Upper Extremity Deep Venous Thrombosis (UEDVT)

Samer Badr
Cooper University Hospital, Camden, NJ, USA

Abstract

Upper extremity Deep Venous Thrombosis (UEDVT) is frequent in the hospital, especially in the intensive care unit. It often complicates the placement of central venous catheters (CVC), notably peripherally inserted central (PICC) lines. Despite a lower rate of pulmonary embolism, UEDVT is as fatal as lower extremity DVT. This is due to its strong association with cancer. Symptoms are often absent, but systematic screening is not recommended. The best prophylaxis is good central catheter management. Pharmacological prophylaxis has questionable effectiveness in the prophylaxis of CVC-associated UEDVT. Compression ultrasonography is the first line diagnostic tool. Treatment is anticoagulation for at least 3 months. A causative central line should be removed as soon as clinically possible. Infrequently, patients with the thoracic outlet syndrome can get an effort related primary UEDVT. It is also known as the Paget-Schroetter syndrome. Along with anticoagulation, surgical referral for decompression of the thoracic outlet is then necessary. The current state of evidence on UEDVT is rather poor, due to the absence of large randomized controlled trials.

Keywords: Venous thromboembolism; Deep venous thrombosis; Upper extremity; Central venous catheter thrombosis

Case Presentations

Case 1

The nurse from the medical-surgical unit calls the attending physician because she is unable to flush the right arm peripherally inserted central (PICC) line of a 60-year-old female getting intravenous vancomycin. The nurse wonders whether a new PICC line needs to be placed to complete the 5 remaining days of the antibiotic course.

Case 2

A 22-year-old left-handed college student developed left arm swelling while painting her apartment. Overnight, the arm started swelling and the worsening pain brought her to the ER. She is otherwise healthy; her only medication is oral contraceptives.

Introduction

The veins of the upper extremity: deep and superficial

The veins of the upper extremity are responsible for 5% to 10% of the cases of venous thromboembolism (VTE) [1]. A superficial venous thrombosis is the formation of a thrombus in the superficial venous system that includes the cephalic and basilic veins. It is often self-limited. A deep venous thrombosis (DVT) is the formation of a thrombus in the deep venous system, mainly in the brachial, axillary and subclavian veins. It can be lethal. An UEDVT can extend to the brachiocephalic veins and to the superior vena cava, it can embolize to the lungs, and it can lead to long-term disability related to the post-thrombotic syndrome (PTS).

The thoracic outlet is the space confined between the clavicle and the first rib. It can be the site of the compression of various neurologic and vascular structures including the subclavian vein. The clinical manifestations of such compression are grouped under the thoracic outlet syndrome. One of these manifestations is the venous thrombosis of the subclavian vein, usually preceded with repetitive effort of the upper extremity; it is therefore named ‘effort related UEDVT’ or the ‘Paget-Schroetter syndrome’. Internal jugular venous thrombosis is often included in the studies addressing the UEDVT, despite its anatomical location in the neck.

UEDVT classification: Primary vs. Secondary

Table 1: UEDVT classification.

<table>
<thead>
<tr>
<th>Primary classification</th>
<th>Secondary classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minority</td>
<td>Vast majority</td>
</tr>
<tr>
<td>Mainly caused by the Paget-Schroetter syndrome. Less likely idiopathic</td>
<td>Caused by central venous catheters, pacemaker leads or cancer</td>
</tr>
<tr>
<td>Younger patients</td>
<td>Older patients</td>
</tr>
</tbody>
</table>

As shown in Table 1, most cases of UEDVT are secondary. Patients with idiopathic primary UEDVT, when compared to effort related primary UEDVT i.e., the Paget-Schroetter syndrome, tend to be older with a female predominance [2].

High and increasing incidence of UEDVT

UEDVT is infrequent in the general population. Its incidence however increases exponentially when moving to the hospital setting,
mainly the intensive care unit (ICU) (Table 2). The incidence of UEDVT is on the rise and parallels the increase in PICC line use.

### Table 2: Incidence of UEDVT.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Yearly Incidence</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population, Sweden</td>
<td>0.0036%</td>
<td>Isma, N., et al. (2010). (3)</td>
</tr>
<tr>
<td>Medical inpatients admissions</td>
<td>0.14%</td>
<td>Winters, J. P., et al. (2015)(5).</td>
</tr>
<tr>
<td>Hospital discharges</td>
<td>1.15%</td>
<td>Khanna, R., et al. (2014)(6).</td>
</tr>
<tr>
<td>ICU, secondary and tertiary</td>
<td>2.2%</td>
<td>Lamontagne, F., et al. (2014)(7).</td>
</tr>
</tbody>
</table>

**UEDVT vs. Lower extremity DVT (LEDVT): same mortality**

Despite a lower rate of pulmonary embolism (PE) on presentation, patients with UEDVT compared to LEDVT had similar mortality outcomes in the RIETE registry [8] and in the review of the medical records of all the residents of Worcester, MA [4]. Smaller studies showed even worse mortality outcomes with UEDVT(9), and estimated the UEDVT mortality rate as 5.4 times (4.2 to 7 CI 95%) higher than the age and sex adjusted population mortality rate [10].

Note that patients with UEDVT tend to be younger and slimmer than LEDVT patients [11,12].

**Critical appraisal of the literature**

Pubmed.gov was researched for articles published before October 15, 2015, using the keywords "deep venous thrombosis or it’s abbreviation ‘DVT’ or venous thromboembolism or it’s abbreviation ‘VTE’ or thrombophlebitis AND upper extremity” as well as “central line thrombosis” and “central venous catheter or it’s abbreviation ‘CVC’ thrombosis”. Filters that were used: articles in English, full text, cost, as shown in a prospective study of 70 patients undergoing chemotherapy for non-hematological malignancies [24]. The incidence of UEDVT is in the single digit (around 2%) in most studies (appendix 2).

Most articles unique to the pediatric population were later removed unless the data could be extrapolated to the adult cases. Clinicaltrials.gov was researched for ongoing trials. The Agency for Healthcare Research and Quality (AHRQ) and the Joint commission websites were used for info about the Patient Safety Indicator (PSI) #12 and the VTE core measure.

The review of the literature points toward many small prospective and retrospective studies addressing the risk factors for UEDVT. Major randomized controlled trials addressing the therapy and prophylaxis of UEDVT are lacking. Guidelines are often extrapolated from trials done on LEDVT. The 2012 American College of Chest Physicians (ACCP) guidelines [1] rate the current quality of evidence as being ‘at best, moderate’.

**Etiology and Pathophysiology**

Central venous catheters (CVC) notably PICC lines and malignancy are the main causes of secondary UEDVT. The thoracic outlet syndrome is the main cause of primary UEDVT.

**Central venous catheters and pacemaker leads**

CVC (subclavian, internal jugular, PICC lines, Hickman catheters etc.) or pacemaker leads placement is the strongest independent predictor of UEDVT. UEDVT cases were, in a case-control study, 1136 times more likely to have a CVC compared with control subjects with no UEDVT [13]. Patients with a CVC were, in a prospective registry, 7.3 (CI 5.9 to 9.2, 95%) times more likely to get an UEDVT than non-CVC patients [12]. The percentage of UEDVT that is associated with a CVC or pacemaker leads varies between studies but is usually higher than 50% (appendix 1).

The incidence of CVC thrombosis varies greatly between studies. It tends to be higher whenever systematic imaging is performed. Thirty-three percent of screened catheters in an ICU [14] and 56% of screened cardiac surgery patients [15] had an UEDVT. Numbers are more modest (below 10%) when only symptomatic cases are accounted for [16,17].

The infusion of veno-toxic substances like chemotherapy and vancomycin [18] tends to cause more UEDVT compared to the infusion of veno-toxic ones like parenteral nutrition.

**PICC lines**

The risk of UEDVT associated with PICC line insertions is high and worse than non-peripherally inserted central lines [19,20]. UEDVT is responsible for the removal of 2 to 3% of placed PICC lines [21,22]. The incidence of PICC associated UEDVT varies drastically between studies (<1% to >70%; appendix 2). The number of PICC lines that are placed is so high, that even in studies with low incidence of PICC line associated UEDVT, a significant portion of all UEDVT is still due to PICC lines: in Liem, T.K, et al. 35% of all UEDVT were caused by PICC lines, despite a low incidence of 2.6% [23].

**Subcutaneously implanted port-chamber catheters**

Cause less thrombosis than PICC lines with no significant increased cost, as shown in a prospective study of 70 patients undergoing chemotherapy for non-hematological malignancies [24]. The incidence of UEDVT is in the single digit (around 2%) in most studies (appendix 3).

**Hickman Catheters**

A retrospective study comparing PICC lines to Hickman catheters in acute myeloid leukemia showed a much better thrombotic profile with the Hickman catheter: 48.2% with PICC lines versus 3.2% with Hickman catheters [25]. Higher thrombosis rate (17%, some upon autopsy) was found in a study of 168 patients with solid tumors, particularly patients with lung adenocarcinoma [26].

**Pacemaker leads**

Pacemaker leads Venography, in a prospective study, was abnormal in 64% of the 202 patients. Patients with low ejection fraction or a previous temporary pacemaker were identified as risk factors [27].

**Malignancy**

Malignancy was the only independent predictor of the incidence of non-leg deep venous thrombosis in a prospective cohort of 3746 ICU patients [7]. Occult malignancy was found in 23.7% of cases of UEDVT compared with 11.1% of the cases of LEDVT in a study of 343
consecutive patients with DVT [28]. The mortality of patients with UEDVT is high, mainly because of its association with cancer. In the Malmö thrombophilia study, 24% of the patients with UEDVT died during Follow up and mortality was as high as 47% in patients with known malignancy [3]. Cancer patients with UEDVT in the RIETE registry had worse outcomes [8].

Other risk factors

Aside from CVC and malignancy, there are other risk factors for UEDVT: chronic kidney disease [29,30], hormone therapy [3], obesity [13] and infection or sepsis [31-33]. The relation between CVC thrombosis and infection goes both ways since a thrombosed CVC is a risk factor for CVC related sepsis [14].

Hereditary thrombophilia has less impact in UEDVT compared to LEDVT [11,34,35], especially in CVC-induced UEDVT(36). The rate of thrombophilia in UEDVT has been addressed in small studies. It ranges between 6 to 9% [37] to 42% in a series of cases of primary UEDVT [2].

Special risk factor: the thoracic outlet syndrome in the Paget-Schroetter syndrome

MRI imaging of the costoclavicular distance was significantly narrower in patients with primary UEDVT when compared to normal cases [38]. Patients with the thoracic outlet syndrome undergoing first rib resection when compared to cadaveric first ribs, were found to have a bony tubercle at the site of the subclavian vein groove causing extrinsic compression of the subclavian vein at rest [39].

Initial Evaluation (Table 3)

History & physical examination: suspected acute UEDVT

Symptoms are frequently absent. The rate of asymptomatic patients varies widely between studies (12% to 94%) [40-42]. In the absence of symptoms, an UEDVT is diagnosed when a CVC is not functioning appropriately or when imaging is performed for a different reason.

Pain and edema are the predominant clinical symptom and sign of UEDVT. In a series of mostly CVC-associated UEDVT, pain and edema were present in 34% and 84% of the cases respectively [43]. Severe syndromes including the superior vena syndrome and the phlegmasia dolens of the upper extremity have been reported. Thrombosis in the brachiocephalic veins and the superior vena cava was retrospectively estimated to have been diagnosed in 0.03% of the patients; the diagnosis had been preceded with symptomatic PE in more than a third of the cases [44].

The use of the Constans Clinical Prediction score (Table 4) is a simple validated score to clinically predict the risk of a suspected UEDVT.

<table>
<thead>
<tr>
<th>History</th>
<th>Physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Edema, erythema or discoloration of the skin</td>
</tr>
<tr>
<td>Presence of CVC, port or pacemaker</td>
<td>Dysfunction of the CVC, port or pacemaker</td>
</tr>
<tr>
<td>Hormone therapy, malignancy, history of thrombophilic states or previous venous thrombotic event.</td>
<td>Signs of PE: tachycardia, tachypnea, hypoxia.</td>
</tr>
<tr>
<td>Effort (repetitive like painting, volleyball hitter etc) in primary UEDVT</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Elements to consider upon the initial evaluation of (a suspected) UEDVT.

<table>
<thead>
<tr>
<th>Item</th>
<th>Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter or access device in a subclavian or jugular vein or a pacemaker</td>
<td>+1</td>
</tr>
<tr>
<td>Unilateral pitting edema</td>
<td>+1</td>
</tr>
<tr>
<td>Localized pain</td>
<td>+1</td>
</tr>
<tr>
<td>Other diagnosis at least as plausible</td>
<td>-1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Prevalence of UEDVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1 or 0</td>
<td>Low (9 to 13%)</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate (20 to 38%)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>High (64 to 70%)</td>
</tr>
</tbody>
</table>

Table 4: The Constans Clinical Prediction Score [45].

History & physical examination: suspected post-thrombotic syndrome (PTS)

The PTS, a long-term complication of DVT, is due to symptomatic venous insufficiency. It is thought to occur in around 20% of the patients [1] but the incidence varies considerably between studies (6% to 44%) [9,46,47]. The severity of the syndrome is often assessed with the Villalta scoring system that has been validated for the lower extremity [48] (Table 5).
Intravenous contrast. Compression ultrasonography is indeed the first line diagnostic study, with a sensitivity and specificity estimated at 97% and 96% respectively in a systematic review of 9 studies [50]. The sensitivity and specificity did interestingly not improve with the addition of Doppler. The risk of false negative ultrasound increases in the proximal subclavian [51] given its anatomical location.

Ddimer in a series of 52 consecutive patients, of whom 23 had cancer, had a sensitivity of 100% (95% CI, 78–100%) and a specificity of 14% (95% CI, 4–29%) [52]. The lab might therefore be valuable to the screening of unlikely UEDVT, similar to its usage in the diagnosis of LEDVT [58], the correct positioning of the tip of a CVC [59], the removal of a thrombosed CVC line placement [61] were shown to decrease the risk of UEDVT.

Non-pharmacological prophylaxis of CVC- associated UEDVT

The preferential usage of smaller gauge and single lumen PICC lines, the correct positioning of the tip of a CVC, the removal of a CVC as soon as clinically possible [60] and the usage of ultrasound for PICC line placement [61] were shown to decrease the risk of UEDVT. The laterality of a CVC is most likely not a risk factor of UEDVT [62,63], despite the presence of some contradictory evidence [59].

Pharmacological prophylaxis of CVC associated UEDVT has shown contradictory results in different studies (Appendix 4 and Appendix 5) and is therefore not recommended for routine universal usage. It might be beneficial in the subgroup of cancer patients with a CVC as shown in a Cochrane database review [64].

CVC prophylaxis with the infusion of low dose anticoagulant or with the usage of anticoagulant-coated CVC has been studied in the pediatric population with mixed results [65-71]. More data is needed.

Treatment of UEDVT (Table 6):

The removal of a thrombosed CVC

The Removal of a thrombosed CVC is not only a prophylactic measure but a therapeutic one too. It was shown to significantly decrease the clot size on ultrasound [72,73]. A CVC does however not need to be removed if the UEDVT occurs in association with a functioning and clinically needed CVC.

If the catheter is no longer required or is not functioning and cannot be made to function it should then be removed (ACCP guidelines 2012, grade 2 C) [1]. This was also shown in a small prospective study of 27 children [74].

Fibrinolytics to restore the flow of a thrombosed CVC

Different fibrinolytics including tenecteplase [75], recombinant urokinase [76,77], reteplase [78], and alteplase [79-81] were found to be beneficial in the subgroup of cancer patients with a CVC as shown in a Cochrane database review [64].

Table 5: Symptoms and signs of the post-thrombotic syndrome as in the Villalta scoring system.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Edema</td>
</tr>
<tr>
<td>Cramps</td>
<td>Skin induration</td>
</tr>
<tr>
<td>Heaviness</td>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>Redness</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Venous ectasia</td>
</tr>
<tr>
<td></td>
<td>Pain on calf compression</td>
</tr>
<tr>
<td></td>
<td>Venous ulcer implies severe PTS</td>
</tr>
</tbody>
</table>

Patients with idiopathic UEDVT tend to be young. The PTS can severely affect their quality of life. Data however shows that the overall quality of life after treatment is satisfactory [49].

Diagnostic Studies

Data is extremely limited. The extrapolation from LEDVT studies is challenging given the different anatomy of the UE where a portion of the deep venous system runs under the clavicle.

Duplex ultrasound

Contrast venography is the gold standard diagnostic test. It is not recommended as a first line diagnostic study given the need for intravenous contrast. Compression ultrasonography is indeed the first line diagnostic study, with a sensitivity and specificity estimated at 97% and 96% respectively in a systematic review of 9 studies [50]. The sensitivity and specificity did interestingly not improve with the addition of Doppler. The risk of false negative ultrasound increases in the proximal subclavian [51] given its anatomical location.

Ddimer in a series of 52 consecutive patients, of whom 23 had cancer, had a sensitivity of 100% (95% CI, 78–100%) and a specificity of 14% (95% CI, 4–29%) [52]. The lab might therefore be valuable to the screening of unlikely UEDVT, similar to its usage in the diagnosis of LEDVT.

Others imaging modality

A chest X-ray is an appropriate first test when suspecting the thoracic outlet syndrome. It is a cheap and a safe modality to detect bone abnormalities [53]. Magnetic Resonance (MR) venography is difficult for the patients [54], yet appropriate for the diagnosis of the thoracic outlet syndrome [53]. Computerized Tomography (CT) venography and contrast venography are occasionally used too.

Diagnostic algorithm

A recently published prospective multicenter study [55] showed that an algorithm combining clinical decision score (the Constans Clinical decision score Table 4), Ddimer and ultrasonography is safe and effective. If confirmed in other studies the algorithm has the potential of becoming standard of care.

The 2012 ACCP guidelines had anyway recommended, with a grade 2C, further testing using Ddimer, serial ultrasonography or venographic based imaging (traditional, CT or MR) whenever the first the clinical suspicion is high but the initial ultrasound is negative [1].

Differential Diagnosis

Superficial venous thrombosis can cause similar symptoms as UEDVT but its risk of complications including PE is very rare. The evidence behind the treatment is limited and of low quality [56]. Treatment is usually symptomatic (anti-inflammatory medications, warm compresses etc.). Unlike the superficial venous thrombosis of the lower extremity, there is no clear indication for anticoagulation. Anticoagulation might however have a role in selected cases, for example when the thrombus is extensive or close to the deep venous systems.

Non-thrombotic causes of UE edema and discoloration include the cellulitis of the UE. It also includes cases of malignant invasion or compression of the venous system by UE or chest tumors. The McLeod syndrome is a rare non-thrombotic intermittent compression of the subclavian vein causing periodic arm swelling and discoloration [57].
be effective, safe and cost-effective in restoring the flow of a thrombosed CVC.

Anticoagulation

As previously stated, the evidence behind the effectiveness of anticoagulation is mainly inspired from LEDVT randomized controlled trials. Rare small retrospective or prospective observational studies address anticoagulation for the UEDVT [82,83].

<table>
<thead>
<tr>
<th>Indication and Recommendation</th>
<th>Grade</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial parenteral anticoagulation</td>
<td>1B</td>
<td>Low-molecular weight heparin or fondaparinux suggested over unfractionated heparin that is intravenous (2C) or subcutaneous (2B).</td>
</tr>
<tr>
<td>Anticoagulation alone without thrombolysis</td>
<td>2 C</td>
<td>Intensity and duration of anticoagulation unchanged if initial thrombolysis (1B)</td>
</tr>
<tr>
<td>Anticoagulation of minimum 3 months</td>
<td>2B</td>
<td>3 months sufficient if: no cancer &amp; not CVC related (1B); CVC removed whether the patient has cancer (2C) or not (1B)</td>
</tr>
<tr>
<td>Thrombosed CVC: Not removing if functioning &amp; needed</td>
<td>2C</td>
<td>Extend the duration of anticoagulation (beyond 3 months) until the CVC is removed, whether the patient has cancer (1C) or not (2C)</td>
</tr>
<tr>
<td>Symptomatic therapy of the PTS: sleeves, compression bandages</td>
<td>2C</td>
<td>Recommendation against the use of compression sleeves or venoactive medications for PTS prevention (2C)</td>
</tr>
</tbody>
</table>

Table 6: Therapy of acute UEDVT: ACCP 2012 guidelines [1].

Despite the guidelines recommending anticoagulation for the treatment of UEDVT, studies have repeatedly shown that many patients with UEDVT do not receive anticoagulation: 56% of 300 cases in a peripheral vascular lab [40] and 20% of 94 cases in an academic center [84]. A bleeding risk was not frequently documented in the patients who did not receive anticoagulation.

Endovascular therapy (thrombolysis, thrombectomy, and stenting) should be used in selected cases only.

Thrombolysis Small retrospective studies have shown that catheter directed thrombolysis [85,86], mechanical thrombectomy [87], and techniques using both mechanical and catheter directed thrombolysis [88-90], were safe, with varying levels of effectiveness. The 2012 ACCP guidelines recommend thrombolysis in patients who fulfill the current criteria: severe and recent symptoms, extensive thrombus, low bleeding risk, and good functional status and life expectancy [1].

Superior vena cava filter placement for patients with contraindication to anticoagulation can be used off-label. Its safety and effectiveness were demonstrated in small studies in which the procedure related complication rate (misplacement or migration of the filter, caval occlusion, pneumothorax, pulmonary embolism) was low. The overall mortality rate was high given the patients' comorbidities [91,92].

Decompression surgery in the thoracic outlet syndrome: First rib resection with scalenectomy decompresses the thoracic outlet. It was found in small studies to decrease the long-term disability related to the PTS. Delay in surgery was associated with worse outcomes [93-96].

Special circumstances/population

Screening of asymptomatic upper extremities was shown to be ineffective [97] and is therefore not indicated.

An UEDVT distal to the axillary vein i.e. in the brachial vein has a probably lower risk of complications compared to an UEDVT at or central to the axillary vein. Anticoagulation might cause an unjustified risk of bleeding. Clinical or ultrasound surveillance to detect the extension of the UEDVT, prophylactic anticoagulation, or shorter duration of anticoagulation (less than 3 months) might be acceptable alternatives. The ACCP favors anticoagulation in cases that are symptomatic, associated with a central line that will remain in place, or associated with cancer in the absence of central venous lines, all in the absence of a bleeding risk [1].

When to get a thrombophilic work-up?

UEDVT is less associated with hereditary thrombophilia than LEDVT. Studies have tried to identify subgroups of patients in whom testing might be cost effective and would result in the extension of the anticoagulation duration. In women taking oral contraceptives, a synergistic association between primary UEDVT and hereditary thrombophilia, mainly prothrombin G20210A, was found in 2 case-control studies [37,98].

Patients with upper & lower extremity DVT

The coexistence of upper and lower extremity is high: 21% of the 211 patients diagnosed with UEDVT were positive for acute LEDVT on ultrasound [99]. An earlier small study by the same authors had showed that patients with a combined upper and lower extremity DVT had higher mortality, despite the same risk of PE, probably due to more severe illness [100].

Post-shoulder replacement UEDVT

Contrary to previous data [101], recent data, including results from the RECONS registry[102], is reporting very low (less than 1%) post-shoulder replacement VTE [103,104]. Systematic VTE prophylaxis is therefore not recommended after shoulder replacement and should be reserved for selected cases only.
Quality Improvement and Cost-effective Strategies

Prevention of hospital-acquired VTE has been the focus of different quality groups and societies, given its high mortality, morbidity and financial burden. The VTE core measure [105] and the Patient Safety Indicator (PSI) # 12 [106] are the main public quality metrics that are now reported by most hospitals. In a level-one trauma center, the introduction of smaller triple lumen and the preferential usage of single lumen PICC lines decreased the risk of UEDVT. Each prevented event saved $15973 and avoided a 4.6 days increase in the length of stay [58]. The introduction of a process that standardized the requests for PICC lines in McGill University Centre lead to an overall savings of approximately 1.1 Million in around 8 months [107].

Controversies and Cutting Edge

The New Oral Anticoagulants are currently being used for the treatment of UEDVT, by extrapolation from their use in the therapy of LEDVT. They however need to be studied in the treatment (and prophylaxis) of UEDVT. Currently, one ongoing study is addressing the problem: A Pilot Study in Cancer Patients With Central Venous Catheter Associated Deep Vein Thrombosis in the Upper Extremity Treated With Rivaroxaban (Catheter 2) http://ClinicalTrials.gov/show/ NCT01708850.

Prophylaxis: While pharmacological prophylaxis is not currently indicated to prevent CVC associated UEDVT, many studies show benefit, especially in high-risk patients, mainly cancer patients. Further studies will be needed to identify subgroups in which prophylaxis is indicated.

Treatment: Major randomized controlled trials in the treatment of UEDVT are needed, as the extrapolation from lower extremity DVT data might not be accurate.

Summary

UEDVT is to be taken as seriously as lower extremity DVT given its frequency and high mortality.

CVC are the main risk factor. Appropriate ordering and usage of CVC are keys for UEDVT prevention.

Primary UEDVT, mainly due to the Paget-Schroetter syndrome is infrequent. Upon diagnosis, a surgery referral is primordial in preventing future disability.

Despite the poor data, anticoagulation of acute UEDVT is indicated.

Research is needed in the areas of prophylaxis and treatment, including the role of the new oral anticoagulants.

Case Conclusions

Case 1

Upon evaluation, the patient denied pain in the right upper extremity. On examination, she had normal vitals and no edema, erythema or tenderness of the right upper extremity. The attending physician ordered an ultrasound of the extremity. He asked the nurse to flush the line with t-PA (alteplase). The t-PA restored the function of the line. The ultrasound showed an acute thrombus of the brachial and axillary veins.

The attending physician considered starting an oral direct factor Xa inhibitor but he ended up choosing enoxaparin as a bridge to warfarin, given the lack of trials supporting the use of the new oral anticoagulants in the treatment of UEDVT. He asked the nurse not to pull the PICC line since it is functioning and clinically needed for 5 more days. He planned on reminding his colleague upon sign out to pull the line as soon as the intravenous antibiotherapy was finished. He notified the patient's primary care physician about the plan to continue the warfarin for 3 months.

Case 2

The patient was not febrile and did not have an elevated white count. The ER team suspected an UEDVT and ordered an ultrasound that came back normal. She was therefore admitted to the hospital for antibiotic therapy of a possible cellulitis. More than 24 hours later, there was no improvement. The Hospitalist team was concerned about a falsely negative initial ultrasound. Ddimer level was checked and was found to be markedly abnormal. A repeat ultrasound this time revealed a small subclavian thrombus.

A heparin drip was immediately started. Vascular surgery recommended against thrombolysis given the lack of convincing data about its usefulness in preventing the post-thrombotic syndrome, especially when the thrombus is small. The Paget-Schroetter syndrome was suspected so the Hospitalist team called thoracic surgery. A hematology specialist discussed with the patient the potential benefit of getting a thrombophilic work-up based on small studies showing higher levels of thrombophilia in women getting a primary UEDVT while on oral contraceptives.

References


### Appendix 1: Percentage of patients with UEDVT that is associated with central lines or leads.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>% UEDVT line related</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mino, J. S., et al. (2014)</td>
<td>Retrospective</td>
<td>1857</td>
<td>95.20%</td>
<td>General surgery cases</td>
</tr>
<tr>
<td>Malinoski, D. J., et al. (2011)</td>
<td>Prospective</td>
<td>129</td>
<td>64%</td>
<td>Surgical ICU, screening with ultrasound</td>
</tr>
<tr>
<td>Munoz, F. J., et al. (2005)</td>
<td>Prospective</td>
<td>512</td>
<td>45%</td>
<td>Symptomatic, no systematic screening</td>
</tr>
<tr>
<td>Blom, J. W., et al. (2005)</td>
<td>Retrospective</td>
<td>179</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Hingorani, A., et al. (2005)</td>
<td>Retrospective</td>
<td>546</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Kooij, J. D., et al. (1997)</td>
<td>Retrospective</td>
<td>78</td>
<td>53%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Number of patients or PICC lines</th>
<th>UEDVT incidence</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin, R. E., et al. (2015)</td>
<td>Retrospective</td>
<td>53 patients</td>
<td>5.50%</td>
<td>Hospitalized burn patients</td>
</tr>
<tr>
<td>Chopra, V., et al. (2014)</td>
<td>Retrospective</td>
<td>966 PICC</td>
<td>3.4%, symptomatic</td>
<td>Risk factors: recent cancer diagnosis; PICC gauge</td>
</tr>
<tr>
<td>Itkin, M., et al. (2014)</td>
<td>Prospective</td>
<td>332 patients</td>
<td>71.90%</td>
<td>Systematic screening</td>
</tr>
<tr>
<td>Leroyer, C., et al. (2013)</td>
<td>Prospective</td>
<td>267 PICC</td>
<td>2.50%</td>
<td>Only 9% of lines used for chemotherapy</td>
</tr>
<tr>
<td>Ahn, D. H., et al. (2013)</td>
<td>Retrospective</td>
<td>237 Patients</td>
<td>15%</td>
<td>Cancer patients</td>
</tr>
</tbody>
</table>
Appendix 2: Incidence of PICC line associated UEDVT.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Number of patients or ports</th>
<th>Incidence of UEDVT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dal Molin, A., et al. (2012)</td>
<td>Prospective</td>
<td>80 patients</td>
<td>1.3%</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Kriegel, I., et al. (2011) [127]</td>
<td>Non Randomized trial</td>
<td>273 ports on and 4196 ports not on bevacizumab</td>
<td>1.5% bevacizumab group; 1.2% control group</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>Yukisawa, S., et al. (2010) [128]</td>
<td>Prospective</td>
<td>92 patients</td>
<td>73%; only 3% causing obstruction of venous flow</td>
<td>Chemotherapy for colorectal cancer, serial ultrasounds</td>
</tr>
<tr>
<td>Lyon, R. D., et al. (1999) [129]</td>
<td>Retrospective</td>
<td>204 patients</td>
<td>2.7%</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Biffi, R., et al. (1997) [130]</td>
<td>Prospective</td>
<td>175 patients</td>
<td>1.12%</td>
<td>Cancer patients</td>
</tr>
</tbody>
</table>

Appendix 3: Incidence of Port associated UEDVT.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prophylaxis used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavau-Denes, S., et al. (2013) [131]</td>
<td>Low-molecular weight heparin, warfarin</td>
</tr>
<tr>
<td>Brismar, B., et al. (1982) [133]</td>
<td>Prophylactic dose of IV heparin</td>
</tr>
</tbody>
</table>

Appendix 4: Studies showing a favorable outcomes of chemoprophylaxis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Warfarin, Low-molecular weight heparin, unfractionated heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marnelijn, T., et al. (2012) [29]</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Treatment</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Couban, S., et al. (2005) [139]</td>
<td>1 mg warfarin</td>
</tr>
</tbody>
</table>

**Appendix 5:** Studies not showing a favorable outcome of chemoprophylaxis.