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# Spontaneous Onset of Bacterial Cellulitis in Lower Limbs with Chronic Obstructive Venous Disease

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## KEYWORDS

Cellulitis;  
Venous obstruction;  
Venous stents;  
Leg swelling;  
Post-thrombotic  
syndrome;  
Chronic venous  
insufficiency

**Abstract** *Background:* Cellulitis, often recurrent is a common complication of severe chronic venous disease (CVD) when dermatitis or ulcer is present. The skin breakdown obviously provides easy entry for bacteria but other factors such as oedema and lymphatic dysfunction likely play a role in pathogenesis as well. An iliac obstructive lesion is commonly present and correction with stent(s) often heals dermatitis/ulcer and relieves cellulitis. The current manuscript focuses on a relatively infrequent "spontaneous" variety of cellulitis which also occurs in obstructive venous disease in the absence of overt skin breakdown. Stenting results are of particular interest in this subset because its therapeutic efficacy can be related to factors other than healing of dermatitis/ulceration (portal of entry).

*Material and methods:* One thousand and nine limbs underwent iliac vein stenting for symptomatic CVD over a 7 year period; 29 limbs that were stented to treat spontaneous recurrent cellulitis of two or more prior attacks and 16 additional limbs with only one prior episode (stented for other indications) are analysed. Eighty two percent of the limbs had obvious swelling and the remainder had none at the time of stenting when cellulitis was inactive. Iliac vein outflow obstruction was found by intravascular ultrasound (IVUS) and all limbs were stented.

*Results:* Median age was 54 and male to female ratio 1:2. Aetiology of iliac obstruction was post-thrombotic in 33% and non-thrombotic in 67%. Preoperatively, lymphatic abnormalities were present in 17 (38%) of the limbs: no activity in 7, delayed flow in 8 and pooling of isotope in the lower leg in 2 limbs. Swelling and pain improved significantly after stent placement. Cumulative freedom from recurrent attacks of cellulitis was 76% at 3 years.

*Conclusion:* Iliac vein outflow obstruction may underlie CVD limbs afflicted with cellulitis. IVUS examination is recommended if cellulitis is recurrent and conventional therapy had failed. Correction of outflow obstruction by venous stent placement appears to yield moderate freedom from repeat infections in the near term.

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Bacterial cellulitis is a common complication of chronic venous disease (CVD) when dermatitis or open ulcers are present. The problem can become recurrent posing a difficult management problem. Even though skin breakdown allowing bacterial entry is the obvious initiating event, factors that favour bacterial growth and compromise local host defences<sup>1</sup> as in lymphoedema are likely present in CVD as well. This is particularly evident in a relatively rare type soft tissue infection that occurs in CVD *in the absence of skin breakdown* i.e., there is no obvious entry point for the infection such as an ulcer, eczema, traumatic skin abrasion or interdigital skin fissure<sup>2,3</sup>. The term 'spontaneous bacterial cellulitis' is used in this manuscript to denote this type of infection. The clinical picture is that of a CVD patient with chronic leg swelling (occasionally no prior swelling) that experiences sudden onset of pain, redness and increased (or new) swelling of the leg, usually below the knee. Other causes of similar clinical presentation such as superficial thrombophlebitis and deep venous thrombosis are ruled out by clinical examination and duplex examination. The cellulitis rarely responds and often progresses on anti-inflammatory regimen alone. Institution of antibiotics with gram positive coverage usually results in quick clinical resolution in a matter of three to four days in most cases. After resolution of the inflammation, swelling often persists and becomes chronic. There is a predilection for recurrent attacks with progressive worsening of swelling and pain. The affected limb is chronically erythematous, sore to touch and presents the clinical picture of chronic low grade cellulitis. The clinical complex is readily recognisable as a distinct clinical entity in CVD patients and is identical in all other respects to the cellulitis seen in the more common variety that occurs in the presence of dermatitis or stasis ulcer.

Spontaneous cellulitis in CVD is analogous to that found in lymphoedema with some differences. The latter is variously referred to as 'erysipelas' or dermatolymphangioadenitis (DLA)<sup>1</sup> and also has a complex pathogenesis. Swelling and infection are confined to the subcutaneous tissues in lymphoedema. In CVD, both swelling and the infection are more diffuse involving both the superficial and deep compartments, often evident on CT or MR imaging. Though 'soft tissue infection' would be more precise, the term 'cellulitis' has become well established by common usage when referring to infections associated with CVD.

Chronic long term antibiotic therapy<sup>1,4,5</sup> is the standard treatment recommendation when cellulitis becomes recurrent. In the course of treating obstructive venous disease with stent placement, we have become aware that cellulitis/recurrent cellulitis are a feature of outflow obstruction and its correction by stent placement is often curative. Though resolution of cellulitis is obtained both in spontaneous cellulitis and in the more common variety with dermatitis and stasis ulcer, the results are of particular interest in "spontaneous" variety, because stenting often results in concurrent healing of dermatitis/ulceration presenting the former. The manuscript focuses on the relatively infrequent spontaneous variety of cellulitis in CVD because efficacy of stenting on host factors uncoupled from portal of entry factors can be ascertained; but the implications are probably relevant as well for the larger group of CVD patients at risk from cellulitis.

## Patients and Study Design

A total of 1,009 limbs were treated with iliac vein stenting to correct deep venous obstruction from 1999 to 2006 for relief of CVD symptoms not responsive to conventional therapy. Among these, a history of prior cellulitis was recorded in 259 limbs (26%), but venous dermatitis or ulcers were present in 214 limbs and were excluded from analysis. Recurrent spontaneous cellulitis with two or more episodes in the absence of skin changes was the primary indication for stenting in 29 limbs (20 with 2–4 episodes and 9 with five or more episodes). An additional group of 16 limbs had only one documented episode of spontaneous cellulitis and were stented not for this reason but for other features of CVD such as severe venous pain (VAS >5/10) or swelling. These limbs too are included in the analysis but the outcome is separately tabulated. Imputation of therapeutic effect is less certain with the single episode subset because not all first episodes become recurrent i.e. absence of infection after stenting could be either because of the stent or natural history. However, clinical features and *failure* of venous stenting to prevent cellulitis in the latter subset are relevant.

## Clinical Assessment

The venous clinical severity scoring system<sup>6</sup> was used as a template in clinical assessment. A detailed venous history included details of cellulitis such as number of episodes, first and last attack dates. Chronic limb pain when cellulitis was not active was scored on a visual analogue scale<sup>7</sup> (VAS) 0 to 10. Chronic limb oedema was assessed when cellulitis was not active and was graded from 0 to 3 (Gr. 0- none; Gr. 1- pitting; Gr. 2 ankle oedema; Gr. 3- gross). Limbs were examined for a portal of entry for the infection including skin eczema/dermatitis and ulcers of various types (traumatic, fungal and venous) and if found are not included in this analysis.

The investigative protocol has been described in detail elsewhere.<sup>8</sup> Briefly, patients underwent a detailed set of venous investigations including duplex, ambulatory venous pressure measurement, Air Plethysmography, and Arm/Foot pressure measurement. An isotope lymphangiogram, ascending and transfemoral venograms with femoral exercise pressure measurements were routinely obtained. Intravascular Ultrasound examination (IVUS) was the key diagnostic investigation<sup>9</sup> as preoperative investigative parameters were only about 50% sensitive for iliac venous obstruction.<sup>8</sup> Iliac vein stent placement was carried out at the same sitting under IVUS guidance.

## Stent Placement

Selection of patients for stent placement was based on severity of symptoms. Generally only patients who had failed conservative therapy of compression stockings and appropriate antibiotic therapy for spontaneous cellulitis were considered. Patients with recurrent episodes not responsive to such measures were candidates. Some patients who had only one attack of spontaneous cellulitis were stented primarily because of severity of other symptoms of venous disease such as severe limb pain (VAS >5/10) or severe limb swelling. Some CEAP class 0–2 limbs

were stented because of pain and/or recurrent cellulitis even though swelling was absent at the time of stenting.

Technical details and results of stenting for outflow obstruction have been published in detail elsewhere.<sup>9–15</sup> The common and external iliac veins and the adjoining caval and femoral segments were the focus of stent treatment. In general, stenotic lesions that showed a 60% or greater reduction in lumen area per IVUS examination were corrected with stents. Percutaneous laser or radiofrequency ablation of the proximal great saphenous vein in the thigh was attempted concurrently<sup>16</sup> in five of eight limbs where saphenofemoral reflux was present (2/5 failed to ablate and underwent stripping later). In the other three, concurrent saphenous ablation was not performed because saphenous access failed (1), the stenting was a complex prolonged procedure involving recanalisation (1) or for unclear reasons (1). Deep reflux when present was not corrected in this series. Below knee varicosities were also not treated as they were not considered to be the dominant factor in onset of cellulitis.

The stenting procedure is percutaneous and is carried out on an outpatient basis (23 hr admission). Most patients are maintained on daily ASA (81 mg) except in cases of thrombophilia or recurrent deep vein thromboses when Warfarin is instituted. Patients were instructed to continue preoperative leg compression they were using for a month after stent placement and were encouraged to abandon compression afterwards if tolerated. Compliance with leg compression regimens is very low in the patient population covered.<sup>17</sup>

## Data Analysis

Clinical features, operative details and follow up data were contemporaneously entered into a time stamped electronics medical records program. Current material is extracted from this database. Commercially available statistical program (Graph Pad Prism for Windows [version 3.0], GraphPad Software, San Diego, CA) was used for statistical analysis. Non-parametric Wilcoxon rank test for unpaired and paired data and chi square were used to analyze groups as appropriate. Cumulative curves using the Kaplan-Meier method were used to analyze clinical outcome. Log rank test was utilized to assess significance between cumulative curves. A *p*-value of less than 0.05 was considered significant.

## Results

According to CEAP method<sup>18</sup> of classifying CVD, the limbs were recorded as follows: C 0 (normal) – 1 (2%); C 1 (spiders) – 0 (0%); C 2 (varices) – 7 (16%); C 3 (swelling) – 36 (82%). C 4, 5, and 6, which involve skin breakdown of various types have been excluded from the material. Male to Female ratio was 1:2. The median age was 54 (range 18–87). The left limb was involved in 49%, right in 51%. Aetiology of venous obstruction was post-thrombotic in 33% and non-thrombotic ('primary') in 67%. The incidence of non-insulin dependent diabetes was 11%, and insulin dependent diabetes was 4%.

Preoperative median venous clinical severity score was 6 (range 0–11) among the 45 limbs. Superficial reflux was present in 18 limbs (40%), which can be grouped according to the lead segment involved as follows: proximal GSV

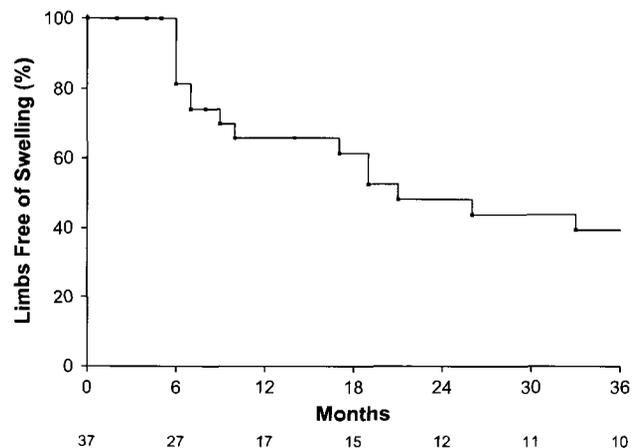
reflux 8, Short saphenous reflux 5, distal GSV reflux and calf varices 5; various combinations of these were present in 6 limbs. In 9 (20%) limbs, deep reflux occurred, all except one in combination with superficial reflux; Deep reflux was axial in 8 limbs. Isotope lymphangiography showed no activity in regional nodes in 7 (16%), and delayed activity in 8 (18%) limbs; pooling or stasis of the isotope in the lower leg was observed in 2 (4%) limbs. Lymphangiogram was normal in 28 (62%) limbs. Preoperative transfemoral venography with simultaneous femoral exercise pressure measurement suggested iliac venous obstruction in 23/45 limbs.

Thirty day mortality of venous stenting was null and morbidity was minor, consisting of back or limb pain easily controlled with analgesics. All stents in this series remained patent during the observation period.

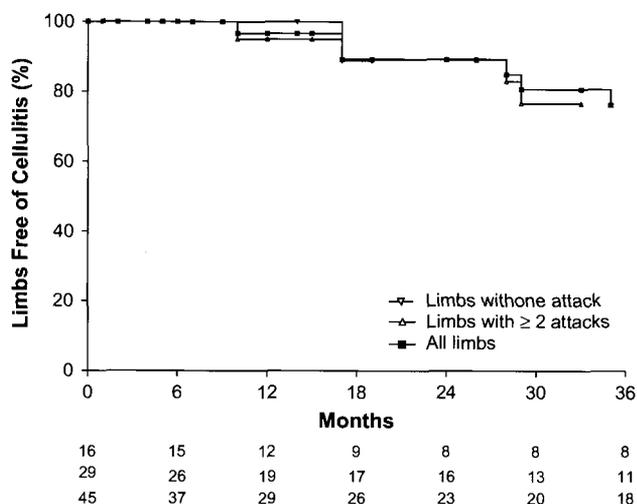
Swelling improved significantly after stent placement, from preoperative median grade 3 (range 1–3) to postoperative grade 1 (range 1–3) ( $p < 0.0006$ ). Eight limbs had no chronic swelling preoperatively though present at the time of active infection. Cumulative complete relief of swelling in the remaining 37 limbs is shown in Fig. 1. Chronic limb pain (when cellulitis was not active) decreased significantly, from preoperative median VAS of 2 (range 0–8) to postoperative VAS of 0 (range 0–6) ( $p < 0.0006$ ). Cumulative freedom from cellulitis for the two subsets (single or  $\geq 2$  attacks) and for the entire group as a whole is shown in Fig. 2. There was no statistical difference between the curves for the subsets (Log Rank Test,  $p = 0.07$ ). Stent placement failed to prevent onset of recurrent cellulitis in 10 patients. Though censored after the first postoperative attack, all have been followed for median 4 years (range 2–7 years); 2 have had more than one postoperative attack, all others single episodes. Instant restenoses ( $>50\%$ ) have been identified in 2/10 on IVUS examination (pending in others).

## Discussion

Twenty six percent of limbs undergoing venous stenting to relieve obstruction in our centre had a prior episode of cellulitis; most had overt venous skin breakdown. The



**Figure 1** Cumulative complete relief of limb swelling after iliac vein stent placement in patients presenting with cellulitis.



**Figure 2** Cumulative freedom from limb cellulitis after stent placement to correct venous outflow obstruction. There is no difference between the subsets.

spontaneous variety where there is no obvious skin breakdown occurred in 5% of stented limbs; the disease was recurrent in over half (3%) of these. Basic work in clinical pathology of bacterial cellulitis specific to CVD is sparse;<sup>4,19–21</sup> many details discussed herein are necessarily conjectural or extrapolated from work on lymphoedema. There is general agreement that the dermal barrier<sup>19,22</sup> is compromised in CVD but it is not clear if overt skin breakdown is necessary for bacterial invasion or if it can occur through intact but diseased (CVD) skin including hair follicles and sweat glands. Bacterial invasion from appendages of axillary skin which is different in structure from that of lower limb skin does appear to occur.<sup>23</sup> An obvious portal of entry is not always evident in erysipelas of lymphoedema. We speculate that bacterial invasion occurs in spontaneous cellulitis of CVD through scratching, invisible micro abrasions or passage through grossly intact skin because of microscopic damage to the dermal barrier from venous disease. Embolic seeding is unlikely but cannot be strictly excluded. Patients often point to a localized area of the limb (with intact skin) where the inflammatory process started before spreading.

In addition to the compromised dermal barrier, the onset and spread of infection may be related to one or more of the following associated with venous stasis: limb swelling providing the substrate for bacterial growth and lymphatic dysfunction. Recurrent cellulitis may damage existing lymphatics perpetuating and exacerbating the vicious cycle.<sup>1,15,24</sup> Decreased regional immunity has been postulated in the presence of post-mastectomy lymphoedema. Indeed the cellulitis even when associated with obvious skin breakdown (dermatitis/ulcer) has anomalous features reminiscent of the immunosuppressed patient. Systemic signs such as fever, leucocytosis, and left shift are not frequently present even though local signs of inflammation may be quite severe (spreading erythema and streaks, increased swelling and pain). Blood cultures are seldom positive. We examined the clinical records of 15 CVD patients (7 were later stented and included in current

analysis) requiring hospitalisation for treatment of spontaneous cellulitis. Despite severe local inflammation, fever was present in only 3/15, leucocytosis was present in only 2/15 and blood culture was positive in only one 93 year old patient. All responded to antibiotics (Penicillin/amoxy-cillin in 10, vancomycin in 1, cephalosporins in 3 and ciprofloxacin in 1) with a median hospital stay of 4 days (range 2–9). Rapid clinical resolution is the rule with gram positive coverage. In a minority, perhaps in about 10%, other organisms may be involved requiring broader antibiotic coverage. The rapid clinical resolution with antibiotics rules out many other conditions that may resemble cellulitis in certain clinical features.<sup>25–27</sup>

Limb swelling is often but not always present in affected limbs during quiescent interludes when cellulitis is not active (8/45 limbs in this series). Other features of CVD can be usually elicited in such cases on careful history and examination. Venous outflow obstruction should be considered when an obvious cause for the infection is not apparent.<sup>1,21</sup> Lymphatic dysfunction can be demonstrated in about a third of CVD cases<sup>28,29</sup> and maybe reversible when the underlying venous insufficiency is corrected.<sup>30</sup> Postoperative lymphangiography was not routinely performed in the current series and therefore relevant data is not available.

Correction of venous outflow obstruction in the iliac vein and adjacent segments afforded relief from recurrent cellulitis in the majority of cases in the current series. Complete relief of swelling was desirable but a partial reduction was helpful in gaining relief from recurrent infections in many cases. The relationship between swelling and infection has been inconsistent<sup>5</sup> probably because swelling is not the only factor in clinical pathology. We assume that integrity of the barrier function of the skin is restored or improved after successful stenting; gross wound healing is certainly restored in chronic ulcer cases after venous stenting. Recurrence of cellulitis after stenting should prompt examination for stent malfunction (IVUS).

The role of iliac outflow obstruction in CVD in general<sup>31</sup> and in 'primary' disease in particular<sup>8</sup> is underestimated. IVUS examination of the iliac veins and stenting of obstructive lesions found should be considered in patients presenting with cellulitis associated with chronic venous disease. Iliac vein stenting is a low risk percutaneous procedure. Long term (6 year) cumulative stent patency is remarkable at 100% in non-thrombotic disease and only slightly less in post-thrombotic disease.<sup>10</sup> Clinical benefit tracks the high patency. In combined obstruction/reflux outcome is good after stenting even when the reflux component is left uncorrected.<sup>8</sup> This mode of therapy may offer a more direct solution to the problem than chronic antibiotic therapy<sup>1,4,5,7,20,24</sup> or other conservative measures<sup>7,18,24,32,33</sup> that require a high degree of patient compliance. The latter tend to have poor patient acceptance.<sup>17</sup>

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