Post Thrombotic Syndrome (PTS)

Thrombosis Canada
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Objectives:

- To briefly review the clinical presentation and diagnosis of Post Thrombotic Syndrome (PTS)
- To help identify deep vein thrombosis (DVT) patients who are at risk of developing PTS
- To review strategies to prevent and treat PTS

Background:

- PTS is a chronic condition that develops in 20% to 50% of patients after DVT.
- PTS is a burdensome condition in terms of effect on quality of life and costly in terms of lost productivity and dollars spent.

How Does DVT Lead to PTS?

DVT-related residual venous obstruction and valvular reflux lead to increased venous pressure (venous hypertension) and inflammation which results in leg swelling, reduced calf muscle and skin perfusion, increased vascular permeability, and the associated clinical manifestations of PTS.

Clinical Presentation of PTS (Table 1)

Symptoms of PTS 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.

Table 1: Typical Clinical Features of the Post-Thrombotic Syndrome

Leg Symptoms	Signs
Heaviness or fatigue	Edema
Pain	Peri-malleolar telangiectasia
Swelling	Venous ectasia, varicose veins
Itching	Hyperpigmentation
Cramps	Redness
Paresthesia	Dependent cyanosis
Bursting pain on walking (venous claudication)	Lipodermatosclerosis
Symptom pattern: Worse with activity, standing, walking; better with rest, recumbency, leg elevation	Healed or open ulcer

How is PTS Diagnosed?

- PTS is primarily diagnosed on clinical grounds.
- There is no gold standard laboratory testing, imaging or functional test that establishes the diagnosis.
- The Villalta PTS scale (Table 2) has been adopted by the International Society on Thrombosis and Haemostasis (ISTH) as a standard to diagnose and grade the severity of PTS in clinical studies. This scale is not specific to PTS and a significant proportion of PTS (up to 40%) may be at least in part attributable to preexisting primary chronic venous insufficiency. Assessment of contralateral leg can constitute a simple way of documenting preexisting chronic venous insufficiency.
- 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 (i.e. 3-6 months) has passed. Assessment of contralateral leg can constitute a simple way of documenting preexisting venous insufficiency.
- Symptoms of PTS usually begin within 3-6 months after DVT but can develop up to 2 years after DVT.

Table 2: Villalta PTS Scale

CRITERIA USED TO DIAGNOSE PTS

- 5 symptoms: pain, cramps, heaviness, pruritus, paresthesia
- 6 signs: edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression
- Each symptom and sign rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe)
- Points are summed to yield total score:
  0–4: No PTS
  5–9: Mild PTS
  10-14: Moderate PTS
  ≥15 or presence of ulcer: Severe PTS

Which Patients with DVT are at Risk of Developing PTS?

Approximately 60% of patients with DVT will recover without any residual symptoms, 30% will have some degree of PTS, and 5-10% will develop severe PTS. Of note, up to 15% of patients with upper extremity DVT also develop PTS. It is not possible to reliably predict which patients with DVT will develop PTS.

Specific risk factors for PTS:

- **Recurrent ipsilateral DVT:** Increases risk of PTS by 6-fold (by damaging already compromised venous valves or aggravating venous outflow obstruction).
- **Extent of initial DVT:** Risk of PTS is 2- to 4-fold higher after proximal (especially iliofemoral) versus distal (calf) DVT.
- **Higher body mass index:** Increases risk of PTS.
- **Preexisting chronic venous insufficiency** increases risk of PTS by approximately 2-fold.
- **Quality of oral anticoagulation:** PTS risk increases if the initial anticoagulation is inadequate (e.g. subtherapeutic INR >50% time during first three months of treatment) but risk is not affected by the intensity or duration of long-term anticoagulation.
- **Residual thrombosis on ultrasound:** Modest (odds ratio of 2) increased risk of PTS.
- **Persistent elevation of D-dimer:** Elevated levels of D-dimer in the weeks to months after DVT may be a modest risk factor for PTS.
- **DVT in pregnancy:** Increases the risk of PTS.

Age, sex, inherited thrombophilia and whether the DVT was unprovoked or secondary (due to surgery, trauma or cancer) do not appear to influence the likelihood of developing PTS. Furthermore, as compared with vitamin K antagonist (VKA) treatment, treatment with low molecular weight heparin (LMWH) and direct oral anticoagulants (DOAC, more particularly rivaroxaban) was shown to be associated with a lower risk of PTS but these results need to be confirmed.

The validated clinical prediction model, the SOX-PTS score (Table 3) may be useful to predict PTS at the time of DVT diagnosis. High-risk predictors include index DVT affecting the iliac vein, body mass index ≥35 kg/m^2, and moderate-severe Villalta score severity category at the time of DVT diagnosis. Compared with patients with a score of 0, those with a score of ≥4 had an odds ratio of 5.9 for developing PTS.

Table 3: SOX-PTS score

Feature	Score
Iliac Vein involvement	1
BMI >35 kg/m^2	2
None/mild (score 0-9) Villalta score	0
Moderate (score 5-9) Villalta score	1
Severe (score ≥10) Villalta score	2

Prevention of PTS (see Table 4):

Primary and secondary prevention of DVT

The best way to prevent PTS is to prevent DVT. As ipsilateral DVT recurrence is a strong risk factor for PTS, preventing recurrent DVT by providing therapeutic and adequate duration of anticoagulation for the initial DVT is important.

Thrombolysis

- Although anticoagulant therapy is the mainstay of treatment for DVT [See the Clinical Guide **Deep Vein Thrombosis (DVT): Treatment**], thrombolysis may be considered for those at high risk of developing PTS. Currently, selection of patients for these thrombolytic techniques is done on a case-by-case basis, and is typically reserved for select patients with extensive (e.g. iliofemoral) thrombosis, onset of symptoms less than 14 days, low risk of bleeding, and long life expectancy.
- 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, which involves infusion of thrombolytic therapy through a catheter inserted directly into the affected vein, is considered to have a lower bleeding risk than systemic thrombolysis; however, this intervention is still associated with an increased risk of major bleeding compared to anticoagulant therapy alone.
- Pharmacomechanical catheter-directed thrombolysis (PCDT) involves infusion of thrombolytic therapy through a catheter inserted directly into the affected vein, along with catheter-based devices that can break up clots.
    - Three contemporary randomized trials of PCDT did not demonstrate a reduction in the overall frequency of PTS in otherwise unselected patients with proximal DVT or in those with iliofemoral DVT compared to anticoagulant therapy. In one study, PTS severity was reduced and, hence, venous disease quality of life appeared better in patients with iliofemoral DVT who received lytic therapy compared to those randomized to standard care. However, in the second randomized trial, lytic therapy did not significantly affect quality of life; both the generic as well as disease-specific patient-reported health-related quality of life scores showed a similar improvement in both groups during follow-up. However, long term-follow-up data showed that benefit of thrombolytic therapy became more apparent and significant with time. Longer follow-up (>2 years) is needed to appropriately assess efficacy of thrombolysis.

Elastic Compression Stockings (ECS)

- There are conflicting RCT data on the long-term effectiveness of ECS.
- Two previous small open label trials reported that ECS were effective in preventing PTS, but a more recent large, multicenter, placebo-controlled trial showed no evidence of benefit of active compression stocking used for two years to prevent PTS. Thus, routine use of ECS for two years to prevent PTS in DVT patients is no longer recommended.
- If one decides to prescribe ECS to prevent PTS:
    - Knee-length ECS should be favored over thigh-length ECS. Knee-length ECS and thigh-length ECS have been shown to have similar physiologic effects but knee-length are easier to apply, more comfortable and less costly.
    - 20-30mmHg strength should be favored over higher strength; A recent RCT has shown that 20-30mmHg ECS were at least non-inferior to higher ECS strength, and they are easier to put on.
    - Duration of ECS therapy should be decided on an individualized basis and, in the absence of PTS most, patients can stop wearing ECS 6 months after acute DVT event.
    - In the absence of significant clinically evident arterial ischemia, compression therapy has not been found to worsen outcomes in patients with peripheral vascular disease and routine studies to rule out PAD are not warranted.
- In patients with significant DVT-related swelling, ECS should be tried to relieve symptoms and used for as long as the patient finds them to be effective.

Choice of anticoagulant treatment

There is growing evidence suggesting that LMWH and DOAC are superior to VKA in preventing PTS but good clinical trial data are still lacking.

Adjunctive treatments

The potential superiority of DOACs and LMWHs over VKAs may be due to their ability to maintain more stable therapeutic anticoagulation levels or to their inherent anti-inflammatory properties which is particularly relevant given the central role of inflammation in the pathogenesis of PTS. Several agents with anti-inflammatory effects are currently being investigated as adjuncts to anticoagulation for the prevention of PTS: (1) low-dose colchicine, being evaluated in the CIHR-funded Conquer-DVT pilot trial (NCT06440694); and (2) statins, whose potential role in PTS prevention is being assessed as a secondary outcome in the large, double-blind SAVER trial (NCT04319627).

Treatment of PTS:

There are few treatment options for symptomatic PTS (Table 3).

- Regular daily use of good-quality ECS as well as exercise may reduce leg swelling and discomfort.
- Exercise training program was reported to improve patients' QOL and PTS symptoms.
- Intermittent pneumatic compression sleeve units can help severe, intractable PTS symptoms or severe edema; however, they are cumbersome and expensive.
- The portable, battery-powered Venowave® intermittent compression device benefits some patients with moderate to severe PTS.
- There is no evidence that diuretics or "venoactive" drugs are effective for PTS-related edema or other manifestations. The ongoing double-blind CIHR-funded MUFFIN-PTS trial (NCT03833024) will assess

whether Micronized Purified Flavonoid Fraction, a venoactive drug, is superior to a placebo to improve PTS symptoms in patients with PTS.

- Post-thrombotic venous ulcers are treated with compression therapy, leg elevation and topical dressings but can be refractory to therapy and tend to recur. Consultation with a dermatologist or wound clinic is often helpful. It is important not to forget to rule out a – concomitant - peripheral arterial disease when a PTS ulcer is not healing despite good compression therapy.
- Surgical treatments for PTS such as venous valve repair or venous bypass have only been evaluated in small patient series at single, specialized centers. The use of endovascular recanalization to treat obstructive proximal PTS is increasing, with encouraging outcomes but in uncontrolled studies. A recent RCT demonstrated the efficacy of rivaroxaban alone (i.e., without low-dose aspirin) in maintaining intra-stent venous patency at 6 months after endovascular recanalization. The ongoing NIH/NHLBI-funded C-TRACT Trial will determine if the use of image-guided, endovascular therapy is effective to reduce PTS disease severity and improve quality of life in patients with disabling iliac-obstructive PTS (NCT03250247).

Table 4: Strategies for the Prevention and Management of PTS

Prevention
• Prevent the index DVT with use of thromboprophylaxis in high-risk patients and settings as recommended by evidence-based guidelines. • 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. • For most patients with DVT, the addition of PCDT to standard anticoagulant therapy does not prevent the development of PTS at least in the short term (2 years) and does involve a small but significant increase in major bleeding complications. • Efficacy of ECS to prevent PTS is debated however their systematic use after a DVT is not recommended. If ECS was to be used for PTS prevention after a symptomatic proximal DVT, 20-30mmHg knee-length ECS should be considered and may be stopped after 6 months in the absence of PTS.
Management
• ECS reduce edema and may improve PTS symptoms. • Exercise training may improve PTS symptoms and QOL. • Intermittent pneumatic compression devices are effective for moderate to severe symptomatic PTS. • Compression therapy, skin care and topical dressings are used to treat venous ulcers.

Special Considerations:

Pediatrics

- The incidence of PTS is reported to be as high as 15% in children with DVT with some studies reporting even higher incidences.
- There are no pediatric RCTs evaluating safety and efficacy of therapy for PTS.

- Symptomatic management of PTS in children may follow adult guidelines. When starting ECS therapy, lower strength ECS (15-20mmHg) should be considered first.
- Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with DVT. When this is not possible, a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist is recommended.

Other Relevant Thrombosis Canada Clinical Guides:

- Deep Vein Thrombosis (DVT): Treatment
- Venous Thromboembolism: Duration of Treatment

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