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Chilblains in immune mediated inflammatory diseases: a review

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Abstract:

Chilblains were first described over a hundred years ago as cutaneous inflammatory lesions, typically on the digits, occurring on cold exposure. Chilblains can be primary, or secondary to number of conditions such as infections, including COVID-19, and immune mediated inflammatory disorders (IMIDs) with systemic lupus erythematosus (SLE) being the commonest. Chilblain Lupus Erythematosus (CHLE) was first described in 1888 as cold induced erythematous lesions before the terms ‘chilblains’ or ‘perniois’ were coined. Diagnostic criteria exist for both chilblains and CHLE. Histopathologically, CHLE lesions show interface dermatitis with perivascular lymphocytic infiltrate. Immunofluorescence demonstrates linear deposits of immunoglobulins and complement in the dermo-epidermal junction. This narrative review focuses on chilblains secondary to immune mediated inflammatory disorders, primarily the epidemiology, pathogenesis and treatment of CHLE.

Introduction

Chilblains are cutaneous inflammatory lesions commonly occurring on exposure to cold and damp conditions. Symptoms develop 12 to 24 hours after a triggering event and characteristically present with burning, painful, pruritic, erythrocyanotic lesions involving extremities. Typically, the lesions are oedematous, tender plaques or papules with purple discolouration or nodules (which may develop central erosions/ulceration) which begin as a pruritic area later becoming tender [1-3]. If located on the soles of the foot, the lesions tend to develop necrosis more rapidly [4]. Involvement of ears and nose is uncommon, as are lesions on the trunk [5].

The term “chilblain” is of Anglo-Saxon origin, referring to “chill” for cold and “Blegen” for sore [6]. Chilblains are also known as Perniosis and were first described in 1912. Perniosis is a more general term applied to chilblain lesions, mainly when they occur in the absence of lupus erythematosus (LE) or another immune mediated inflammatory disorder (IMID) [2,3,7]. Perniosis should not be confused with the term ‘lupus pernio’, which is a misleading name used for cutaneous sarcoidosis and was first described in 1959 [8].

Chilblains can be primary or secondary. Secondary chilblains are associated with IMIDs, infections (including hepatitis), haematological disorders, malignancy and drug-related causes. By far, the most common association is with SLE [4,9,10,11-13] although since 2020, chilblains have been reported in association with COVID-19 [14]. In primary chilblains, the lesions often resolve within a few days to three to four weeks [5]. Persistence of lesions, appearance in warmer temperatures or unusual features such as ulceration or scarring should lead to a search for a secondary cause [9,10]. A full list of conditions associated with chilblains is shown in table 1.

Chilblain lupus erythematosus (CHLE) is an uncommon variant of cutaneous LE first described by Jonathan Hutchinson in 1888 as cold-induced erythematous lesions. He had initially termed it 'Lupus Pernio' 24 years before the initial description of primary chilblains [12]. Millard et al classified these lesions as chilblain lupus erythematosus of Hutchinson's; they can be a symptom of cutaneous lupus erythematosus (CLE) or SLE [5]. Raynaud's-associated discolouration can occur concomitantly with CHLE lesions in some cases. CHLE can occur in the context of SLE and is a specific subtype of chronic cutaneous LE in the SLICC 2012 Classification Criteria for SLE [13]. In a prospective study of 33 patients affected by severe chilblains, Viguier et al. proposed that persistence of lesions during hot seasons was an important criterion that might delineate CHLE from idiopathic chilblains [9].

The purpose of this narrative review is to describe the epidemiology, management and complications of chilblains secondary to immune mediated inflammatory diseases (IMIDs).

Methods

Search strategy: This review was supported through a MEDLINE and Embase search (29th April 2021) using the terms: ('chilblains' OR 'pernio' OR 'chilblain' OR 'perniosis' OR 'acrosyndrome'). Our initial search identified 334 articles in English language, the titles and abstracts of these were reviewed for inclusion in the review. Since there are limited clinical trials in this area (and no randomised controlled clinical trials in CHLE), we also included case reports of treatments that had been effective. Publications that did not provide any new information were not referenced. This led to the identification of 49 articles selected on the basis of their relevance and originality. Additional manuscripts, including those describing

COVID-19 and immune mediated inflammatory conditions with skin lesions such as SLE were identified through searches of cited articles or through personal contact.

Results

With the exception of CHLE, there is paucity of data on the occurrence of chilblains in other IMIDs therefore the results focus on CHLE.

Incidence/Prevalence

A small study by Takci et al including 51 patients reported that the majority (86%) of chilblains seen in a dermatology outpatient department were primary and only 14% secondary to another cause such as a connective tissue disorder or hepatitis [22]. Conversely, Yell et al report that 15/73(20.5%) of SLE patients had chronic CHLE [33]. Gold had reported in 1960 that 3% of discoid LE patients had chilblains [34]. There is paucity of good quality epidemiological data on secondary chilblains and CHLE. Hedrich et al reported that an estimated 20% of patients with CHLE will go on to develop features of SLE, although this was based on only 17 patients [7]. A French study of 50 consecutive patients with SLE and digital cutaneous lesions identified CHLE in 15 (30%) of patients, and also reported progression to SLE in approximately 18% of patients [35]. In contrast, CHLE has been quoted as being present in about 6% of patients with SLE, predominantly females [5]. Although some reports suggest that CHLE is commoner in females [5], others indicate that there is no sex difference when secondary chilblains are considered together [22]. Familial CHLE is rare, and reports are typically limited small families, and is discussed in more detail below.

Pathogenesis

The pathogenesis of CHLE is not well understood. Vasoconstriction provoked by exposure to cold leads to the occlusion of the capillary bed and a circulation slowdown with the presence of aggregates of red blood cells visible on capillaroscopy [5, 36]. Antibodies to Ro/SSA may be demonstrated in a subset of CHLE patients [36]. However, in patients with SLE, Bouzaiz et al did not find association with anti-Ro antibodies [35]. Full-thickness skin grafts from unaffected regions resulted in persistent improvement in 2 reported cases, implying that local factors might be crucial in the pathophysiology [37].

Familial chilblain lupus (FCL) can arise due to loss-of-function mutations in TREX1, or less commonly SAMHD1, or gain-of-function mutations in TMEM173 (which encodes stimulator of interferon genes, STING). TREX1 is a 3'-to-5' DNA exonuclease which clears single and double stranded DNA in the cytoplasm. Defects in TREX1 leads to increased activation of the cGAS/STING pathway and subsequently increased expression of type 1 IFNs. Enhanced 1 IFN responses may therefore also be important in COVID-19-associated chilblains in which there are also high levels of type 1 interferon (IFN) as part of the antiviral response [41,42]. FCL has onset in childhood and may improve with age which contrasts with sporadic CHLE which is usually observed in middle-aged women [7]. Mutations in TREX1, SAMHD1 and TMEM173, along with RNASEH2A/B/C, ADAR and IFH1, are also associated with Aicardi-Goutières syndrome (AGS) which can cause retinal vasculopathy with cerebral leukodystrophy; up to 40% of patients with AGS experience CHLE-like lesions [1,38-40]. Chilblains or chilblains type lesions have been described quite frequently following development of COVID-19 [14,43]. COVID-19 toes/pseudo-chilblains seem to occur predominantly in children and young adults and appear to be a relatively late feature of COVID-19 [44,45]. Livedo or necrosis, with lesions suggesting occlusive vascular disease usually affects people with more severe COVID-19 whilst chilblains might be associated with

less severe manifestations of COVID-19 [14,46]. Histological studies suggest that chilblain-type lesions are associated with microthrombi [47]. Microhaemorrhages, pericapillary oedema and dilated capillary loops were observed on capillaroscopy [47]. A causative link between chilblains and COVID-19 remains inconclusive, especially since cold exposure does not appear to be a precipitating factor [48].

Diagnosis

Chilblains are generally diagnosed on clinical grounds with supporting histopathology in some cases (see Figure 1).

Diagnostic criteria have been proposed by the Mayo clinic for both CHLE (based on 5 patients in 1994) [10] and idiopathic chilblains [49]. To diagnose definite CHLE, patients must fulfil both the major criteria and at least one of the minor criteria (Table 2).

Some immunological anomalies are frequently observed (although not necessary for diagnosis) in CHLE, including hypergammaglobulinemia (>2/3 of patients), positive RF (~50%), ANA, anti-Ro/SSA, and antiphospholipid (APL) antibodies [5,7,50]. Skin biopsy can be helpful in diagnosis (see below).

Differential diagnosis

There is a broad range of differential diagnoses that one needs to consider (see Table 3).

Histopathology:

A skin biopsy may be useful in confirming as CHLE has specific pathological features which can help to differentiate CHLE from idiopathic chilblains and other skin lesions. Biopsies in idiopathic chilblains demonstrate an interface dermatitis, superficial and deep perivascular

lymphocytic infiltration with deep perieccrine reinforcement and dermal oedema. The epidermal changes include orthohyperkeratosis, necrotic keratinocytes and variable atrophy [5,51-53]. In CHLE, as opposed to idiopathic chilblains, epidermal spongiosis and perieccrine inflammatory infiltrate are not commonly seen [51], however there is vacuolisation of the basal layer of epidermis [9,10,53] (Figures 2 and 3). Wang et al reported a case-control study of 39 patients with idiopathic chilblains and 20 patients with CHLE. This study identified that increased dermal interstitial mucin deposition and fibrin exudate may help in distinguishing CHLE from idiopathic chilblains [54]. Studies with immunofluorescence have demonstrated that CHLE lesions are typified by linear deposits of immunoglobulins and complements in the dermo-epidermal junction, similar to discoid lupus – Table 4 describes the principal differences between idiopathic chilblains and CHLE [10]. There remain concerns about doing biopsies in patients with vasospastic conditions and impaired peripheral circulation, which reduces our understating of the etiopathogenesis and thereby treatment.

Immunohistochemistry is not helpful in distinguishing idiopathic chilblains from CHLE. In both idiopathic chilblains and CHLE the infiltrate shows CD3+ T cells associated with CD68+ macrophages and a few CD20+ B lymphocytes. A similar percentage and distribution of CD123 + cells in idiopathic pernio and CHLE is seen [51,54].

Treatment

Although chilblain lesions may respond to conservative measures, in refractory, recurrent or severe lesions, pharmacological interventions may be necessary [7]. The treatment aim in CHLE is to prevent development of new lesions and expedite the healing of current lesions to reduce discomfort and avoid scarring.

Conservative management

Conservative management includes avoidance of cold and damp, and use of insulated clothing, gloves and footwear [7]. There are no studies assessing the impact of these measures.

Pharmacological

The majority of studies describing treatment of chilblains are focused on primary chilblains. There are no randomised controlled trials (RCTs) of any agent in secondary chilblains. The majority of trials have included relatively small numbers of patients with short follow-ups, heterogenous outcomes and no data on recurrence and longer-term outcomes. As there are no trials in secondary chilblains, extrapolation of limited data in primary chilblains may be helpful. We identified RCT data for nifedipine, pentoxifylline, prednisolone and Tadalafil in primary chilblains. The key findings from trials are summarised in Table 5.

Topical treatments:

Topical corticosteroids do not appear to be particularly effective, although may be of some benefit [7,55,43]. Topical Glyceryl Trinitrate (GTN) 0.4% was found to be similar in efficacy to Nifedipine (initially 10-20mg daily, increased to 20-40mg daily) in a single blind randomised trial, although resolution was slower in the GTN arm [57]. Topical Tacrolimus and pimecrolimus have been used anecdotally with some benefit [7, 66].

Systemic treatments:

Vasodilators:

Nifedipine has inconsistent evidence in the treatment of primary chilblains. Studies suggest superiority to placebo in some studies but not others [56-60], with reports of superiority to Diltiazem [61] and topical 5% minoxidil solution [62].

Pentoxifylline

Pentoxifylline is a xanthine derivative that non-selectively inhibits phosphodiesterase [67] and has been shown to decrease blood viscosity and improve erythrocyte flexibility which have been postulated to be an important factor in the pathogenesis of chilblain lesions. It has demonstrated superiority to placebo [63, 65], oral Prednisolone and topical clobetasol [64] in studies.

Tadalafil

Tadalafil is a selective phosphodiesterase type 5 (PDE5) inhibitor with a long half-life (17.5 hours). An open label study demonstrated superiority over both pentoxifylline and prednisolone in terms of lesion severity after 2 weeks [65].

Immunomodulators and Immunosuppressive agents:

Prednisolone

As described above, RCT data for oral Prednisolone is inferior to both Pentoxifylline and Tadalafil in primary chilblains [64, 65].

Chloroquine or Hydroxychloroquine

There are no randomised controlled trials of Hydroxychloroquine (HCQ) or Chloroquine in CHLE. In 1912 Chipman et al were the first to report use of anti-malarials for perniosis. Quinine was suggested as being effective for both SLE and chilblains, although no data are

provided in this article [68]. A French meta-analysis of cutaneous manifestations of SLE (Chasset et al) suggested that anti-malarials were less effective in CHLE (response rate 31%) compared to acute cutaneous LE (response rate 91%) [69]. In a retrospective study of 5 patients by Yang et al, three with primary chilblains and two with SLE, HCQ improved chilblains in four patients which included both patients with SLE [70]. Patel et al and Horino et al reported successful use of HCQ in a patient with CHLE [71,72]. In a case series, Millard and Rowell reported HCQ and chloroquine were of benefit to three patients with CHLE. Discontinuation resulted in relapse of symptoms [5]. In case series of 15 patients Doutre et al reported that HCQ at 600mg dosage was effective after 3 months [4]. HCQ was found to be effective in four out of 15 patients with CHLE in a study by Bouaziz et al [35]. Su et al reported that only 1/5 patients treated with chloroquine saw a complete resolution of lesions within two months [10].

Mycophenolate Mofetil (MMF)

MMF has been successfully used in recalcitrant CHLE lesions in two cases [73,74]. Gammon et al reported 2 cases of CHLE with partial response to MMF as part of an open label series of 24 patients with different manifestations of CLE [75].

Anecdotal use of other therapies:

Due to lack of good quality evidence, a number of different drugs have also been tried in single or more cases and found to be of benefit (more often in primary chilblains). These include

Vasodilators: Etretnate, Diltiazem, amlodipine, Phenoxybenzamine, thymoxamine, prazosin (the last 3 are alpha blockers), Nicotinamide and niacin derivative pyridyl carbinol.

Others: Phototherapy, full thickness skin graft [37], chemical lumbar sympathectomy [76], Dapsone, vitamin D3 and vitamin K.

The authors are aware of the use of aspirin, together with vasodilators and HCQ in some patients, but we could not find any evidence for this. In CHLE, Raynaud's phenomenon often co-exists with chilblains, so a number of patients with CHLE may be prescribed vasodilators for this indication.

There are no studies looking at long term outcomes. In CHLE, experience suggests that it tends to fluctuate, and often the lesions recur in the same location. In some patients, there appears to be a correlation between lupus activity and CHLE flares whilst not in others. However, there are no studies describing this.

Limitations:

There are a number of limitations of this review particularly around the paucity and poor-quality data available on all aspects of secondary chilblains.

Conclusions:

Chilblains can be secondary to a number of different IMIDs with SLE being the commonest. Histologically, the skin in CHLE demonstrates other features of CLE such as deposition of immunoglobulins and complement in the dermo-epidermal junction as well as lymphocytic vasculitis. Studies in primary chilblains suggest better response to pentoxifylline and Tadalafil compared to topical corticosteroids and Nifedipine. Limited data are available on the epidemiology, treatment and long-term outcomes of secondary chilblains. More research is needed to understand the impact of chilblains in IMID patients and also to assess efficacy of Pentoxifylline and Tadalafil. Combination therapy with aspirin, vasodilators and

Hydroxychloroquine is also worthy of further study. The role of immunosuppression in CHLE remains unclear and well-designed clinical trials are needed.

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Data availability statement

All data relevant to the study are included in the article

Authorship:

All listed authors provided substantial contributions to this work. SD and NJ were involved with the conception and design. The literature review was led by NJ with help from SD and all the other listed authors. OS provided the figures for the article. All authors have contributed to the critical revision of the manuscript and agreed on the final version.

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Key messages:

1. Chilblains can be secondary to many different inflammatory conditions, SLE is the commonest (CHLE)
2. CHLE is differentiated from idiopathic chilblains by characteristic changes on histopathology and immunofluorescence.
3. Pentoxifylline and Tadalafil appear to have good efficacy in primary chilblains

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Tables and figures:

Table 1

Primary
Idiopathic
Secondary
IMIDs
Systemic Lupus erythematosus [4,11,12,13,14] including sporadic and familial forms
Antiphospholipid syndrome [15,16]
Behcet's disease [14]
Cryoglobulinemia [7,17-20]
Cold agglutinin [21]
Infections
Hepatitis B and C [22,23]
Covid-19 [11]
Haematological and Malignancy
Acute lymphoblastic leukaemia [24]
Chronic myelomonocytic leukaemia [25]
Monoclonal gammopathy of undetermined significance [22]
Leukaemia cutis [26]
Lymphoma [27]
Drug induced
Sulindac [28]
Infliximab [29] and other anti-TNF agents [30]
Others
Post traumatic perniosis [31]
Pregnancy [32]

Table 1: Conditions associated with chilblains

Table 2.

Two major criteria:

1. Skin lesions of acral sites induced by exposure to cold or a drop in temperature
2. Evidence of lupus erythematosus in the skin lesions, as determined by histopathologic examination or direct immunofluorescence

Three minor criteria:

1. Coexistence of systemic lupus erythematosus (SLE) or other skin lesion of discoid lupus erythematosus
2. Response to anti-lupus therapy
3. Negative cryoglobulin and cold agglutinin studies

Patients must fulfil both major criteria and at least one of the minor criteria to be diagnosed as having definite CHLE.

Table 2: Diagnostic criteria for CHLE proposed by Mayo clinic

Table 3

Frostbite and cold urticaria	are not confined to the extremities and can be reproduced by the ice cube test
Acrocyanosis	is permanent and painless. It presents with chronic coolness and violaceous discoloration of extremities
Erythromelalgia	evolves in paroxysmic crisis and is characterized by the triad of burning pain, recurrent redness and warmth of the extremities. These symptoms occur during exposure to heat, during exercise and in response to gravity and can be relieved by cooling and elevation.
Raynaud's phenomenon	is ischemic discolouration of fingers, toes, nose, etc on exposure to cold, stress or emotional upset due to spasm of blood vessels with vasodilatation and hyperaemia on removal of the stimulus.
Vasculitis	purpuric and more necrotic and is often associated with systemic symptoms but is easily confused with chilblains
Cold panniculitis	is common in young children is a form of lobular panniculitis that results from direct cold exposure. It typically occurs on cheek and chin. Erythematous, indurated plaques develop at the sites of cold exposure and resolve within a few weeks. In this condition, biopsy show lobular panniculitis and a superficial and deep perivascular lymphohistiocytic infiltrates
Blue toe syndrome	Embolism induced ischemia including Blue toe syndrome can often present with distal blue discolouration of a digit and can involve hands or feet
Cryofibrinogenemia	Can cause cryopathy which can lead to cold intolerance, Raynaud phenomenon, purpura, or livedo reticularis and in severe cases skin necrosis, acral ulcers, and gangrene.
Lupus pernio	Cutaneous sarcoidosis can present various types of lesions some of which are reddish purple nodules which may occur at peripheral site, but usually in the face or nose
Achenbach syndrome	is a benign condition associated with spontaneous bruising over the fingers along with burning pain usually on volar aspect of the hand.
Thromboangiitis obliterans or Buerger's disease	Is a rare inflammatory condition affecting young or middle aged smoking men causing distal ischemia and sometimes necrosis.

Table 3: Differential diagnosis of chilblains

Table 4.

	Idiopathic	CHLE
Histology	Dermal oedema with mixed immune infiltrate invading papillary and or reticular dermis. Inflammatory infiltrate is composed of mononuclear cells, mainly lymphocytes. Necrotic keratinocytes are seen, but commoner in idiopathic	
	Inflammation typified by perieccrine distribution	Perieccrine inflammation not typically seen
	Epidermal spongiosis may contain necrotic keratinocytes	Epidermal spongiosis not typically seen
	Vascular microthrombi can be found in the dermis.	
	Papillary dermal oedema commonly seen	
		Vacuolization of the basal layer of the epidermis is commonly seen
		Perivascular lymphocytic infiltrates and lymphocytic vasculitis in both superficial and deep layers seen
Immunopathology		Deposits of complement and immunoglobulins at dermo-epidermal junction
	Dermal interstitial fibrin exudate and mucin – less common	Dermal interstitial fibrin exudate and mucin – common
Immunohistochemistry	Infiltrate - mainly of CD3 + T cells associated with CD68 + macrophages and a few CD20 + B lymphocytes. Similar percentage and distribution of CD123 + cells in idiopathic chilblains and CHLE	

Table 4: Pathology and differences between primary and secondary chilblains.

Table 5

Study type, location, type of CB, year of publication	Intervention	Comparator	Numbers recruited (completed)	Outcome	Limitations
Topical corticosteroids					
Randomized placebo-controlled crossover trial, Netherlands, Primary, 2017 [55]	Betamethasone valerate (BMV) 0.1% cream twice daily for 6 weeks	Placebo	34 – 19 in intervention, 15 in placebo, no dropouts	No difference in outcomes VAS over 13 weeks	Study size
Vasodilators – Calcium channel blockers					
Randomized placebo-controlled crossover trial, England, primary, 1986 [56, 57]	Nifedipine retard 20 mg PO TID for 6 weeks	Placebo	10 in both arms	Positive nifedipine: 7/10 patients (70%) in the nifedipine group had resolution of lesions within 10 days (vs 20-28 days with placebo), and no new lesions developed while on treatment. Five patients initially treated with placebo relapsed within one week of starting placebo. For 3/5 patients (60%) in the placebo group, code was broken due to relapse severity and nifedipine was restarted with good response	Study size
RCT, India, unspecified, 2003 [58]	Nifedipine (plain) 10 mg PO TID until complete relief and then nifedipine extended release 20 mg PO daily (total duration 21 days)	Diltiazem 60 mg PO TID for 21 days	21 patients in nifedipine arm, 12 in diltiazem arm	Positive nifedipine: 21/24 patients (88%) in the nifedipine group showed 80% to 90% improvement by the 14th day, vs only 5/12 patients (42%) in the diltiazem group. 7/12 (58%) who had no response to diltiazem were switched to the nifedipine group between days 7-10.	Study size, blinding and type of chilblains not specified

RCT single blind, Pakistan, primary, 2014 [59]	Nifedipine retard 10-20 mg PO daily for 1 week, then 20-40 mg PO daily for 5 weeks if tolerated	Topical GTN (0.4%) cream applied twice daily for 6 weeks	34 (27) in Nifedipine arm, 31 (26) in GTN arm	Positive nifedipine: Nifedipine group achieved earlier clearance compared to GTN cream (10.9 +/- 6 days vs 16.6 +/- 11.5 days, P = 0.05)	Study size, blinding, ~ 18% drop out
RCT Single blind, Iraq, primary, 2010 [60]	Nifedipine Sustained Release 20 mg PO daily for 1 week, followed by 20 mg PO BID for 1 week	Topical 5% minoxidil solution applied twice daily for 2 weeks	42 (35) Patients in nifedipine arm, 20 (17) patients in minoxidil arm	Positive nifedipine: 20 patients (57%) in the nifedipine arm showed good improvement, 9 (25%) very good improvement, compared to 6 patients (35%) with good improvement and 1 patient (6%) with very good in the minoxidil group (P < 0.05)	Study size
Randomized placebo-controlled crossover trial, Netherlands, primary, 2016 [61]	Nifedipine controlled release (CR) 30 mg PO daily for 2 weeks, followed by nifedipine CR 30 mg PO BID for 4 weeks	Placebo	32(32)	No difference: After 6 weeks of treatment, mean scores on the VAS on symptoms showed no significant difference between nifedipine and placebo (P = 0.44). VAS on disability also no significant difference (P = 0.75)	Study size
RCT, open label, India, primary, 2018 [62]	Nifedipine 10 mg PO daily and oral antihistamines for 2 weeks	Topical 5% minoxidil gel twice daily and oral antihistamines for 2 weeks	42 in each – all completed	Positive nifedipine: 10/42 patients (23.8%) in the nifedipine group vs 3/42 patients (7%) in the minoxidil group showed very good improvement (P = 0.001)	
Vasodilators: other					
RCT, Iraq, primary, 2008 [63]	PTX 400 mg PO TID for 2 weeks	Prednisolone 2.5 mg/kg PO BID and clobetasol ointment for 2 weeks	20 (9) in pentoxifylline group, 20 (11) in corticosteroid group	Positive PTX: Prednisolone and clobetasol group 3/11 (27%) who completed treatment had “good improvement,” compared to 5/9 (56%) in the PTX group (P < 0.05)	Study size, very high dropout rate

RCT, open label, Iraq, primary, 2015 [64]	Group A: Tadalafil 5 mg PO daily for 2 weeks. Group B: PTX 400 PO TID for 2 weeks Group C: prednisolone 15 mg PO BID for 2 weeks		Group A: 19 (15) Group B: 18 (13) Group C: 21 (19) Overall, 58 (47) patients recruited	Tadalafil > PTX > prednisolone: Percentage improvement in severity score was 50.65, 44.16, and 31.51%, for tadalafil, PTX, and prednisolone groups respectively (ANOVA P value = 0.004)	
RCT, double blind placebo controlled, Iraq, primary, 2016 [65]	PTX 400 mg PO TID for 3 weeks	Placebo	59 (55) PTX 59 (55) Placebo	Positive PTX: 40/55 (72.7%) PTX patients achieved very good response at 3 weeks vs 11/55 (20%) placebo patients (P < 0.0001)	

Legend: RCT: Randomised controlled trial; PO: per oral; GTN: Glyceryl Trinitrate; VAS: visual analog scale; TID: thrice daily, BID: twice daily; PTX: pentoxifylline

Table 5: Summary clinical trial data in chilblains.