Treatment of
Thrombophlebitis

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No Financial Disclosures
Anatomy – LE Superficial Veins

Superficial Phlebitis. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2009
Pathophysiology of Venous Thrombosis

Virchow’s Triad

- Stasis
  - Immobilization
  - Limb paralysis
    - (stroke, plaster cast, spinal cord injury)
  - Heart failure
- Varicose vein or chronic venous insufficiency
Pathophysiology of Venous Thrombosis

Virchow’s Triad

- Intimal injury
  - Direct vessel injury
    - Surgery
    - Central venous catheter
    - Trauma
  - Indirect vessel injury
    - Chemotherapy
    - Vasculitis
    - Sepsis
    - Hyperhomocysteinemia
Pathophysiology of Venous Thrombosis

Virchow’s Triad
- Hypercoagulable State
  - Hereditary
    - Factor V Leiden
    - Prothrombin gene mutation
    - Antithrombin III deficiency
    - Protein C
    - Protein S
  - Acquired
    - Malignancy
    - Hormone replacement therapy
    - Anticardiolipin antibodies
    - Nephrotic syndrome
Natural History (Flowchart)

- Extension
- Resolution
- Pulmonary embolism
- SVT
- Resolution
- Ongoing resolution
- Recurrence
Superficial Thrombophlebitis

- Importance
  - underestimated!!
  - Although it causes significant discomfort
    - Benign and self-limiting

- Literature Review
  - 1-40% Progress to DVT
    - 11%
  - 0-17% Progress to Pulmonary Embolus
    - 2%
SVT Association with VTE

- 6-53% coexistence with DVT
- 2.6-15% propagation to DVT
- 20-33% coexistence with asymptomatic PE
- 2-13% symptomatic PE

Eur J Vasc Endovasc Surg 2005;29:10-17.
Cochrane Database of Systematic. Reviews 2007;Issue 2:Art #CDOO4982
SVT and Malignancy

- Literature review looking at vascular disorders preceding a diagnosis of cancer found an association between STP and malignancy suggesting a causal link.
- SVT involving the legs in 106 limbs
  - Malignancy in 14 cases (13%)
  - 3 of the 14 cancers were diagnosed after SVT.
- SVT involving GSV or LSV in 398 pts
  - Ascending thrombosis in 56
  - 10 of these (18%) had malignancy.

SVT and Hypercoagulability

- Association with hypercoagulable state in absence of varicose veins, autoimmune disease, malignancy
  - Factor V Leiden OR = 6
  - Prothrombin mutation OR = 4
  - Deficiency of AT, prot C, prot S OR = 13
- Anticardioliopin Ab associated with recurrent SVT
- Multiple small studies suggest an association between hypercoagulable states and SVT, especially when the saphenous trunk is involved

Superficial Thrombophlebitis

- Associated with Thrombophilias
  - 35%
- Associated with Varicose Veins
  - 50-93%
- All patients should undergo Duplex scanning once diagnosis suspected
  - To confirm diagnosis
  - To assess for DVT
Superficial Thrombophlebitis:

Etiology

- Traumatic Thrombophlebitis
  - Direct injury
  - Tender cord along the course of the vein
Superficial Thrombophlebitis: *Etiology*

- **Varicose Veins**
  - May be antecedent to DVT
  - May occur after trauma
  - Most commonly due to stasis
  - Presents
    - Woody induration
    - Tender hard nodule
Superficial Thrombophlebitis: Etiology

Thrombophlebitis and Infection

- DeTakats 1932, Altemeier 1969
- Potentially lethal complication
  - S aureus
  - Pseudomonas
  - Klebsiella
  - Peptostreptococcus
  - Propionibacterium
  - B fragilis
  - Prevotella
  - Fusobacterium
  - Fusarium proliferatum
- 1/3 cause Septicemia

HIGH INDEX OF SUSPICION in FUO
Superficial Thrombophlebitis: 

Etiology

Migratory Thrombophlebitis
- Jadioux 1845
- Trousseau 1856
  - Trousseau’s syndrome
    - Pancreatic Cancer
- Polyarteritis nodosa
- Buerger’s disease
- DDX:
  - Erythema nodosum
  - Erythema induratum
  - Behcet’s disease
Superficial Thrombophlebitis: Etiology

Mondor’s Disease: Thrombophlebitis of Superficial Veins of the Breast
   - Anterolateral portion of upper breast
   - Lower breast into epigastrium
   - Cordlike structure palpable
   - Etiologies:
     - s/p breast surgery
     - Oral contraceptive use
     - Hereditary protein C deficiency
     - Presence of anticardiolipin antibodies
Superficial Thrombophlebitis: 

**Etiology**

Unusual Forms

- Penile (Dorasl Vein) Mondor’s Disease
  - Prolonged excessive intercourse
  - Hernia operations
  - Extension of Pelvic DVT
Superficial Thrombophlebitis: Treatment

- **Infusion Thrombophlebitis**
  - Diclofenac oral (75mg bid)
    - 60% vs 20% at 48h (p=0.0001)
  - Diclofenac topical (tid)
    - 60% vs 20% at 48h (p=0.0001)
  - Heparin gel (1000IU/g)
    - 44% vs 26% at 7 days (p=0.03)
  - Essaven gel (aescinate, phospholipids, heparin)
    - 66% vs 20% at 14 days (p<0.05)
For patients with symptomatic infusion thrombophlebitis as a complication of IV infusion, we suggest oral diclofenac or other NSAID, topical diclofenac gel, or heparin gel until resolution of symptoms for up to 2 weeks.

We recommend against systemic anticoagulation.
Superficial Thrombophlebitis: *Treatment*

‘Simple’ Thrombophlebitis
- Superficial, highly localized, mildly tender area, away from main saphenous vein
  - Aspirin and elastic support
- Associated with varicosities or when symptoms persist
  - Phlebotomy or excision of vein speeds recovery
Superficial Thrombophlebitis: Treatment

‘Extensive’ Thrombophlebitis
- Severe pain, redness, brawny induration
- Bed rest, elevation, warm wet compress
Superficial Thrombophlebitis: *Treatment*

- ‘Extensive’ Thrombophlebitis
  - Short Duration (8-12 days) Heparin, LMWH, NSAIDs
    - Enoxaparin 40mg SC daily
      - 8.3% @ 12 days, 14.5% @ 90 days
    - Enoxaparin 1.5mg/kg SC daily
      - 5.7% @ 12 days, 15.5% @ 90 days
    - Tenoxicam 20mg PO daily
      - 13.1% @ 12 days, 15.2% @ 90 days
    - Placebo
      - 29.5% @ 12 days, 33.0% @ 90 days
NSAIDS in Addition to LMWH For Symptom Management?

- 50 pts with SVT involving the GSV randomized to therapeutic nadroparin (190 anti-Xa IU/kg qd) OR nadroparin and acemetacine 60mg bid
- Duration of treatment 10 days
- No major complications in either group
- Significant reduction in pain and local tenderness with acemetacine

Phlebology 2009;24(2):56-60
Superficial Thrombophlebitis: Treatment

‘Extensive’ Thrombophlebitis

- Longer Courses of Heparin or LMWH
  - 4 week unmonitored course in GSV thrombosis
    - 12,500 IU bid for 1 week, 10,000 bid
      - 3.3% @ 6 months
    - Low dose SC Heparin (5000 IU bid)
      - 20% @ 6 months
Consensus Recommendation

For patients with spontaneous superficial vein thrombosis, we suggest *prophylactic or intermediate doses of LMWH* or intermediate doses of UFH for at least 4 weeks. As an alternative, Vitamin K therapy (target INR 2.5, range 2.0-3.0) can be overlapped with 5 days of UFH/LMWH and continued for 4 weeks.

We recommend medical treatment with anticoagulants over surgical treatment.
Take Home Points

Infusion thrombophlebitis and varicose vein thrombosis are generally benign and do not require systemic treatment.

Superficial venous thrombosis near the saphenofemoral junction has a significant risk of extension or recurrence:
- Systemic anticoagulants are generally indicated and are preferred over surgical treatment.
- Duration of therapy should probably be at least 4 weeks.
- Optimal dosing is unclear.
Initial Therapy for Acute DVT

- Recommend that patients receive anticoagulants as soon as the diagnosis of DVT is confirmed.

- Interim treatment should be started if suspicion is high and confirmation is delayed.
## Guidelines for Initial Treatment

<table>
<thead>
<tr>
<th>CLINICAL SITUATION</th>
<th>RECOMMENDED TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed acute DVT of the leg</td>
<td>Options: SC LMWH, IV UFH, or SC UFH</td>
</tr>
<tr>
<td>High suspicion of DVT of the leg</td>
<td>Anticoagulants, while awaiting the outcome of diagnostic tests</td>
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Initial UFH or LMWH Therapy

IV UFH

- Continuous infusion (bolus 80U/kg or 5000U followed by initial infusion of 18U/kg/h or 1300U/h)
- Adjust dosage to prolong the APTT to a range that corresponds to a plasma heparin level of 0.3 to 0.7 IU/mL antifactor Xa activity by amidolytic antifactor Xa assay
- If therapeutic levels of APTT are not reached despite large daily doses of UFH: measure antifactor Xa levels for dosage guidance
Initial UFH or LMWH Therapy

- **SC UFH**
  - SC UFH is an alternative to IV UFH; initial dose 17,500 U/12h or 250U/kg/12h, then maintain the APTT within therapeutic range

- **SC LMWH**
  - Recommend initial treatment with SC LMWH qd or bid, over UFH, as outpatient therapy if possible, as inpatient therapy if necessary
  - Recommend **against** routinely monitoring antifactor Xa levels
  - Treat until INR >2.0 for 24 hours
Initial Warfarin Therapy

- Starting Warfarin at a dose of 5mg, compared to 10mg, is associated with less excessive anticoagulation.
- Start at 10mg in younger (<60 years), otherwise healthy outpatients, and at 5mg in older and hospitalized patients.
Systemic Thrombolysis as Initial Therapy

- IV Thrombolysis
  - Recommend **Against** Routine Use
Catheter Directed Thrombolysis

- Recommended in ‘Extensive Acute Proximal DVT’
  - Iliofemoral or Axillosubclavian DVT
- In ‘Selected’ patients
  - Symptoms for < 14 days
  - Good functional status
  - Life expectancy > 1 year
  - Low risk of bleeding
- “Can reduce symptoms and post-thrombotic morbidity if appropriate expertise is available”
“After successful CDT, we suggest correction of underlying venous lesions using balloon angioplasty and stents.”

Recommend pharmacomechanical (with inclusion of thrombus aspiration and/or fragmentation) thrombolysis in preference to CDT
Immobilization?

- **Early Ambulation**
  - When feasible
Long-term Therapy for DVT

First DVT episode, secondary to a transient (reversible) risk factor
  – VKA therapy for 3 months

First episode of idiopathic DVT
  – Proximal
    ▪ 6-12 months
    ▪ If no risk factors for bleeding and can monitor
      – → indefinite
  – Distal
    ▪ 3 months
Risk-Stratification for ‘Indefinite Therapy’

- Increases risk in unprovoked DVT
  - More than one episode – RR 1.5
  - Antiphospholipid antibody – RR 2.0
  - Hereditary thrombophilia – RR 1.5
  - Male – RR 1.5
  - Residual thrombus in vein – 1.5

- Protective
  - Calf DVT – RR 0.5
  - (-) d-dimer 1 month after stopping VKA – RR 0.4
  - Asian ethnicity – RR 0.8
Risk-Stratification for ‘Indefinite Therapy’

Increases risk of bleeding
- Older age (esp >75)
- Previous GI bleed (esp. if not assoc w\ rev cause)
- Previous noncardioembolic stroke
- Chronic kidney or liver disease
- Concomitant antiplatelet therapy
- Suboptimal monitoring
Cancer and DVT

- 11% of patients with known cancer will develop DVT/PE
- 3-5% of patients with DVT and PE unprovoked will have previously unknown diagnosis of malignancy at the time DVT is diagnosed.
- DVT/PE is the 2nd leading cause of death in those with malignancy.
- Those with DVT at the time of their cancer diagnosis are more likely to have metastasis of their cancer and have lower overall survival rate.
# Cancer and DVT

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<tr>
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<tr>
<td>DVT and cancer</td>
<td>LMWH for the first 3 to 6 months of anticoagulant therapy</td>
</tr>
<tr>
<td></td>
<td>Recommend giving anticoagulants indefinitely, or until the cancer is resolved</td>
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## Long-term Therapy for DVT

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<td>First DVT episode and either documented antiphospholipid antibodies (APLAs) or two or more thrombophilic conditions, eg, combined factor V Leiden and prothrombin 20210 gene mutation</td>
<td>VKA therapy for 12 months</td>
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<td>Suggest giving anticoagulants indefinitely</td>
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### Long-term Therapy for DVT

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| First DVT episode and any of the following: documented antithrombin deficiency, deficiency of protein C or protein S, factor V Leiden, prothrombin 20210 gene mutation, homocystinemia, factor VIII levels > 90th percentile of normal | VKA therapy for 6 to 12 months  
Suggest continuing treatment indefinitely |
| 2 or more episodes of documented DVT | Suggest continuing treatment indefinitely |
# Initial Therapy for PE: LMWH Or UFH Therapy

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<tr>
<th>CLINICAL SITUATION</th>
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<tr>
<td>Confirmed, non-massive PE</td>
<td>SC LMWH or IV UFH</td>
</tr>
<tr>
<td>High suspicion of PE</td>
<td>Anticoagulants, while awaiting test outcomes</td>
</tr>
<tr>
<td>Coexisting severe renal failure</td>
<td>IV UFH over LMWH</td>
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</table>
### Initial Therapy for PE: Thrombolytic Agents

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<tr>
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<tr>
<td>Most patients</td>
<td>Recommend clinicians <strong>not</strong> use systemic thrombolytic therapy</td>
</tr>
<tr>
<td>Selected patients, <em>eg</em>, hemodynamically unstable patients</td>
<td>Systemic thrombolytic therapy</td>
</tr>
<tr>
<td>Patients receiving thrombolytic therapy</td>
<td>Suggest regimens with a short infusion time over those with a prolonged infusion time</td>
</tr>
</tbody>
</table>
# Initial Therapy for PE: Additional Recommendations

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<tr>
<td>Most patients</td>
<td>Recommend against mechanical approaches. Recommend against pulmonary embolectomy.</td>
</tr>
<tr>
<td>Selected, highly compromised patients (those who are unable to receive thrombolytic therapy, or whose critical status does not allow enough time for infusion)</td>
<td>Mechanical approaches may be used</td>
</tr>
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<td>Pulmonary embolectomy may be used</td>
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**Initial Therapy for PE: Additional Recommendations**

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<td>Patients with a contraindication for, or complication of, anticoagulant treatment; or patients with recurrent thromboembolism, despite adequate anticoagulation therapy</td>
<td>Suggest clinicians place an IVC filter</td>
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# Long-Term Therapy for PE: VKA Therapy

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<td>First episode of PE, secondary to a transient (reversible)</td>
<td>VKA therapy for $\geq 3$ months</td>
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<td>risk factor</td>
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<td>First episode of idiopathic PE</td>
<td>VKA therapy for $\geq 6$ to 12 months</td>
</tr>
<tr>
<td>Concomitant cancer</td>
<td>Consider giving anticoagulants indefinitely</td>
</tr>
<tr>
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<td>Most patients: LMWH for 3 to 6 months; then anticoagulants</td>
</tr>
<tr>
<td></td>
<td>indefinitely, or until the cancer is resolved</td>
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## Long-Term Therapy for PE: VKA Therapy

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<td>First episode of PE, and either documented APLAs or ≥ 2 thrombophilic conditions (eg, combined factor V Leiden and prothrombin 20210 gene mutations)</td>
<td>Treat for 12 months; Suggest giving anticoagulants indefinitely</td>
</tr>
<tr>
<td>First episode of PE, and any of the following: documented antithrombin deficiency, protein C or protein S deficiency, factor V Leiden, prothrombin 20210 gene mutation, homocystinemia, high factor VIII levels (&gt; 90\textsuperscript{th} percentile of normal)</td>
<td>Treat for 6 to 12 months Suggest giving anticoagulants indefinitely</td>
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## Long-Term Therapy for PE: VKA Therapy

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<td>≥ 2 episodes of documented PE</td>
<td>Suggest giving anticoagulants indefinitely</td>
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Postthrombotic Syndrome
aka “Chronic Thrombophlebitis”

- 5% of population
  - 6-7 million people have venous stasis changes
  - 400,000-500,000 have ulcers
- Causes more socioeconomic morbidity than PE
- After DVT, develops in 30%-80%
  - Pain
  - Edema
  - Hyperpigmentation
  - Ulceration
Postthrombotic Syndrome

- Caused by ambulatory venous hypertension
  - Valvular reflux
  - Persistent venous obstruction

- Not inevitable after DVT
  - 31% of involved extremities show no reflux on duplex 1 year after event

- Can we predict who is susceptible
  - Recurrent thrombotic events
  - Long recanalization time
  - Proximal DVT
Postthrombotic Syndrome

Cumulative incidence continues to rise for 20 years after initial episode.
Postthrombotic Syndrome: Prevention

- 30-40 mm HG Compression Stockings
  - Reduce cumulative incidence of PTS at 2 years
  - You would decrease your risk by 70%

Recommendation is for immediate initiation after diagnosis and continuation of therapy for 2 years
- 30-40 mm Hg
Postthrombotic Syndrome without Ulcers

- Severe edema
  - Stockings did not show significant benefit
  - Intermittent pneumatic compression at 40 mm Hg was beneficial
    - Improved symptoms
    - No ulcers
      - *study not powered for ulcers

- Mild edema
  - Elastic compression stockings
Postthrombotic Syndrome with Ulcers

- **Venous Ulcers**
  - Primary venous insufficiency vs. Postthrombotic
  - Postthrombotic limbs
    - Higher venous pressures
    - More likely to have ulceration

- **Treatment**
  - IPC devices if resistant to wound care and compression
  - Surgical treatment of superficial venous reflux
  - Hyperbaric oxygen did not show benefit
  
  *only one study*
Postthrombotic Syndrome with Ulcers

Treatment Venous Ulcers

- Pentoxifylline 400mg po tid
  - Cochrane review of 8 RCT’s
  - In addition to wound care and compression +/- IPC
Postthrombotic Syndrome with Ulcers

Treatment Venous Ulcers

- Rutosides
  - Micronized Purified Flavanoid Fraction (Daflon 500mg)
  - Sulodexide (Sulonex)
    - Reduce capillary permeability
    - Reduce inflammation
    - Improve lymphatic function
    - Improve symptoms
- Recommend addition to local wound care and compression
- RCT’s showed 32% RR reduction for persistent ulcers