



## Post-Thrombotic Syndrome

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### Guideline objectives

- To briefly review the clinical presentation and diagnosis of PTS
- To help identify DVT patients who are at risk of developing PTS
- To review strategies to prevent PTS
- To review treatment of PTS

### Introduction

The post thrombotic syndrome (PTS) is a chronic condition that develops in 20% to 50% of patients after deep venous thrombosis (DVT)<sup>1,2</sup>; it is thus the most common complication of venous thromboembolism (VTE). PTS is not merely a cosmetic or “nuisance” problem. Rather, it is a costly and burdensome condition in terms of dollars spent and effect on quality of life and productivity.

### How does DVT lead to PTS?

When DVT is diagnosed, standard anticoagulant treatment prevents thrombus extension and embolization to the pulmonary arteries, but does not directly lyse the acute thrombus. In most patients, only partial clearance of thrombus occurs and return of normal physiological function of the vein is rare. Even when clot lysis is achieved, permanent damage to venous valves occurs frequently, leading to valve incompetence (reflux). Residual venous obstruction and valvular reflux lead to increased venous pressure (venous hypertension), which results in reduced calf muscle perfusion, increased tissue permeability and the associated clinical manifestations of PTS.

### Clinical presentation of PTS

PTS is termed a “syndrome” because it is associated with groupings of symptoms and clinical signs which may vary from patient to patient. Patients with PTS experience pain, heaviness, swelling, cramps, itching, or tingling in the affected limb. Symptoms may be present in various combinations and may be persistent or intermittent. Typically, symptoms are aggravated by standing or walking and improve with resting, leg elevation and lying down. Signs that may be noted on physical examination of the limb include edema, telangiectasias, hyperpigmentation, eczema, varicose collateral veins and, in severe cases, lipodermatosclerosis and ulceration (**Table 1**).

### How is PTS diagnosed?

- PTS is primarily diagnosed on clinical grounds.
- There is no gold standard laboratory, imaging or functional test that establishes the diagnosis.
- In patients with objectively confirmed prior DVT who have typical PTS symptoms and signs, PTS is usually the correct diagnosis.
- In some patients, it may take a few months for the initial pain and swelling associated with acute DVT to resolve, hence a diagnosis of PTS should be deferred until after the acute phase has passed.
- Many DVT patients develop valvular incompetence but do not have symptomatic PTS. Objective evidence of venous valvular incompetence (e.g. by Doppler ultrasound) may help to confirm the diagnosis of PTS in symptomatic patients, but PTS should not be diagnosed if clinical symptoms are absent.
- The Villalta PTS scale<sup>3</sup> (**Table 2**) has been used in clinical studies to diagnose and grade the severity of PTS.

## Which patients with DVT are at risk of developing PTS?

In general,

- ~60% of patients will recover from a leg DVT without any residual symptoms, ~30% will have some degree of PTS, and ~5% will have severe PTS.
- ~15% of patients with upper extremity DVT develop PTS <sup>4</sup>.
- It is not possible to reliably predict which DVT patients will develop PTS.
- Symptoms of PTS usually occur within the first 6 months, but can occur up to 2 years after the DVT. If a patient has done well for 1/2 - 2 years after DVT it is unlikely that he will develop the PTS.

Specific risk factors <sup>5</sup>

- **Recurrent DVT:** Recurrent ipsilateral DVT increases the risk of PTS as much as 5 to 10-fold, probably by causing further damage to compromised venous valves or by aggravating venous outflow obstruction.
- **Body mass index:** Higher BMI is associated with a greater risk of PTS.
- **Characteristics of initial DVT:** The risk of PTS is probably higher after proximal than distal (calf) DVT, but in some prospective studies distal DVT was associated with high rates of subsequent PTS. Whether DVT is unprovoked or secondary (due to surgery, trauma or cancer) does not influence the likelihood of developing PTS.
- **Quality, intensity, and duration of oral anticoagulation:** Limited data suggest that PTS may be promoted by inadequate initial anticoagulation (e.g. subtherapeutic INR >50% time during first three months of treatment), but not influenced by intensity or duration of long-term anticoagulation.
- **Residual thrombosis on ultrasound:** In recent studies modest (odds ratio <2) or no associations between residual thrombosis and development of PTS were found.
- **Persistent elevation of D-dimer:** In one study, elevated levels of d-dimer measured 3 weeks after withdrawal of oral anticoagulant therapy was a modest risk factor for PTS.
- **Age and sex:** No consistent relationships have been reported between age or sex and the development of PTS.
- **Thrombophilia:** Inherited thrombophilia does not appear to increase the risk of developing PTS.

## Strategies to prevent PTS

### Primary and secondary prevention of DVT

- Appropriate use of thromboprophylaxis to prevent DVT in high risk patients and settings as recommended in evidence-based consensus guidelines <sup>6</sup> will prevent cases of PTS.
- Since ipsilateral DVT recurrence is a risk factor for PTS, preventing recurrent DVT by providing anticoagulation of appropriate duration and intensity for the initial DVT is an important goal <sup>7</sup>.

### Thrombolysis

- Thrombolytic therapy in conjunction with heparin to treat acute DVT leads to higher rates of vein patency and better preservation of valve function than the use of heparin alone.
- Catheter-directed thrombolysis may be safer and more effective than systemic thrombolytic therapy and holds promise as a means of preventing PTS.
- However, as yet, there is no high quality evidence to support the use of thrombolysis to prevent PTS.
- Large, rigorously conducted multicenter controlled trials of standard anticoagulation vs. catheter-directed thrombolysis to prevent PTS are needed.

### Elastic Compression Stockings

- The effectiveness of long term (up to 2 years) use of 30-40 mm Hg knee-length elastic compression stockings (ECS) for the prevention of PTS after proximal DVT has been evaluated in three trials (2 positive, 1 negative). A metaanalysis that pooled these studies reported a 54% relative risk reduction in PTS with use of ECS compared with no stockings <sup>8</sup>.
- It is not known for how long ECS need to be worn, which compression strength is optimal and whether they are of benefit to patients with distal DVT.
- Providing ECS to patients who have residual leg pain or swelling after DVT and continuing them for two years or as long as the patient derives symptomatic benefit is a reasonable approach.
- Knee-length and thigh-length ECS appear to have equal physiologic effects, but the former are easier to apply and more comfortable.

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## Treatment of PTS <sup>9-12</sup>

There are few treatment options for PTS.

- ECS on an as-needed basis may reduce swelling in some patients with mild or moderate PTS.
- Intermittent pneumatic compression units are of benefit for the management of severe, intractable PTS symptoms or severe edema, however these are cumbersome, expensive and there are no data on their long term effects.
- Post-thrombotic venous ulcers are treated with compression therapy, leg elevation and topical dressings but are often refractory to therapy and tend to recur.
- “Venoactive” medications such as aescin or rutosides reduce symptoms of chronic venous insufficiency and in one study, provided short-term improvement of symptoms in patients with PTS. The long-term benefit and safety of these medications have not been evaluated in large controlled trials.
- Surgical treatments for PTS such as venous valve repair or venous bypass have been evaluated primarily in small patient series at single, specialized centers and appear to be of limited value.
- There is no evidence that long-term use of diuretics is effective for the treatment of PTS-related edema

## Summary

PTS is a common, burdensome complication of DVT. Effective, evidence-based treatments for PTS are lacking. Until effective treatments are found, prevention of PTS is the key to reducing its overall impact on patients and society. Preventing DVT recurrence is likely to reduce the risk of PTS. Daily use of graduated ECS after DVT appears to reduce the risk of PTS. As of yet, there is no established role for thrombolysis in preventing PTS.

Table 1. Typical clinical features of the post-thrombotic syndrome

Leg Symptoms	Signs
<ul style="list-style-type: none"> <li>• Heaviness or fatigue</li> <li>• Pain</li> <li>• Swelling</li> <li>• Itching</li> <li>• Cramps</li> <li>• Paresthesia</li> <li>• Bursting pain</li> <li>• Symptom pattern: Worse with activity, standing, walking; better with rest, recumbency</li> </ul>	<ul style="list-style-type: none"> <li>• Edema</li> <li>• Peri-malleolar telangiectasiae</li> <li>• Venous ectasia, varicose veins</li> <li>• Hyperpigmentation</li> <li>• Redness</li> <li>• Dependent cyanosis</li> <li>• Lipodermatosclerosis</li> <li>• Healed or open ulcer</li> </ul>

Table 2. Villalta PTS scale

Criteria Used to Diagnose PTS
<ul style="list-style-type: none"> <li>• 5 symptoms (pain, cramps, heaviness, pruritus, paresthesia)</li> <li>• 6 signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression)</li> <li>• Each symptom and sign rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe)</li> <li>• Points are summed to yield total score:               <ul style="list-style-type: none"> <li>0–4: No PTS</li> <li>5–14: Mild/moderate PTS</li> <li>15 or more, or presence of ulcer: Severe PTS</li> </ul> </li> </ul>

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Table 3. Strategies for the prevention and management of PTS

Prevention
<ul style="list-style-type: none"> <li>• Prevent index DVT with the use of thromboprophylaxis in high-risk patients and settings as recommended in evidence-based consensus guidelines</li> <li>• Prevent recurrent ipsilateral DVT by providing anticoagulation of appropriate intensity and duration for the initial DVT and by targeted use of appropriate thromboprophylaxis if long-term anticoagulation is discontinued</li> <li>• Use of knee-length, 30– to 40–mm Hg ECS elastic compression stockings for up to 2 years after DVT; optimal duration uncertain</li> <li>• The role of thrombolysis for the prevention of PTS is not yet established. Catheter-directed thrombolysis requires further evaluation in properly designed trials before it is endorsed as being effective in reducing the risk of PTS.</li> </ul>
Management
<ul style="list-style-type: none"> <li>• Elastic compression stockings reduce edema and may improve PTS symptoms</li> <li>• Intermittent pneumatic compression units are effective for severe symptomatic PTS</li> <li>• Venoactive agents such as aescin (e.g. as found in horse chestnut) or rutosides may offer short term improvement of PTS symptoms</li> <li>• Compression therapy, skin care and topical dressings are used to treat venous ulcers</li> </ul>

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