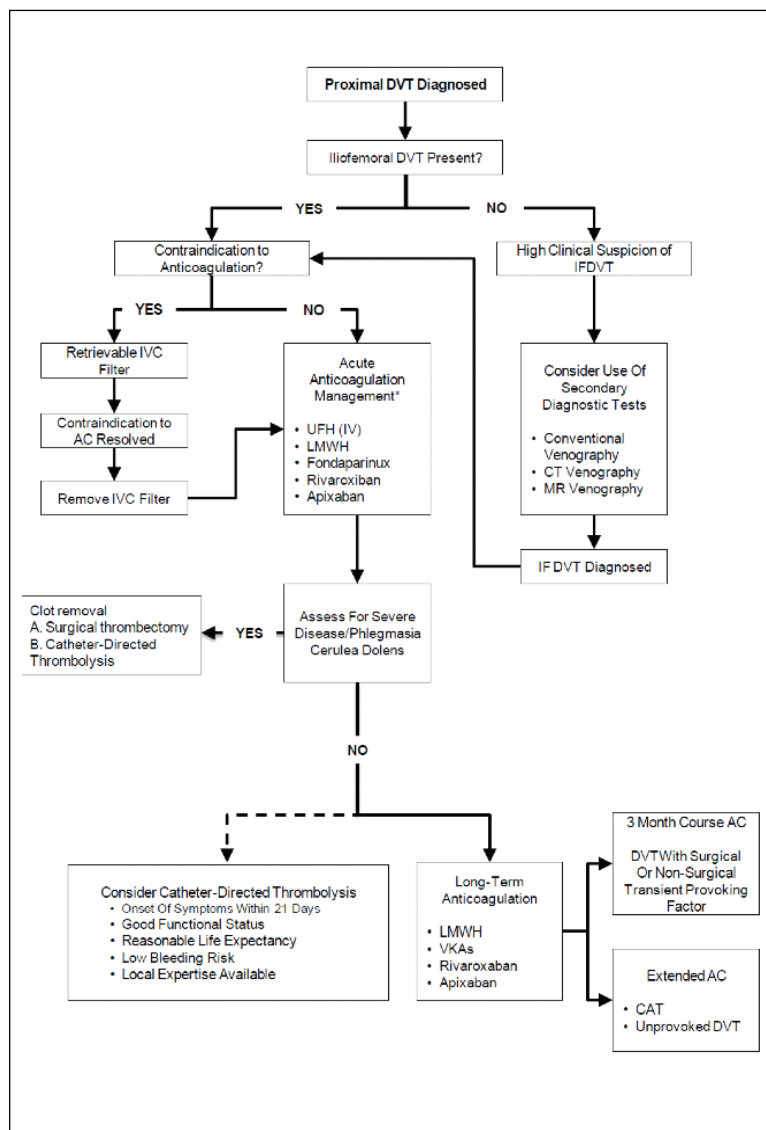
Understanding the continuum of care through a team-based approach.

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A 22-year-old athlete with a history of the factor V Leiden mutation and previous deep vein thrombosis (DVT) presented to his primary care physician with a swollen right leg after running a race over the weekend in hot weather. A 46-year-old woman bound to a wheelchair who had stage IV ovarian cancer developed progressive bilateral lower extremity leg swelling that had become intolerable and a remote history of an inferior vena cava (IVC) filter placed. A 32-year-old woman with intrauterine fetal demise underwent therapeutic abortion with a dose of mifepristone. A 50-year-old man with recent air travel history experienced sudden increased swelling and erythema of the right thigh to the ankle. These patients have a suspicion of iliofemoral DVT and present with different prodromes, circumstances, and needs in the management of their suspected DVT. The intent of this article is to provide a general outline and flow, taking into consideration the continuum of care in a multidisciplinary hospital-based model utilizing the recently published *Interdisciplinary Expert Panel on Iliofemoral DVT (InterEPID)* as the basis for discussion (Figure 1).<sup>1</sup>

## INTAKE AND DIAGNOSIS

Early clinical suspicion and initiation of appropriate workup is key to improving overall outcomes of lower extremity DVT. There are no symptoms specific to lower extremity DVT; however, lower extremity swelling, pain, and warmth are common.<sup>2</sup> Risk factor assessment and a thorough history eliciting the timing and onset of symptoms, baseline functional status, presence of underlying systemic disease, family history of venous



**Figure 1.** Multidisciplinary decision tree-based approach to the diagnosis and management of IF-DVT. In the absence of severe symptoms, catheter-directed thrombolysis may be considered in select patients with iliofemoral DVT (dotted line). Abbreviations: AC, anticoagulation; CAT, cancer-associated thrombosis; IF-DVT, iliofemoral DVT; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKAs, vitamin K antagonists. Reproduced with permission from CMAJ. 2015;187:1288–1296.

thromboembolism, and history of medications that may cause lower extremity edema is paramount at presentation. Postpartum state, recent lower extremity trauma, major surgery, and immobilization, among other factors, have been identified as major risk factors for the development of DVT and should be sought out at initial clinical assessment.<sup>3</sup>

On physical examination, it is important to assess the location and laterality of lower extremity edema and to characterize any associated skin changes or ulcerations. The presence of phlegmasia cerulea dolens, which includes the triad of edema, cyanosis, and pain heralds underlying hypercoagulable state or malignancy, indicating the need for urgent treatment escalation beyond anticoagulation, must be excluded.<sup>4</sup>

The Wells score can be used in the decision-making process to establish the pretest probability of DVT. A large meta-analysis concluded that individual clinical features have a limited value in the diagnosis of DVT, and overall assessment of clinical probability using the Wells score is more useful. However, it has not been validated as a severity score and therefore cannot be utilized to differentiate patients that may potentially benefit from endovascular intervention or thrombolysis.<sup>5</sup> D-dimer has a limited value in the diagnostic algorithm, but has a very high negative predictive value in the setting of venous thromboembolism, and can be used if the pretest probability of DVT is low.<sup>2</sup>

An objective test, most commonly duplex venous sonography, is required to establish the diagnosis of lower extremity DVT. This can be supplemented with CT or magnetic resonance venography to better assess the IVC and iliac veins. If endovascular therapy is planned, CT or magnetic resonance venography may provide useful information that may alter the therapeutic approach, such as the site of venous access and thrombus removal methods. Further imaging such as echocardiography and lymphoscintigraphy and other laboratory tests (thyroid function, complete blood count, antinuclear antibody) play adjunct roles in select patients with lower extremity edema to assess for alternative diagnoses.

Thrombophilia testing can be initiated in select patients who are considered at high risk for having a hypercoagulable disorder but is not routinely offered to all patients with DVT because, in most patients with DVT, the identification of an inheritable defect does not alter the anticoagulation regimen.<sup>6</sup> Furthermore, studies have shown that the presence of single or multiple thrombophilic defects does not seem to be associated with a higher risk of recurrent venous thromboembolism.<sup>7</sup>

### THERAPY OBJECTIVES

Each of the previous case examples is provided to emphasize the high degree of variability in presentation and the need to appreciate the context in which therapy is to be considered. In some cases, the acuity and/or severity of symptoms mandates urgent intervention. In other cases, where the onset is gradual and symptoms are less severe, practical application of the principle of the open vein hypothesis (to preserve or maintain normal venous hemodynamics and valvular function) may justify intervention.

Regardless of whether endovascular intervention is warranted, anticoagulation is the mainstay of therapy for patients with lower extremity DVT. All patients, with no contraindications, should be anticoagulated for a finite period following the first episode of lower extremity DVT, although some may benefit from indefinite anticoagulation to reduce the risk of recurrent thrombosis.<sup>8</sup> IVC filter placement is a consideration in appropriately selected patients. Furthermore, studies have shown early ambulation is not associated with progression of DVT or development of pulmonary embolism and should be encouraged.<sup>9,10</sup> At this point in time, anticoagulation is the only therapy that has demonstrated a decrease in mortality related to subsequent events, such as fatal pulmonary embolization.<sup>11</sup>

Despite optimal anticoagulation, > 30% of patients with a history of symptomatic DVT will develop symptomatic post-thrombotic syndrome (PTS), likely due to chronic venous occlusion, suboptimal collateralization pathways, and venous valvular dysfunction. Up to one-third of these patients will develop severe debilitating symptoms.<sup>12</sup> Based on generic and disease-specific quality-of-life measures, it is well established that PTS has a significant negative impact on a patient's quality of life.<sup>13,14</sup> Kahn et al have demonstrated that self-reported physical quality of life in patients with PTS is comparable to patients with other chronic illnesses such as diabetes, chronic obstructive lung disease, and congestive heart failure.<sup>14</sup> There is no convincing evidence that the use of graduated compression stockings in the setting of lower extremity DVT reduces the incidence of PTS with more recent definitive studies (such as the SOX randomized controlled trial) demonstrating no significant reduction in the incidence of PTS.<sup>15,16</sup> Furthermore, cost and lack of comfort reduce patient compliance.

Lack of endoluminal venous recanalization within the first 6 months after an acute lower extremity DVT has been shown to be an important predictor of PTS.<sup>17</sup> Based on similar observations, the open vein hypothesis

postulates that immediate and effective removal of acute venous thrombus will reduce the risk of PTS and thereby improve quality of life.<sup>18</sup>

The ATTRACT (Acute Venous Thrombosis: Thrombus Removal and Adjunctive Catheter-Directed Thrombolysis) randomized controlled trial is looking to demonstrate PTS incidence reduction.<sup>19,20</sup> The CaVenT trial, which randomized 209 patients with iliofemoral DVT to catheter-directed thrombolysis (CDT) plus anticoagulation or anticoagulation alone, showed that 43% of patients in the CDT arm developed PTS, while 71% of patients who underwent anticoagulation alone developed PTS, based on the Villalta score at 5 years. The difference in PTS between the two arms corresponded to an absolute risk reduction of 28% and a number needed to treat (NTT) of 4.<sup>21</sup> The study suggests that early clot removal, by means of absolute PTS risk reduction, may have a beneficial long-term effect and should be offered to appropriately selected patients. It may also be that “the low incidence of adjunctive venous stenting in the CaVenT trial may have diminished the overall benefit of CDT.”<sup>22</sup>

Therefore, after a thorough workup, it may be appropriate to apply the open vein hypothesis, escalate therapy beyond standard anticoagulation, and offer endovascular options to appropriately selected patients. According to the 2016 American College of Chest Physicians guidelines, “patients who are most likely to benefit from CDT, who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.”<sup>23</sup>

## THE SYSTEM BEYOND THE PROCEDURE

The treatment of acute iliofemoral DVT does not begin and end in the angiography suite and requires a methodical approach to treatment. Due to the multitude of presentations, in addition to the many diagnostic and therapeutic pathways that exist in both outpatient and hospital-based practices, there is a need to identify all stakeholders and incorporate institutional knowledge and experience to develop system-wide protocols and evidence-based programs that provide common pathways from multiple intake sources.

The consideration of clot removal strategy (eg, surgery, mechanical, pharmacological) should only be made after appropriate diagnosis and a recognition of postprocedural care is determined. Rather than creating arbitrary criteria for intervention, decisions and options should be considered at the time of primary intake. Whether from the emergency room physician, hospitalist, or primary care provider, the appropriateness of consultation for

further management relies on confirmation of diagnosis, urgency, and goals of therapy.

Patient management considerations, such as anticoagulation (heparin, vitamin K antagonists or direct oral anticoagulants), rehabilitation, follow-up imaging, and potential management of PTS should be recognized as part of the care continuum. Establishing response teams, core expertise, and executive decision guided by a treatment algorithm based on best evidence or local expertise provides clear management pathways (Figure 1).<sup>1</sup>

## CONSIDERATIONS TO THERAPY

### Patient Considerations

First and foremost, having an established acute iliofemoral DVT intake institutional protocol that directs patients presenting in different settings (inpatient, outpatient referral, emergency room) toward a common multidisciplinary assessment pathway (that may include interventional radiology, vascular surgery, and hematology) optimizes downstream decisions (Figure 1).<sup>1</sup>

A standardized assessment can then be performed, which could take into consideration numerous patient factors, including:

- *Acuity of thrombus/DVT symptoms.* It has been established that acuity of < 21 days benefits the most from an intervention. Beyond this time, retraction and solidification of thrombus limits the efficacy of chemical lysis.<sup>1,21</sup>
- *Type of patient.* A young, active patient is likely to suffer far more from PTS than a bedridden or wheelchair-bound patient who may already have very limited mobility at baseline. In the former, more aggressive thrombus clearance may be beneficial.<sup>1,19,21</sup>
- *Severity of symptoms.* In a patient with relatively mild symptoms, such as minor leg swelling and short-segment femoral-only DVT, medical management can be first-line treatment with early follow-up (at 2 weeks). This contrasts with severely symptomatic patients with phlegmasia and extensive occlusive iliofemoral DVT, in which case more aggressive thrombus clearance/lysis may be warranted for limb preservation.<sup>1</sup>
- *Temporal evolution of symptoms.* Patients who present with worsening symptoms after successful anticoagulation represent a population that may require further intervention. Clinical follow-up at 1 week after anticoagulation initiation may help identify this subpopulation.
- *Underlying contributions to acute DVT.* Primary or secondary pelvic neoplasia can physically compress pelvic veins and incite DVT formation. If the patient presents with unilateral left leg DVT, consideration for underlying May-Thurner syndrome should be made (extrinsic compression of the left common iliac vein with reac-



tive intimal hyperplasia due to an overlying right common iliac artery).

- **Contraindication to systemic anticoagulation.** If the patient is immediately postoperative from major neurological surgery, has suffered from an acute cerebral infarct, or has some other contraindication to systemic anticoagulation, consideration could be given to limited pharmacomechanical thrombectomy (PMT) or even solely mechanical thrombectomy in the first instance.

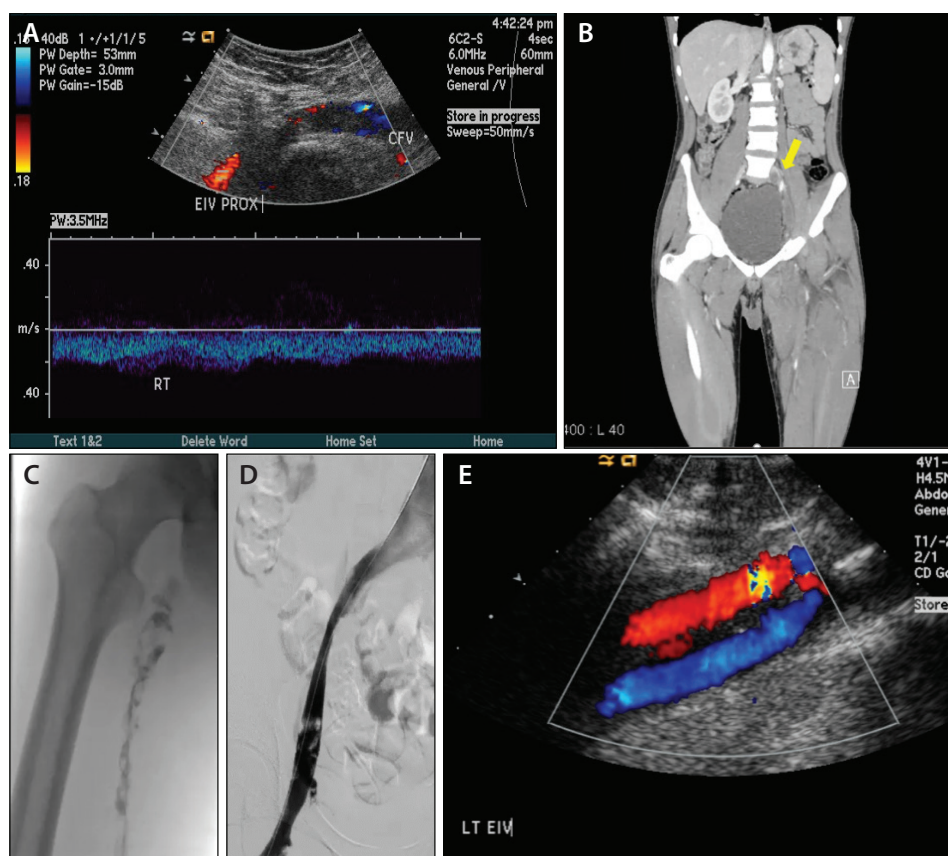
## Procedural and Postprocedural Considerations

Assuming CDT or PMT therapy has been chosen, a range of currently available treatment devices exist. The most basic of these is CDT, in which an infusion catheter is placed across the acute thrombus, and slow, continuous infusion of a chemical thrombolysis agent is initiated. Newer devices combine some form of mechanical disruption of the thrombus in conjunction with chemical lysis. The two most widely used of these pharmacomechanical thrombolytic (PMT) devices are the AngioJet™ (Boston Scientific Corporation) and EKOS (BTG International) systems. Several alternative PMT devices have become available to the market, however, the aforementioned devices represent those with the longest history of safety and use.

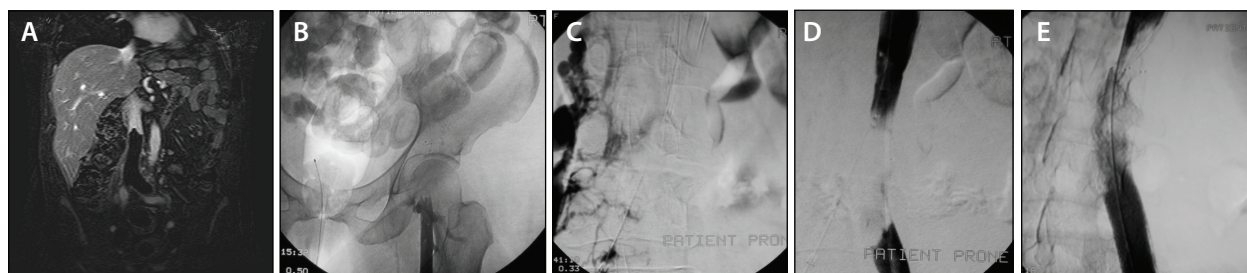
A detailed discussion regarding techniques specific to the PMT devices is beyond the scope of this article. Briefly, however, AngioJet combines chemical thrombolysis via Power Pulse™ with rheolytic fluid-based disruption of thrombus and catheter-based aspiration thrombectomy.<sup>24</sup> EKOS combines chemical CDT with low-power,

high-frequency ultrasound application to the proprietary infusion catheter/wire combination, with the ultrasonic vibration purported to hasten thrombus disruption.<sup>25</sup> There is evidence suggesting PMT quickens thrombolysis in the early setting compared with CDT alone.<sup>24,25</sup> The AngioJet Power Pulse technique is preferred in our institutions when approaching acute iliofemoral DVT with subsequent TPA infusion if required and reconstruction either via venoplasty and/or stent placement when maximum clot removal has been achieved.

The primary postprocedure consideration for CDT is the availability of continuous in-hospital monitoring for CDT patients to minimize and expedite early detection of CDT-related complications. In institutions where beds with continuous monitoring are limited or not available, PMT may be chosen over standard CDT to reduce the continuous monitoring requirements, sometimes as a single-session PMT without postprocedural continuous infusion CDT.<sup>24</sup>



**Figure 2.** A 22-year-old athlete with factor V Leiden mutation and previous DVT. Ultrasound confirming external iliac DVT (A). CT confirming iliofemoral DVT (B). DSA angiogram demonstrating extensive clot in common femoral distribution (C). After AngioJet Power Pulse technique utilizing a Solent Omni catheter with 20 mg TPA and balloon venoplasty (D). Six-month follow-up ultrasound following anticoagulation with NOAC demonstrating patency, with return to baseline function (E).



**Figure 3.** A 46-year-old woman with stage IV ovarian cancer and bilateral lower extremity swelling with IVC filter in place. Coronal contrast-enhanced MRI demonstrating extensive clot initiating from the IVC filter (A). Left popliteal venogram showing complete occlusion of the left superficial femoral vein (B). Right iliac venogram demonstrating extensive collateralization from the venous plexus and occlusion of the common iliac vein (C). After 24-hour TPA via catheter-based infusion, both legs reestablished flow in the left femoral and iliac systems with markedly reduced edema and persistent occlusion of the IVC from residual clot/tumor (D). Subsequent stenting returned inline flow (E) and alleviation of leg pain, edema, and swelling. The patient was placed on lifelong low-molecular-weight heparin and palliative care for 4 months prior to death.

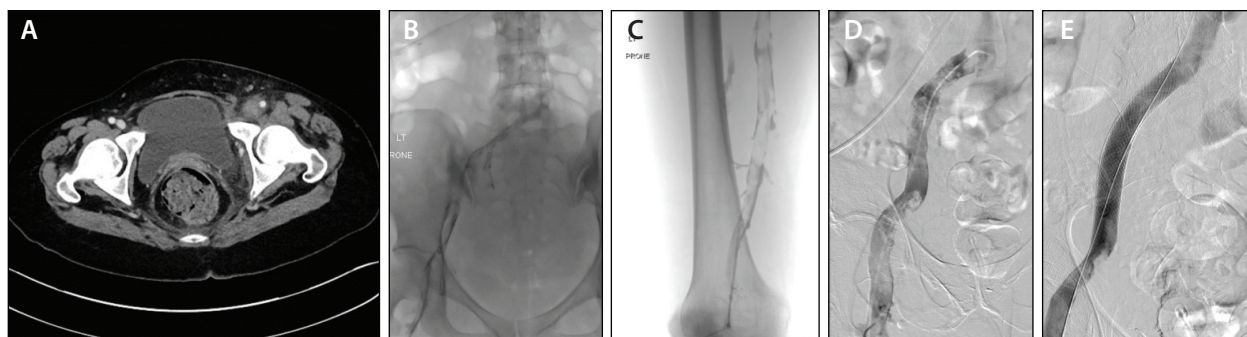
### Considerations and Case Examples

The 22-year-old male athlete presented with symptoms of acute DVT (Figure 2). Initial standardized intake assessment should be performed to substantiate a diagnosis of acute iliofemoral DVT. Given the patient's age, it would be reasonable to pursue CDT/PMT over standard anticoagulation to expedite thrombus clearance and minimize the propensity of PTS, especially if the DVT extends into the iliac veins.<sup>1,19,21</sup> Because he has an underlying coagulopathy and history of prior DVT, hematology assessment with consideration for long-term anticoagulation could be made.<sup>1</sup>

The middle-aged, wheelchair-bound woman with advanced-stage cancer and progressive, intolerable leg swelling is a much more complex case (Figure 3). To start, iliofemoral DVT should be established. More in-depth imaging is likely necessary to determine the extent of the pelvic cancer and the degree to which the

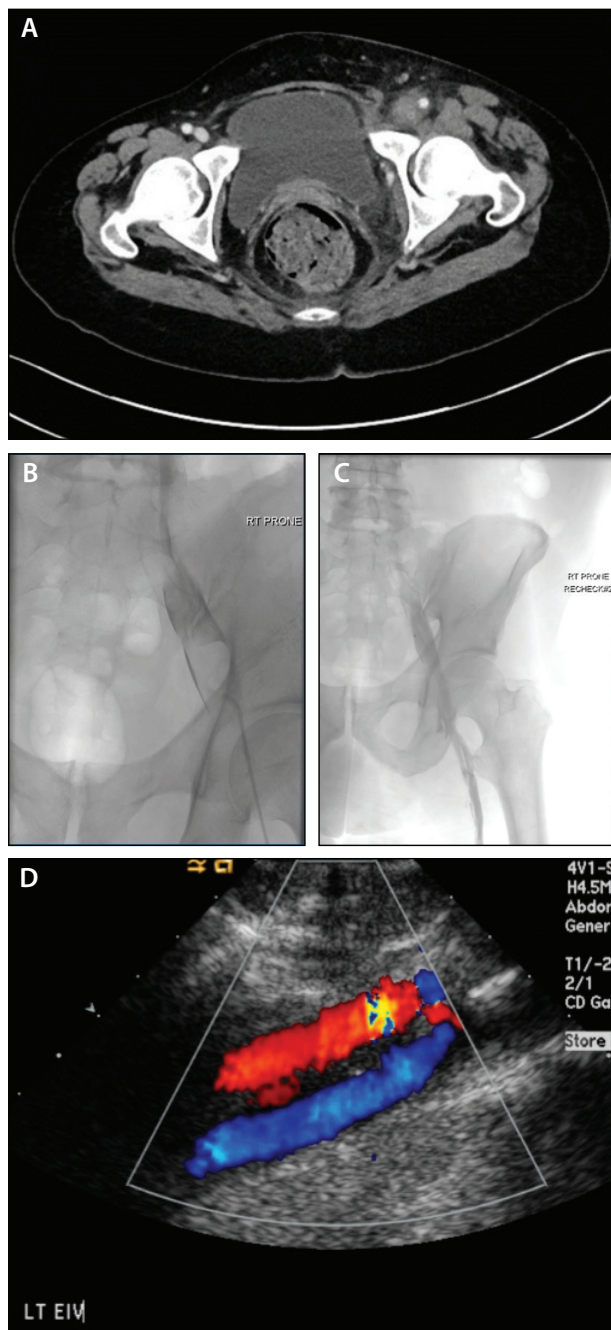
neoplasia is contributing to venous occlusion either by vascular invasion or extrinsic compression. The end objective for this patient should also be clearly established to help determine the type of treatment to pursue. Treatment could range from conservative with pneumatic compression stockings with or without anticoagulation (and in the case of cancer-related thrombosis, be restricted to low-molecular-weight heparin) to palliative surgical debulking with thrombectomy.<sup>1</sup>

The 32-year old woman who was posttherapeutic abortion presented with bilateral DVT (Figure 4). As with the other cases, iliofemoral DVT should be substantiated. Given the patient's young age, it would be reasonable to pursue CDT/PMT over standard anticoagulation to expedite thrombus clearance and minimize the propensity of PTS (especially in iliofemoral DVT) given the potential greater long-term deleterious consequences of PTS in this patient population.<sup>1,19,21</sup>



**Figure 4.** A 32-year-old postpartum woman with acute onset DVT. Pregnant with intrauterine fetal demise, she underwent therapeutic abortion with a dose of mifepristone. CT scan demonstrating left-sided common femoral DVT (with extension to common iliac vein not shown) (A). Injection venogram revealing extensive iliofemoral DVT (B,C). After AngioJet Power Pulse technique utilizing a ZelanteDVT catheter with 20 mg TPA, there was return of flow and persistent clot/stenosis in the left common iliac vein (May-Thurner syndrome) (D) with subsequent stenting (Innova [Boston Scientific Corporation], 12 X 80 mm) (E). She was placed on warfarin for 6 months with return to baseline function.





**Figure 5.** A 50-year-old man with sudden increased right-sided leg swelling after air travel. Ultrasound confirmed lack of flow in the external iliac vein confirming iliofemoral DVT (A), with injection venogram demonstrating significant clot burden in the right common iliac vein (B). TPA infusion initiated via infusion catheter (0.75 mg TPA/hour) with 24-hour recheck demonstrating patency with no stenosis (C). Follow-up ultrasound at 6 months (D) with novel oral anticoagulant demonstrated patency but required use of a class II compression stocking for symptomatic relief of mild post-thrombotic syndrome.

The 50-year-old man turned out to have had a hip replacement 2 weeks earlier and had not informed his medical team of his intended travel and was not on anti-coagulation (Figure 5). To start, iliofemoral DVT should be established. Standard therapy for postoperative DVT is anticoagulation and continued use of graduated compression stockings.<sup>1</sup> Caution should be given toward more aggressive chemical lysis-based therapies due to increased risk of hemorrhage at the surgical site. Should catheter-directed therapies be pursued due to the severity of symptoms/extensiveness of DVT, consideration could be given to solely mechanical thrombolysis in the first instance.

## CONCLUSION

As demonstrated by these case examples, the myriad of presentations and the need for personalized follow-up requires a dedicated group of individuals to commit to hospital-based algorithms based on evidence, expertise, and local institutional experience. The disparity between reported results of clinical studies emphasizes the fact that PMT strategies may not provide a clear benefit in all patients presenting with iliofemoral DVT, creating the need for personalized approaches.

Factors relating to outcome and risk/benefit analysis have not yet been clearly defined, however, losing the context of a patient-centered model of care while these factors are elucidated is not an acceptable approach to therapy. The management of iliofemoral DVT in the real-world setting has become more complex and as such, requires the development of a multidisciplinary program, not just perfection of any particular technique. ■

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