Diagnosis and management of upper extremity deep-vein thrombosis in adults

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Summary
Upper extremity deep-vein thrombosis (UEDVT) is common and can cause important complications, including pulmonary embolism and post-thrombotic syndrome. An increase in the use of central venous catheters, particularly peripherally inserted central catheters has been associated with an increasing rate of disease. Accurate diagnosis is essential to guide management, but there are limitations to the available evidence for available diagnostic tests. Anticoagulation is the mainstay of therapy, but interventional treatments may be considered in select situations. The risk of UEDVT may be reduced by more careful selection of patients who receive central venous catheters and by use of smaller catheters. Herein we review the diagnosis, management and prevention of UEDVT. Due to paucity of research, some principles are drawn from studies of lower extremity DVT. We present a practical approach to diagnosing the patient with suspected deep-vein thrombosis of the upper extremity.

Keywords
Venous thrombosis, diagnosis management, deep-vein thrombosis, magnetic resonance, risk factors

Background
Upper extremity deep-vein thrombosis (UEDVT) refers to the formation of fibrin clots within the subclavian, axillary, and brachial veins of the arm (1). Two proximal superficial veins, the basilic and cephalic, have anastomoses with the deep veins and can be the location of superficial thrombophlebitis.

"Primary UEDVT" refers to thrombosis without apparent precipitant, or in the setting of anatomic variants. An image of primary UEDVT is shown in Figure 1. Thrombosis occurring in the setting of a central venous catheter (CVC), malignancy, pregnancy, recent surgery or trauma is termed "secondary UEDVT" (2). An image of secondary UEDVT, associated with a PICC device, is shown in Figure 2.

UEDVT can cause symptoms, including pain, swelling, and skin discoloration, or can be detected by imaging studies in asymptomatic patients.

Epidemiology and risk factors
Approximately 10% of all DVT occurs in the upper extremities, which translates into an annual incidence of 0.4 to 1 case per 10,000 persons. The incidence is increasing with time, due to increasing numbers of secondary UEDVT due to medical devices (2).

The majority of primary UEDVT cases are caused by anatomic abnormalities of the costoclavicular junction. Thoracic outlet syndrome, a disorder in which the nerves, artery and veins are compressed passing through the costoclavicular space, is associated with DVT (3). Effort thrombosis results from repetitive injury to the vein in a tight thoracic outlet induced by arm movements, especially frequent use of arms above shoulder level. This entity is also referred to by the eponym Paget-Schroetter syndrome (PSS) (4). Idiopathic cases, in which no anatomic abnormalities are identified, also occur. Primary UEDVT comprises about 20–30% of total UEDVT (5).

CVCs are the predominate cause of secondary UEDVT, and the overall incidence of UEDVT is increasing coincident to the increasing use of CVCs, particularly peripherally-inserted central catheters (PICCs). A venous catheter is present in about half of all cases of UEDVT (6–8). CVCs precipitate thrombus formation via stasis, platelet adherence, and endothelial trauma (9). The incidence of symptomatic and asymptomatic UEDVT following CVC placement is 2–6% and 11–19%, respectively (Table 1) (10–22). Catheter diameter and type, tip location, and concurrent infection have all been shown to affect the risk of DVT. In a recent analysis of 2,014 CVC placements, larger-diameter triple-lumen PICCs were
shown to carry a 20-fold higher risk for UEDVT compared with single-lumen PICCs (23). Peripheral misplacement of the CVC tip has been associated with a 46% rate of thrombosis, and concomitant infection confers a relative risk of up to 17.6. PICCs appear to carry higher risk of DVT than surgically tunneled catheters (10, 24, 25). Cardiac pacemaker systems with intravenous leads have also been associated with DVT (26). Odds ratios (OR) for risk factors are presented in Table 2.

Malignancy is an independent risk factor for UEDVT, present in about one-third of cases (6, 27). Cancer, especially of the lung and

Figure 1: Primary UEDVT. Multiple foci of thrombosis are seen in the right subclavian vein with innumerable collaterals draining the right upper extremity to the central venous outflow in this 33-year-old woman with PSS and recurrent episodes of thrombosis.

Figure 2: Secondary UEDVT. 45-year-old woman requiring long-term IV antibiotics with a 5-French double lumen PICC placed in the left basilic vein. Four days later, patient developed left upper-extremity pain, US showing non-occlusive thrombus in left axillary vein. A) Longitudinal gray scale US shows presence of PICC line (arrow) in distal subclavian vein. B) Longitudinal gray scale US shows echogenic mass (arrow) within the lumen of the axillary vein, implying an acute thrombus. C) Transverse gray scale US shows a non-occlusive hypoechoic mass (arrow) within the axillary vein. In the right image, the vessel lumen shows no compressibility, indicating the presence of an intra-luminal thrombus. D) Longitudinal colour Doppler US shows peripheral blood flow around the non-occlusive thrombus (arrow) with increased central velocity due to the narrowed channel.
GI tract may further increase the risk of DVT in patients with a CVC (8, 28). UEDVT may also herald an undiagnosed cancer—one series found a 23.7% rate of occult malignancy in apparently unprovoked UEDVT; higher than that found in unprovoked lower extremity DVT (29).

The association between hereditary and acquired thrombophilia with UEDVT is unclear, with varying rates (11–60%) of thrombophilia in DVT cases reported. The utility of screening for thrombophilia in cases of UEDVT is controversial (3, 30), and identifying a hereditary thrombophilia does not clearly impact management decisions (31). Multiple case reports of DVT of the upper extremity in pregnant women have been described in the setting of assisted reproductive techniques and ovarian hyperstimulation syndrome (32).

Prognosis and complications

Overall two- and 12-month mortality rates following diagnosis of UEDVT are 30 and 40%, respectively; however, these studies included patients with significant comorbidities (33, 34). Patients with PSS generally have good functional status with longer life expectancies.

The reported rate of symptomatic PE in the setting of UEDVT ranges from 3–12.4% (Table 3) (9, 35–38). The asymptomatic incidence is several-fold higher. A study by Prandoni et al. used prospective imaging to show evidence of PE in 36% of patients with confirmed UEDVT (35). Of patients enrolled in the RIETE registry, 9% with UEDVT had symptomatic PE at presentation, versus 29% of patients with DVT of the lower extremities. The rate of new PEs during follow-up, however, was similar between these groups, and those with UEDVT had higher three-month mortality (11% vs. 7% in the lower extremities, 95% confidence interval [CI] 1.18–2.21) (39). As noted above, UEDVT, even in unprovoked cases, is substantially less likely to recur than lower extremity DVT (7, 35, 40, 41). The annualised recurrence rate after a first UEDVT ranges from 2.3 to 4.7% (7, 27). Patients with thrombophilia may have a higher yearly risk of symptomatic recurrence than those without thrombophilia (4.4% vs. 1.6%) (33); but data are limited.

PTS is a late complication characterised by chronic pain, oedema, and functional limitation of the affected arm as a result of persistent obstruction and valvular reflux. The reported incidence of PTS following UEDVT is 7–46%, a wide range reflecting the lack of a standardised definition in relevant studies (42). Residual thrombosis has been associated with a four-fold increased risk of developing PTS following UEDVT (4), but it is not clear whether endovascular interventions alter the rate of this outcome. While compression garments decrease the risk of PTS of the legs following DVT, no such studies have been performed for UEDVT. An evidence-based practice guideline suggests against using compression sleeves to prevent PTS of the upper extremity; though it does suggest a trial of compression therapy to treat symptoms of established PTS of the arm (31).

Prevention

Risk reduction

A large body of literature focuses on the prevention of DVT in various patient groups, though few trials have focused specifically on UEDVT. Evidence-based clinical practice guidelines from the American College of Chest Physicians (ACCP) provide specific recommendations for prevention of venous thromboembolism in

<table>
<thead>
<tr>
<th>Table 1: Incidence of catheter-related thrombosis*.</th>
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<tbody>
<tr>
<td>Author (n, indication)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Bern, 1990 82 (40), chemotherapy</td>
</tr>
<tr>
<td>Bonfils, 1996 78, chemotherapy</td>
</tr>
<tr>
<td>De Cicco, 1997 95, chemotherapy, TPN, or both</td>
</tr>
<tr>
<td>Martin, 1999 60, critical care</td>
</tr>
<tr>
<td>Luciani, 2001 145, chemotherapy</td>
</tr>
<tr>
<td>Mismetti, 2003 45, cancer care</td>
</tr>
<tr>
<td>Couban, 2005 255 (125), cancer care</td>
</tr>
<tr>
<td>Verso, 2005 310 (155), chemotherapy</td>
</tr>
<tr>
<td>Karthaus, 2006 439, chemotherapy (or 145)</td>
</tr>
<tr>
<td>Niers, 2007 87 (46), chemotherapy</td>
</tr>
<tr>
<td>Cortelezzi, 2005 458, cancer care</td>
</tr>
<tr>
<td>Lee, 2006 444, cancer care</td>
</tr>
<tr>
<td>Young, 2009 812 (404), chemotherapy</td>
</tr>
</tbody>
</table>

*Numbers in parentheses represent rates in the control groups in studies which tested a prophylactic intervention. +Outcomes for symptomatic and surveillance-detected thrombosis were not reported separately.
Table 2: Significant risk factors for development of UEDVT.

<table>
<thead>
<tr>
<th>Author</th>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joffe, 2004</td>
<td>Indwelling CVC</td>
<td>9.7</td>
<td>7.8–12.2</td>
<td>-</td>
</tr>
<tr>
<td>Joffe</td>
<td>CVC within 30 days</td>
<td>7.3</td>
<td>5.79–9.21</td>
<td>-</td>
</tr>
<tr>
<td>Saber, 2011</td>
<td>Implanted port (vs. PICC)</td>
<td>0.43</td>
<td>0.23–0.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Saber</td>
<td>Subclavian vein insertion site (vs. upper arm vein)</td>
<td>2.16</td>
<td>1.07–4.34</td>
<td>0.029</td>
</tr>
<tr>
<td>Saber</td>
<td>Catheter tip not in right atrium or SVC/atrial junction</td>
<td>1.92</td>
<td>1.22–3.02</td>
<td>0.034</td>
</tr>
<tr>
<td>Saber</td>
<td>Prior DVT</td>
<td>2.03</td>
<td>1.05–3.92</td>
<td>0.004</td>
</tr>
<tr>
<td>Evans, 2010</td>
<td>Double lumen PICC (vs. single-lumen)</td>
<td>7.54</td>
<td>1.51–100</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Evans</td>
<td>Triple lumen PICC (vs. single-lumen)</td>
<td>19.50</td>
<td>3.45–100</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CI, confidence interval; CVC, central venous catheter; OR, odds ratio; PICC, peripherally-inserted central catheter; SVC, subclavian vein catheter.

Table 3: Rates of symptomatic PE in patients with UEDVT.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients, n</th>
<th>PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munoz, 2008</td>
<td>512</td>
<td>9%</td>
</tr>
<tr>
<td>Horattas, 1998</td>
<td>539</td>
<td>12.4%</td>
</tr>
<tr>
<td>De Cicco, 1997</td>
<td>63</td>
<td>3%</td>
</tr>
<tr>
<td>Hingorani, 1997</td>
<td>170</td>
<td>7%</td>
</tr>
<tr>
<td>Koolj, 1997</td>
<td>78</td>
<td>12%</td>
</tr>
<tr>
<td>Kern, 1990</td>
<td>693</td>
<td>8%</td>
</tr>
</tbody>
</table>

Randomised studies evaluating the benefit of heparin-bonded catheters in preventing catheter-related thrombosis have centered on the paediatric population. Two prospective trials comparing heparin-bonded with standard non-heparin bonded catheters with surveillance ultrasound found a decrease in both radiographic and symptomatic thrombosis as well as infection in critically-ill children (46, 47). A more recent study limited to infants ≤1 year old with congenital heart disease found no such benefit (48).

Pharmacologic prophylaxis

The use of prophylactic anticoagulation for the prevention of CVC-related UEDVT is controversial. While early studies reported significant benefit, recent prospective randomised trials have not. A meta-analysis of nine randomised clinical trials found a trend towards decreased incidence of symptomatic DVT in cancer patients with a CVC treated with prophylactic heparin or low-dose warfarin, but these results were not statistically significant (relative risk [RR] 0.43, 95% CI 0.18–1.06 for heparin and RR 0.62, 95% CI 0.30–1.7 for low-dose warfarin) (49). The ACCP and NCCN guidelines recommend against routine use of anticoagulant prophylaxis solely on the basis of an indwelling CVC (31, 50).

Diagnosis

Clinical presentation

The most common clinical features of UEDVT are unilateral arm swelling, discomfort, and erythema. Additional signs include dilated superficial veins, dyspnea, low-grade fever, and the development of superior vena cava syndrome (8). The most common signs and symptoms of PSS are venous distention (100%), swelling of the arm (93%), blue discoloration (77%) and aching pain with exercise (66%) (51). As a tight thoracic outlet may also compromise arterial circulation, physical examination maneuvers such as Adson’s test (neck is rotated ipsilaterally and extended) and Wright’s test (arm is hyperabducted) work to compress the thoracic outlet and may result in a diminished radial pulse (52).

Clinical evaluation has low specificity (30–64%) (41, 53, 54). A clinical pre-test probability score has been reported (53) but has yet to be used in a prospective management study.

Laboratory testing

In contrast to diagnosis of lower extremity DVT, sensitive D-dimer testing has not been prospectively tested in high-quality management studies, and a low quantitative (or negative qualitative) D-dimer cannot be used to exclude UEDVT (55).

Imaging studies are required when UEDVT is suspected.
Diagnostic imaging

Research evaluation of diagnostic tests may broadly be classified as accuracy or management studies. The former compares a diagnostic test against a reference standard, while the latter focuses on clinical outcome over a pre-defined period of follow-up. In contrast to suspected lower extremity DVT, few management studies for suspected UEDVT have been performed and the literature is largely limited to accuracy studies. Some of the following studies relate to thrombosis of the lower extremity and must be extrapolated for application to the upper extremities.

Ultrasound

Ultrasound (US) is the most commonly used initial test for suspected UEDVT. It is widely available, non-invasive and does not result in exposure to radiation. Assessment for UEDVT can be performed with B-mode US with compression (henceforth compression US) and with assessment of venous flow using Doppler or colour Doppler for central veins not amenable to direct compression. Figure 3 shows an example of images obtained during US.

On B-mode imaging, acute thrombi may appear as areas of variable echogenicity within the vessel lumen. Non-compressibility of a venous segment defines the presence of DVT. Compression US is performed by applying pressure to the overlying tissues to compress the visualised vein in the transverse plane. Veins should easily collapse under the applied pressure, with lack of expected venous collapse indicating a thrombus. Because this technique requires direct manual compression, it cannot be used to evaluate the centrally-situated brachiocephalic vein and superior vena cava (SVC), nor the medial segment of the subclavian vein underlying the bony clavicle.

Doppler and colour-flow Doppler US assess venous blood flow. Absence of flow, particularly in a vein which cannot be subjected to compression, suggests DVT (41, 56). Alterations of the normal biphasic pattern on pulsed-wave Doppler flow analysis can also suggest the presence of DVT. Patel et al. reported that absence of biphasic flow had 75% sensitivity and 100% specificity (compared to contrast venography) for DVT not found on preliminary gray-scale or color Doppler examination (57).

A systematic review by di Nisio et al. evaluated nine studies using US to diagnose UEDVT; 75% of studies used CV as the reference standard (58). Overall, the methodological quality of the included studies was poor. Summary estimates of sensitivity/specificity for each modality are presented in Table 4. Due to limited negative predictive value, a normal US does not exclude DVT when there is high clinical suspicion, and additional tests are required. A recent evidence-based clinical practice guideline suggests use of compression and Doppler US (termed “Combined Modality US” in the guideline) as the initial diagnostic test for suspected UEDVT (59).

Figure 3: Example of venous ultrasound. A 77-year-old man status post orthotopic heart transplant with a left internal jugular central venous catheter developed left upper-extremity swelling. US showing occlusive thrombus in cephalic and basilic veins. A and B) Longitudinal colour Doppler US shows echogenic material in the lumen of the cephalic and basilic veins with complete lack of flow. Spectral waveform is markedly dampened. C) Transverse gray scale US shows echogenic material in basilic vein (left image). On compression, basilic vein does not obliterate (arrow- right image), suggesting the presence of a thrombus. Note compressibility of neighboring structures.
Contrast venography

Contrast venography (CV) has been the accepted reference standard for suspected DVT; although it has never been tested in a management study of suspected UEDVT. A management study of patients with suspected lower extremity DVT and a technically adequate, negative venogram revealed a subsequent rate of DVT or PE of 1.2% (95% CI, 0.2%-4.4%) during three months of follow-up. (60) CV is invasive, requires patient exposure to radiation and intravenous contrast, and is technically demanding. CV is therefore broadly reserved for instances when the results of initial non-invasive imaging are insufficient to reach a diagnostic conclusion – such as a technically inadequate US, or when an ultrasound is negative for DVT but a high clinical suspicion for DVT persists. CV visualises the veins at the thoracic outlet and can be used to confirm the diagnosis of right thoracic outlet and planning of possible interventional therapy (2).

To perform CV, contrast is injected into a distal vein of the affected arm. Thrombus is defined by a constant intraluminal filling defect present on more than one view. Non-filling of a venous segment on repeat injections suggests thrombosis, but is not diagnostic (61). Inter-observer agreement for interpreting venograms in suspected UEDVT is 71–83% (kappa 0.48–0.71) (62).

In studies of suspected lower extremity DVT, CV are technically inadequate in 10–15% of cases, largely due to insufficient contrast filling and poor image quality (63). Corresponding failure rates for venography for suspected UEDVT are not available.

In a small accuracy study with 22 subjects, CO2 venography, which does not require iodinated contrast, had a sensitivity of 97% and specificity of 85% versus standard CV (64). Further research of this method is needed before it can be considered for clinical use.

Computed tomography venography

Computed tomography venography (CTV) is performed by imaging veins during the equilibrium phase of the contrast injection. A recent systematic review of CTV in the diagnosis of lower-extremity DVT reported a pooled sensitivity of 95.9% (CI 93% to 97.8%) and specificity of 95.2% (CI 93.6–96.5%) (65). The reference standard was ultrasound in 12 and CV in one of the analysed studies. Limited data exist regarding its use for the upper extremity. A small study by Kim et al. reported 100% concordance between CTV and standard CV in 27 patients with central venous obstruction (66). Drawbacks of CTV include additional ionising radiation exposure to the patient, and risk associated with intravenous iodinated contrast. The relative performance of CTV vs. CV in suspected tight thoracic outlet is not known. A sample image from CTV is shown in ► Figure 4.

Magnetic resonance venography

Magnetic resonance venography (MRV) may be performed using a variety of techniques and methods of image processing, which may be broadly categorised as contrast and non-contrast enhanced, based on whether Gadolinium is utilised. MRV does not expose patients to radiation or iodinated contrast; though methods which employ Gadolinium carry the risk of nephrogenic systemic fibrosis. MRV is able to produce images of the central veins of the thorax, a region where ultrasound has limitations. In a recent meta-analysis for MRV of the lower extremities, the pooled sensitivity and specificity were 91.5% and 94.8%, respectively, with 13 of 14 studies using CV as a reference standard (67). While the possibility of simultaneous evaluation of PE is attractive, a recent clinical trial suggested that MRV is insufficiently sensitive to exclude suspected PE (68). To date, however, no management studies of MRV for suspected upper-extremity DVT have been performed.

MRV techniques which require contrast administration include 3-dimensional (3D) MRV, which utilises a systemic gadolinium bolus injection and 3D spoiled gradient echo sequence with subtraction or timed imaging to eliminate arteries. A small retrospective study reported good-quality images using partition analysis, with accurate evaluation of central vein thrombosis in all seven cases (69). 3D MRV requires a large amount of contrast agent. Direct MRV uses a dilute bolus (typically 1:20 gadolinium dilution in saline), which prevents T2 shortening and reduces the risk of toxicity, injected distal to the vein of interest (70). The segment from the axillary vein to the superior vena cava can typically be captured with 20–30 second breath hold (71). Two studies which evaluated a total of 46 patients with suspected UEDVT reported 100% concordance between direct MRV and traditional imaging techniques (mostly CV) (70, 71). In contrast, Baarslag et al., using non-dilute contrast, reported only 50% sensitivity and 80% specificity in a study of 17 patients comparing direct MRV with CV (72). An example of a direct MRV image is shown in ► Figure 5.

Techniques which do not require contrast include time-of-flight (TOF) MRV which relies on the intrinsic properties of flowing blood.

<table>
<thead>
<tr>
<th>Author</th>
<th>Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reference Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Nisio, 2010</td>
<td>Ultrasound</td>
<td>97%</td>
<td>96%</td>
<td>Mostly contrast venography</td>
</tr>
<tr>
<td></td>
<td>Compression</td>
<td>84%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colour-flow Doppler Duplex</td>
<td>91%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Thomas, 2008</td>
<td>Computed tomography venography</td>
<td>95.9%</td>
<td>95.2%</td>
<td>Mostly ultrasound (12 of 13 studies)</td>
</tr>
<tr>
<td></td>
<td>(lower extremity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sampson, 2007</td>
<td>Magnetic resonance venography</td>
<td>91.5%</td>
<td>94.8%</td>
<td>Mostly contrast venography (13 of 14 studies)</td>
</tr>
<tr>
<td></td>
<td>(lower extremity)</td>
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Table 4: Diagnostic accuracy in UEDVT (meta-analyses).
for signal acquisition. Studies evaluating TOF MRV for thrombosis detection and prediction of CVC access sites in the upper extremities report 71–97% sensitivity and 89–94% specificity (73–75). The reference standard for these studies, however, is inconsistent. TOF MRV is clinically limited due to its long examination time and cumbersome interpretation. Magnetic resonance direct thrombus imaging (MRDTI) detects the formation of methemoglobin from hemoglobin within a blood clot, which manifests as T1 shortening. MRDTI can distinguish recent from chronic thrombus in the evaluation of recurrent DVT, can visualise smaller vessels and complete occlusions, and has a fast scanning time (76). No studies have evaluated MRDTI for UEDVT. In a study of 101 patients with suspected DVT of the lower extremities, the overall sensitivities and specificities were 96% and 94%, respectively (76).

A general approach to selecting a diagnostic modality for suspected UEDVT is provided in Figure 6. An evidence-based clinical practice guideline has been published, which includes a section on diagnosis of UEDVT (59). Data for the usefulness of both CTV and MRV to assess for UEDVT at this time are limited and the possible benefits of gadolinium in MRV as a means of avoiding X-ray contrast nephrotoxicity should be weighed against its implication in causing nephrogenic systemic fibrosis. High quality management studies are needed. Therapeutic outcomes of various treatments are presented in Table 5.

### Treatment

Goals of therapy can be divided into the “active treatment” phase, defined as the first three months following diagnosis, and the secondary prevention phase, which refers to therapy beyond three months (77). Acute treatment phase goals are to prevent DVT progression and embolisation. Interventions in the acute phase may also reduce the risk of post-thrombotic syndrome (PTS). The goal of therapy in the secondary prevention phase is to prevent new episodes of DVT. Due to limited data regarding treatment of UEDVT, many treatment recommendations are extrapolated from trials of lower extremity DVT (1). In addition to anticoagulation, a number of interventions may be useful in the treatment of select cases, the indications for which continue to evolve.

### Anticoagulation

Anticoagulation – typically consisting of therapeutically-dosed parenteral anticoagulant bridged to an oral anticoagulant – is the mainstay treatment for acute DVT (31). Parenteral anticoagulation is achieved with therapeutically-dosed low-molecular-weight heparin (LMWH), fondaparinux, subcutaneous unfractionated heparin or intravenous unfractionated heparin (UFH) and is initiated at the time of diagnosis. Subcutaneous regimens are suggested over intravenous UFH, except in cases of severe renal insufficiency (31). Warfarin may be initiated on the same day, and the parenteral anticoagulant is continued for at least five days overlapping with warfarin, and until the International Normalised Ratio (INR) is 2.0 or higher on two measurements, separated by at least 24 hours (h) (31). The acute phase of treatment consists of three months of therapeutic anticoagulation.

Though no randomised-controlled trials exist for treatment of UEDVT, a retrospective analysis comparing conservative measures to anticoagulation reported a 48% and 70% rate of symptomatic resolution, respectively (78). Therapeutic anticoagulation decreases the risk of pulmonary embolism (PE) and recurrence by preventing thrombus extension. Complications from anticoagulation include a 2–4% rate of major bleeding (2).

Indications for extending anticoagulation therapy beyond three months into the secondary prevention phase, and the optimal treatment duration for UEDVT are uncertain. Unprovoked DVT has a lower rate of recurrence in the upper extremity than in the lower extremity (79–82) and therefore is not a compelling indication for long-term anticoagulation. When the provocation for DVT is ongoing, such as active cancer, or when a CVC is not removed, extended duration anticoagulation may be merited (31). A guidance statement from the International Society of Thrombosis and Haemostasis (ISTH) also suggests considering long-term anticoagulation for primary UEDVT with tight thoracic outlet which has not been surgically corrected (83).
Novel oral anticoagulants, such as direct thrombin inhibitors and Xa inhibitors have not yet been studied for the treatment of UEDVT.

Endovascular therapy

Because anticoagulation has no direct thrombolytic effect, recanalization depends on endogenous fibrinolysis. In a study of combined upper and lower extremity DVT, 82% of patients treated with anticoagulation alone had no change or worsening of the thrombus load (84). Residual clot has been associated with compromised valvular function and a higher rate of PTS and DVT recurrence (85). Various interventional therapies have been evaluated as a means of attempting to accelerate the process of recanalization, which has been hypothesized to reduce the risk of PTS and perhaps the risk of DVT recurrence.

Thrombolysis

Thrombolysis involves the infusion of thrombolytic agents which activate fibrin-bound plasminogen. Systemic thrombolysis has largely been abandoned in favor of catheter-directed thrombolysis (CDT) due to fewer bleeding complications and superior rates of valvular competence. Studies have found no major differences in safety or efficacy between urokinase, alteplase, or reteplase (86).

CDT utilises a multi-port catheter embedded directly into the thrombus under image guidance. Venous access is typically obtained peripheral to the obstruction, and the thrombus is traversed with a guidewire. For select cases of lower extremity DVT, the Society of Interventional Radiology recommends a continuous high-volume drip regimen (25–100 ml/h) with dilute thrombolytic and concomitant unfractionated heparin (86). However, no published guideline specifies thrombolytic dosing for cases of UEDVT. When undergoing CDT, the patient is typically monitored in an ICU or stepdown unit and follow-up venograms are obtained every 8–24 h with repositioning of the infusion catheter into residual thrombus (87).

Published reports demonstrate initial thrombus clearance rates between 72 and 91% for CDT of DVT of the upper extremities and torso (88, 89). Organised clots older than two weeks are generally less susceptible to thrombolysis (85). No randomised comparisons between thrombolysis and anticoagulation exist, but a retrospective long-term analysis of 95 UEDVT patients showed a 60% adjusted reduced risk for residual thrombosis compared with anticoagulation alone (95% CI 0.2–0.9) (90). However, there was no significant difference detected between these groups in the frequency of PTS.

The most common complication of thrombolysis is bleeding, typically at the access site. In large cohorts examining CDT of lower extremity DVT, published rates of major bleeding for CDT of the lower extremities are 8–11% (85, 91). This rate has decreased in recent years with improved techniques and better patient selection (92). Risk factors for bleeding include recent surgery, liver dysfunction, thrombocytopenia, advanced age, and prior stroke (85).

In a recent study, the presence of malignancy did not affect the frequency of bleeding complications (89).

Because thrombolysis increases the risk for major bleeding, and because high-quality evidence demonstrating long-term reduction of recurrent DVT and PTS symptoms are lacking, appropriate case selection is challenging. Evidence based practice guidelines from the ACCP suggest thrombolysis be considered in cases meeting the following criteria: “severe symptoms, thrombus involving most of the subclavian vein and the axillary vein, symptoms for 14 days, good functional status, life expectancy of 1 year, and low risk for bleeding” (31). NCCN guidelines recommend CDT in appropriate candidates based on institutional expertise (44).

Percutaneous mechanical thrombectomy

Percutaneous mechanical thrombectomy (PMT) refers to a group of catheter-based devices that remove clot through aspiration, fragmentation, or maceration. PMT can be used alone or in combination with pharmacologic thrombolysis (pharmacomechanical catheter-directed thrombolysis or PCDT) (87). There are two single-session systems in broad use. The AngioJet (Possis Medical, Minneapolis, MN, USA) which macerates the thrombus with a high-velocity jet and the Trellis-8 (Covidien, Boulder, CO, USA) which utilises a mechanical dispersion wire (85, 87).

Published data for these devices in the treatment of UEDVT are very limited. In a report of eight patients with subclavian and axillary vein thrombosis treated with the AngioJet Powerpulse system,
all patients were treated in a single setting and had patent central veins at six-month follow-up. Two of the eight procedures were complicated by puncture site haematomas (93).

Published rates of major bleeding from PCDT are 3–4% for DVT of both upper and lower extremities (85). Other potential complications include endothelial damage, traumatic haemolysis, and pulmonary microemboli. As with CDT, the balance of risks and benefits remain uncertain and guidelines suggest similar principles be applied regarding case selection.

Angioplasty and endovascular stenting

Balloon angioplasty of veins, along with endovascular stenting, has undergone limited evaluation for UEDVT. A published series of 22 patients with PSS reported stent occlusion in all patients within six weeks (94). The location of occlusion in PSS may subject stents to repetitive forces in the arm which promote stent fracture, compression, and migration. A series of 65 stent placements for central and peripheral limb obstructions of various causes reported a clinical success rate at the peripheral sites of 75% and 42% at 12 and 24 months, respectively. Most patients underwent repeat intervention (95). Angioplasty use has been reported in conjunction with surgical decompression for PSS (see below) (96). Indications for these interventions are uncertain, and long-term outcome data is lacking.

Unless contraindicated, a conventional course of anticoagulation should follow all interventional treatments for UEDVT (31). To date, studies of endovascular treatment of UEDVT have not demonstrated a lower rate of PTS or recurrent DVT than anticoagulation alone.

Table 5: Summary of therapeutic outcomes for UEDVT.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Benefit</th>
<th>Major complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation</td>
<td>48–70% symptom resolution</td>
<td>2–4%</td>
</tr>
<tr>
<td>Catheter-directed thrombolysis</td>
<td>72–91% initial thrombus clearance</td>
<td>8–11% (data from lower extremities)</td>
</tr>
<tr>
<td>Pharmacomechanical catheter-</td>
<td>8/8 treated patients had patent central veins at six months</td>
<td>3–4% (data from both upper and lower extremities)</td>
</tr>
<tr>
<td>directed thrombolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVC filter placement</td>
<td>Uncertain benefit</td>
<td>3.8%</td>
</tr>
</tbody>
</table>
SVC filter

The placement of a filter device in the SVC has been reported in patients with UEDVT and a contraindication to anticoagulation. No Food and Drug Administration (FDA)-approved SVC filter exists. Greenfield filters have been employed because of their smaller caval footprint. The Gunther Tulip filter has been reported to carry a lower relative risk of strut perforation (97). When utilised, an SVC filter is typically deployed at the convergence of the left and right brachiocephalic veins, with the hooks positioned above the origin of the azygous vein to avoid occlusion in the event of filter thrombosis. An SVC diameter greater than 28 mm is considered a contraindication by most authors due to the risk of filter migration (6).

A recent systematic review by Owens et al. analysed 209 published SVC filter placements (6). The major complication rate was 3.8%, largely caused by filter strut perforation through the SVC; in some cases leading to cardiac tamponade, aortic perforation, and pneumothorax. Given the known risks, and uncertain benefit provided by an SVC filter against PE, they have little role in the management of UEDVT. Evidence-based practice guidelines suggest SVC filters should be reserved for “exceptional circumstances in specialised centres” (31).

Treatment modification based on type and location of DVT

PSS/primary UEDVT

Surgical correction with resection of the first rib aims to correct the extrinsic vein compression in PSS, which occurs at the thoracic outlet, with the goal of reducing the risk of recurrent thrombosis. The rationale for surgical correction arise from the observation that anticoagulation was associated with persistent symptoms and recurrent thrombosis in more than 50% of cases (98). Urschel and Razzuk reported outcomes in a registry of 294 patients with a mean age of 32 years in three groups (initial anticoagulation alone, initial CDT, initial CDT plus prompt first rib resection). The latter groups required fewer subsequent thrombectomies, but assessments and interventions were not dictated by a study protocol and were performed at clinician discretion (51). As noted above, angioplasty use has been described in combination with surgical decompression (96). ACCP guidelines suggest that surgical correction be reserved for highly select cases in specialised centres (31). High-quality studies assessing long-term outcomes are lacking.

Secondary UEDVT due to CVC

In CVC-related UEDVT, an initial treatment decision is whether to remove the CVC. A prospective study of 72 cancer patients with symptomatic CVC-related thrombosis evaluated the consequences of anticoagulation while leaving the catheter in place and continuing to use it. Patients were treated with dalteparin for 5–7 days as a bridge to oral warfarin, and up to two administrations of tPA were allowed per blocked lumen. No recurrent DVTs or line blockages were reported, and all 42 patients who had a persistent need maintained a functional CVC at three months (99). No events of PE were reported. In the absence of infection or catheter damage, guidelines support leaving a functional CVC in place if it has an ongoing indication for use (31, 83). If the catheter is no longer needed, however, the National Comprehensive Cancer Network (NCCN) does recommend removal (44). The ACCP and ISTH both recommend anticoagulation for three months when a CVC is removed shortly after diagnosis of UEDVT in patients with or without cancer (83). While not the subject of a specific guidance statement, the ACCP text indicates that a CVC may be removed either immediately after DVT diagnosis or after a short period of initial anticoagulation, but favours the former (31). In patients with cancer and an indwelling catheter, the NCCN recommends anticoagulation during catheter use and for a course of at least three months after the catheter is removed (44).

Conclusions

The incidence of UEDVT is increasing, likely attributable to the increasing use of CVCs. Pharmacologic prophylaxis has not proven effective in reducing the risk of CVC associated UEDVT.

Clinical prediction scores and D-dimer assays have not undergone sufficient study, so imaging tests are required for diagnosis. US is the initial imaging test recommended, and CV should be considered if a negative US is discordant with clinical suspicion. Data regarding CTV and MRV are presently limited. High-quality management studies of diagnostic strategies for suspected UEDVT are needed.

Anticoagulation is the mainstay treatment for UEDVT; duration of anticoagulation is limited to the acute phase (three months) in most cases. Interventional techniques are gaining supportive evidence, but appropriate case selection is challenging. Thrombolysis with or without mechanical thrombectomy can achieve high rates of early vein patency, but whether this changes long-term rates of PTS or DVT recurrence is presently not known.

UEDVT results in symptomatic PE in about one in 10 cases. DVT recurs in about 2% annually and PTS in about a fifth of cases. No preventive measures have been proven to reduce the risk of PTS, but compression may improve symptoms in established cases.

Evidence-based practice guidelines from the NCCN, last full revision in 2008 and last updated in 2011, the ACCP, last updated in 2012, and a guidance statement from the ISTH, published in 2012, are available. Further research should focus on high-quality diagnostic management studies, case selection for long-term anticoagulation, use of novel anticoagulants, and long-term outcomes from endovascular and surgical interventions.

Conflicts of interest

None declared.
References


