Post-thrombotic syndrome: a potential cause of venous ulcer

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INTRODUCTION

Venous thromboembolism (VTE) consists of deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a major cause of disease burden in Australia. A prospective study conducted in Perth, Western Australia, estimated the age-adjusted annual incidence of VTE to be 0.57 (95% CI, 0.47–0.67) per 1000 residents[1]. There were over 14,700 cases of VTE in Australia in 2008, contributing to an estimated financial cost of $1.72 billion for that year[2]. Post-thrombotic syndrome (PTS) is a frequently overlooked chronic complication of DVT, specifically proximal DVT (occurring at or above the popliteal vein). It is a clinical syndrome encompassing the presence of chronic pain, swelling, skin discolouration and, in severe cases, venous ulceration. It affects approximately one-third of patients following DVT, and about 5% to 10% of patients progress to severe PTS[3,4]. It is the cause of significant morbidity and health care utilisation.

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AETIOLOGY

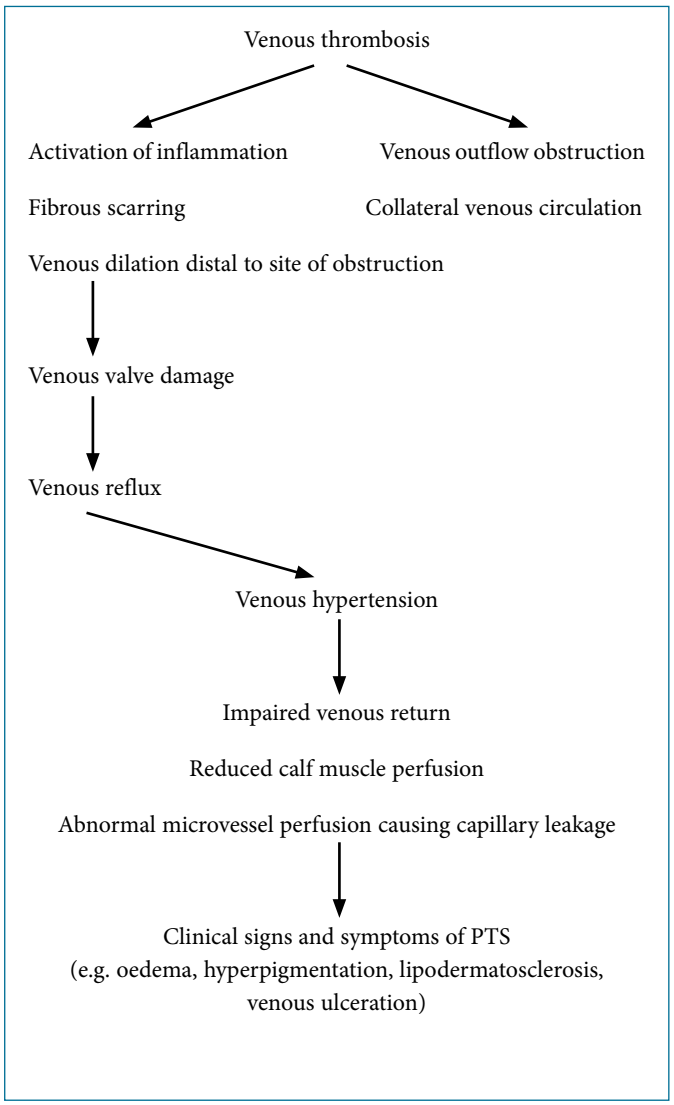
Venous thrombosis may cause venous outflow obstruction (due to incomplete vein recanalisation), and may cause valvular damage resulting in venous reflux. This can lead to venous hypertension, which is central in the development of PTS and, in turn, leads to further pathophysiologic changes, resulting in the classical clinical manifestations of PTS. These changes include decreased venous return, decreased calf muscle perfusion, and increased capillary permeability leading to oedema. This is illustrated in Figure 1[3,4].

DIAGNOSIS

Clinical presentation is critical in the diagnosis of PTS. Patients can present with typical symptoms (for example, pain, swelling, itchiness) and signs (for example, oedema, lipodermatosclerosis, hyperpigmentation) in the affected limb. Figure 2 demonstrates a typical example of PTS of the leg. The symptoms usually worsen with use of the limb (for example, after walking or prolonged standing) and improve with rest. Certain radiologic findings (for example, valvular incompetence) may support the diagnosis of PTS; however, they are insufficient for the diagnosis in the absence of clinical features of PTS. Some experts have recommended deferring the diagnosis until three to six months after the acute thrombotic event, in order to differentiate true PTS symptoms from the limb swelling and discomfort of the acute thrombosis that might persist[4].

There is no gold standard for the diagnosis of PTS. A number of clinical scoring systems are in use. Of these, the Villalta scoring system is the most widely used[5]. This score has been recommended for use by the International Society of Thrombosis and Haemostasis[6] as well as by a recent systematic review[7]. The Villalta score is a disease-specific score, which can be used for diagnosis and grading of severity of PTS. It was initially developed in a cross-sectional study of 100 patients, assessed greater than six months following DVT. The score evaluates the presence and severity of five symptoms (pain, heaviness, cramps, paresthesia, pruritus) and six signs (pretibial oedema, skin induration, hyperpigmentation, redness, venous ectasia and pain on calf compression). Patients are defined as having PTS if the score is

Figure 1: Aetiology of post-thrombotic syndrome
Adapted from references 3 and 4



greater than 5 (5–9 mild PTS, 10–14 moderate PTS, ≥15 severe PTS). If a venous ulcer is present, the patient is automatically classified as having severe PTS. This score has been summarised in Table 1. Adaptations of the score with visual aids are also available.

The Ginsberg measure has also been widely used in clinical trials[8]. This diagnoses patients as having PTS if there is leg pain and swelling (daily for ≥1 month), typical in character (aggravated by standing, improved by rest/leg elevation), occurring at least six months after the initial DVT and with objective evidence of valvular incompetence. A study comparing the Villalta and Ginsberg clinical scales found that the Ginsberg measure seemed to identify a patient population with more severe disease and worse quality of life than the Villalta score[9]. In this study, the Villalta score diagnosed almost five times as many patients with PTS at one year than the Ginsberg score.

Brandjes and colleagues also developed a clinical scale for PTS but this is less frequently used[10]. Additionally, there are a number of scores used to assess chronic venous insufficiency more broadly (rather than PTS specifically), including the Widmer score[11], the CEAP[12] measure and its related score the Venous Clinical Severity Score[13].

It is important to distinguish PTS from recurrent DVT. This can be challenging given the overlap in symptomatology between the two conditions. However, severe symptoms that persist or worsen over 24 hours rather than improving[4] should prompt consideration of a recurrent DVT, and perhaps further investigation (most commonly with Doppler ultrasonography).

RISK FACTORS

Known risk factors for the development of PTS include recurrent ipsilateral DVT[4], incomplete resolution of leg symptoms and signs by one month post-DVT[14], more proximal DVT (that is, involving the common femoral or iliac veins rather than the popliteal or more distal veins), higher body mass index and older age[3]. Retrospective studies have also suggested female sex, hormonal therapy, varicose veins and abdominal surgery as possible risk factors[15].

Thrombophilic states such as antiphospholipid antibodies, factor V Leiden, prothrombin gene mutation, elevated factor VIII and deficiencies of proteins C, S or antithrombin III do not appear to predict for the development of PTS[16]. Family history of venous thromboembolism also does not appear to be a relevant risk factor[4].

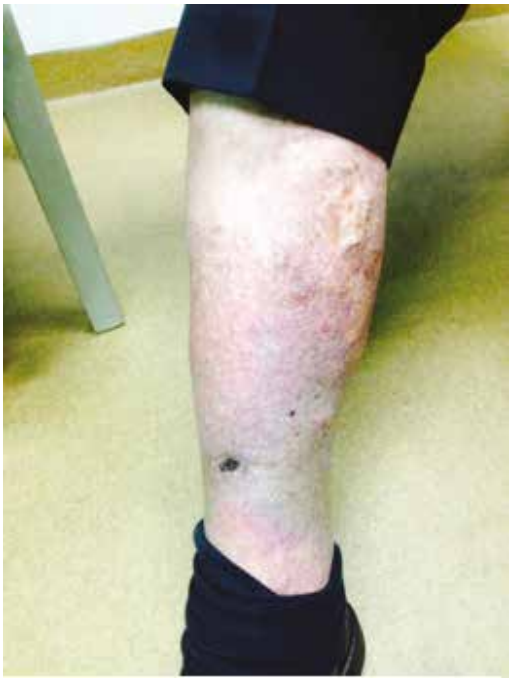
PREVENTION

Given the relative lack of effective therapeutic options for PTS, prevention of the initial DVT is of primary importance. However, this section will deal only with the prevention of PTS after a DVT has already occurred.

The American College of Chest Physicians 2012 guidelines provide evidence-based guidelines on the therapy of DVT in different situations[17]. Adequate duration and dosing of anticoagulation following the initial DVT event may decrease the risk of PTS. For example, one study found that patients treated with a vitamin K antagonist who had sub-therapeutic INRs for more than 50% of the time in the first three months of their therapy were at greater risk of PTS[18]. Extension of therapeutic anticoagulation beyond six months does not appear to reduce the risk of PTS.

Thrombolysis of initial DVT may lead to earlier restoration of venous patency and perhaps lower rates of PTS. A Norwegian randomised controlled trial (RCT) (the CaVenT study) assessed 189 patients with iliofemoral DVT and reported that those who had received catheter-directed thrombolysis (CDT) were less likely to have PTS at 24 months (as assessed by the Villalta scale) and more likely to have iliofemoral vein patency at six months compared to those who did not undergo CDT[19]. The ATTRACT study is an ongoing, multicentre randomised trial comparing pharmacomechanical CDT plus standard care with standard care alone in 700 patients with acute proximal DVT[20]. The primary outcome measure is the incidence of PTS at 24 months, assessed with the Villalta scale. The findings of this study should be very informative.

Figure 2: Clinical signs of post-thrombotic syndrome
This picture demonstrates typical signs of severe lower limb PTS, such as hyperpigmentation, oedema, lipodermatosclerosis and ulceration.



THERAPY

Elastic compression stockings

Graduated elastic compression stockings (ECS) apply the greatest amount of pressure at the ankle (usually 30 to 40 mmHg), with decreasing pressure proximally. For many years, ECS were commonly used to prevent PTS following the findings of several studies. In 1997, Brandjes and colleagues reported the results of an RCT which separated patients with a first episode of proximal DVT into a control arm (who did not receive stockings) and an intervention arm, who received made-to-measure ECS which applied 40 mmHg pressure at the ankle[10]. Approximately 60% of patients in the control arm went on to develop PTS after two years, and this rate was halved in the ECS arm. In 2004, a further RCT with a similar study design also demonstrated a 50% reduction in patients with PTS using ECS compared to those not using ECS[21]. This study recruited 180 patients with a first presentation of proximal lower limb DVT, and randomised them either into an ECS arm (applying 30 to 40 mmHg pressure at the ankle) or a control arm. At the end of the two years, the cumulative incidence of PTS was 24.5% in the ECS arm and 49.1% in the control arm, representing a hazard ratio of 0.49 in the ECS arm compared to the control arm (95% CI 0.29 to 0.84, p=0.011).

By contrast, some studies with a different methodology have found that ECS have not been effective in preventing PTS. A three-part

Table 1: Villalta post-thrombotic syndrome score[5]

Clinical feature	None	Mild	Moderate	Severe
Symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paresthesia	0	1	2	3
Pruritus	0	1	2	3
Signs				
Pretibial oedema	0	1	2	3
Indurated skin	0	1	2	3
Hyperpigmentation	0	1	2	3
Erythema	0	1	2	3
Venous ectasia	0	1	2	3
Pain on calf compression	0	1	2	3
Venous ulcer	Absent or present			

Mild PTS: 5-9 points; moderate PTS: 10-14 points; severe PTS: ≥ 15 points or the presence of venous ulceration.

Canadian study evaluated the rates of PTS in patients who previously had a proximal DVT, *and* who did not have PTS one year following this diagnosis[22]. The Ginsberg score was used to evaluate for PTS. Eligible participants were then randomised to receive a below-knee stocking (20 to 30 mmHg compression) or placebo stockings. After approximately five years of follow-up, none of the 24 patients in the active arm and one patient (out of 23, that is 4.3%) in the placebo arm developed PTS. This difference was not statistically significant (p=0.49), which may be contributed to by the small numbers of patients in each arm of this multi-part study.

The discrepancy in the results between these different studies has been attributed to the utilisation of different methodologies, including different patient populations, duration of follow-up, and clinical scores to diagnose PTS. One of the key limitations of previous studies has been the lack of a double-blinded design, which is of particular importance given the subjective elements in the PTS scoring systems[3].

The results from the SOX trial have recently been published[23]. This was a well-designed, international, multicentre, prospective, blinded, RCT, which compared graduated ECS with placebo stockings involving 806 patients. The placebo stockings looked identical to the ECS, but applied less than 5 mmHg of compression at the ankle. Patients who had a first proximal DVT were eligible for enrolment, and were required to wear their stockings during their waking hours for two years. The primary outcome was the cumulative incidence of PTS, as diagnosed by the Ginsberg criteria. Cumulative incidence and severity of PTS as diagnosed by the Villalta score was recorded as a secondary outcome. This study showed that graduated ECS did not prevent PTS after first proximal DVT, regardless of whether PTS was defined using the Ginsberg or Villalta scores. The 750-day cumulative incidence of PTS as measured by the Ginsberg scale was 14.2% in the active ECS arm versus 12.7% in the placebo stocking arm (p=0.58). The equivalent figures when using the Villalta scale were 52.6% and 52.3% respectively (p=0.96). The higher incidence when the Villalta scale was used supports the notion that the Ginsberg scale seems to identify a population with more severe PTS than the Villalta scale[9].

The results of this major and methodologically rigorous trial do not support the routine use of ECS to prevent PTS following DVT. Patients may well be pleased to hear this, given that ECS are often uncomfortable to use, challenging to put on, can be expensive, and need to be replaced after a period of wear and tear. Furthermore, they are contraindicated in those with severe peripheral arterial disease (Ankle-Brachial Pressure Index <0.7)[24]. However, given the previous uncertainty about the efficacy of ECS in preventing PTS, it would be valuable if another well-designed clinical trial could provide further evidence in this area to either support or contradict the findings of the SOX trial. Perhaps future studies could also attempt to identify subpopulations at particularly high risk of PTS to evaluate the benefit of ECS. At present, our clinical practice is to offer knee-high class II compression stockings (that is, applying 20–30 mmHg at the ankle) to all patients with DVT at or above the popliteal vein, unless the patient has severe peripheral arterial disease or an active skin condition (for example, dermatitis, cellulitis or ulcer). We advise patients to use the stocking on the affected leg during their waking hours and to remove it at night. If the patient derives symptomatic benefit, we suggest they continue using the stockings. However, if the patient is unable to tolerate the stocking, finds no symptomatic benefit from it or finds it too costly, we then suggest that they discontinue its use.

Intermittent pneumatic compression

Intermittent pneumatic compression can be supplied by portable, lower limb venous return assist devices such as the Venowave™ (Saringer Life Science Technologies Inc., Stoufville, Ontario, Canada). These units provide calf compression and increase venous return. The use of such devices alone or in combination with ECS appears to be associated with decreased severity PTS and improved quality of life in a small RCT[25]. However, owing to the limited and lack of high-quality data in this area, this therapy is not routinely used at present.

Venoactive medications

Venoactive medications are believed to reduce capillary permeability and prevent leukocyte activation, thereby potentially ameliorating the pathophysiology of PTS[4]. A Cochrane review concluded that aescin (derived from horse chestnut seed) is effective to reduce symptoms of chronic venous insufficiency and appears to be well tolerated[26]. However, note that horse chestnuts (Aesculus hippocastanum) and their leaves must not be consumed whole or without proper preparation, due to the risk of poisoning.

A trial has compared the use of oral hydroxyethylrutosides with ECS and found that they appear to decrease PTS symptoms at least to the same extent as ECS[27], with no apparent additional benefit from the combination of both together.

Preparations containing aescin and hydroxyethyrutosides are available from pharmacies and health food stores in Australia. Larger, longer term studies are required to assess the safety and efficacy of venoactive medications before a decision can be made regarding their clinical utility. We do not use these agents in our practice.

There is no proven role for long-term use of diuretics or non-steroidal anti-inflammatory drugs in PTS[3,4].

Venous ulcer management

Patients with venous ulcers benefit from specialist management from those with expertise in this area. Ulcers are usually managed with some combination of compression, limb elevation and topical dressings.

In selected cases, surgery (for example, perforator vein ligation, valvuloplasty) and other invasive techniques (for example, endovascular stent placement) may be beneficial, as reported in small case series[28]. However, large trials specifically exploring this issue are lacking.

Exercise

Early physical activity following DVT seems to be safe for most patients[29] and does not increase the risk of PTS[30]. A small study has suggested that supervised exercise programs may decrease PTS rates compared to bed rest[31], although there does not seem to be any difference in rates of vein recanalisation[29].

PROGNOSIS

In the majority of cases, PTS appears to remain stable or resolve over time, regardless of its initial severity. Ongoing clinical monitoring of the patient is valuable to facilitate early detection and management of PTS and its complications[3].

SUMMARY POINTS

- Post-thrombotic syndrome (PTS) is common and under-appreciated
- Venous ulcers can result in severe cases of PTS
- The Villalta score is the most widely used score for diagnosis and characterisation of severity
- Elastic compression stockings may not necessarily prevent PTS but may offer symptomatic benefit
- Ongoing monitoring for PTS is required as it may be a delayed complication of DVT

DISCLOSURES

Both authors have no relevant disclosures.

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