BMJ Best Practice

Raynaud's phenomenon

The right clinical information, right where it's needed

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Summary

- Raynaud's phenomenon (RP) is common, affecting between 1% and 3% of the population.
- The diagnosis is made clinically: digits turn white (pallor) then blue with deoxygenation and/or red with reperfusion; pallor is well demarcated.
- Primary RP often needs no pharmacological treatment. Keeping warm, smoking cessation, regular exercise, and avoiding stress are recommended.
- Secondary RP can be severe, especially when associated with scleroderma. Other connective tissue diseases, malignancy, and atherosclerosis may also be the underlying cause.
- In secondary RP, calcium-channel blockers, angiotensin receptor antagonists, ACE inhibitors, SSRIs, systemic and topical nitrates, phosphodiesterase-5 inhibitors, and prostacyclins are potential treatment options.
- Complications in secondary RP include severe digital ischaemia, gangrene, digital ulcers, and infection.
- Pain relief may be an important adjunctive treatment. There are few data for complementary therapies.

Definition

Raynaud's phenomenon (RP) is characterised by vasospasm that causes digits to change colour to white (pallor) from lack of blood flow, usually brought on by cold temperatures. Affected areas subsequently turn blue due to de-oxygenation and/or red due to reperfusion. It can be a painful condition and can lead to complications.

Epidemiology

RP occurs in approximately 1% to 3% of the population and is more common in women. The prevalence of primary RP varies by sex, country, and exposure to vibration in the workplace. One large US cohort study found symptoms in 9.6% of women and 8.1% of men, of whom 81% had primary RP.[3] Smaller cohort studies from Spain[4] [5] and Japan[6] have estimated the prevalence of RP to be 3.0% to 4.0%, with 90% having primary RP.

Aetiology

The cause of primary RP is not known. Vasospasm is a normal reaction to cold or temperature change, but this is exaggerated in primary RP. Many factors are up-regulated in primary RP and more so in secondary RP. These factors include calcitonin gene-related peptide (CGRP), substance P, neurokinin A, vasoactive intestinal peptide (VIP), serotonin receptors, and endothelin. Dermal arterioles from uninvolved skin in diffuse systemic sclerosis have shown increased adrenoreceptor reactivity that is endothelium independent.[7] Genetics is associated with RP, but this relationship appears to be polygenic and differs according to ancestry. For instance, in idiopathic/primary RP, there may be a family history of primary or secondary RP. Likewise, in secondary RP, a family history of connective tissue disease with/without RP or a family history of idiopathic RP may be present.[8] [9] [10] [11] Glaucoma and migraines have also been associated with RP. It has been thought that beta-blockers may worsen RP, but this now appears unlikely. Randomised controlled trials have shown that beta-blockers may decrease vasospasm, although the mechanism of action is unclear. This reduction in symptoms may represent a similar mechanism to that seen when beta-blockers are used for migraine prevention.[12] [13]

Pathophysiology

RP is reversible vasospasm causing pallor and cyanosis and/or rubor, especially of the fingers. It may also appear on the toes and more rarely the ears or nose. The onset of secondary RP may pre-date a connective tissue disease, such as limited cutaneous systemic sclerosis, by several years or may coincide with onset of diffuse cutaneous systemic sclerosis or polymyositis. RP can occur at any time with rheumatoid arthritis, SLE, or Sjogren's syndrome. It is often an early feature of many connective tissue diseases. Secondary RP is characterised by abnormal vasospasm, but abnormalities of the blood vessel endothelium such as calcitonin gene-related peptide (CGRP), endothelin, and vascular endothelial growth factor are also evident.[14] Also, nitrous oxide production changes when the endothelium is damaged, which is important in RP, especially in systemic sclerosis. In connective tissue disease, the most severe RP is associated with scleroderma where the blood vessels are in spasm. However, significant intimal proliferation and limited blood flow occur in blood vessels affected by scleroderma, thus worsening the symptoms of RP.

Classification

Primary or idiopathic Raynaud's phenomenon (RP)

RP not associated with an underlying cause.

Secondary Raynaud's phenomenon (RP)

RP associated with an underlying cause such as connective tissue disease (especially systemic sclerosis, also known as SSc or scleroderma), vasculitis, malignancy, or peripheral vascular disease.

Secondary prevention

The risk of attacks can be mitigated by avoiding cold, dressing warmly, not smoking, exercising, and avoiding stress.

Case history

Case history #1

An 18-year-old healthy woman presents with fingertips that turn white, then blue and red, in the cold. She is otherwise well and is a non-smoker. Her symptoms have been occurring for 3 years. Her mother has RP. The remainder of her history and physical examination are unremarkable. She has a normal full blood count and a negative ANA. She has primary RP.

Case history #2

A 50-year-old woman has developed puffy hands, new RP, and difficulties swallowing over the last year. Her chest and abdominal examinations are unremarkable. She does not have inflammatory arthritis. She has some small dot-like telangiectasia on her hands and lips. Her ANA is positive and has a nucleolar pattern. There are dilated capillaries seen at the nailbed, proximal to the nail, on several fingers. She currently has a digital ulcer. She has systemic sclerosis (scleroderma).

Other presentations

RP causes pain, discomfort, and sometimes paraesthesia. Rarely, ulcers on the fingers and toes occur (and much less commonly on the ears, nose, hand, wrist, or forearm). More severe cases usually occur only when RP is secondary to an underlying cause, in particular connective tissue disorders such as scleroderma, SLE, Sjogren's syndrome, rheumatoid arthritis, or polymyositis. Secondary RP is associated with vasculitis, severe peripheral vascular disease (such as Buerger's disease), and rarely malignancy or chemotherapy. Vibration trauma (e.g., occupational exposure in jackhammer operators) can precipitate RP. This form of secondary RP is different from others in that there is not necessarily a fixed defect of the vascular walls of arteries/arterioles, whereas in other secondary RP there are potentially more exaggerated vascular abnormalities and endothelial dysfunction.[1] [2] In medium vessel vasculitis disorders such as polyarteritis nodosa and occasionally SLE, gangrene of the fingertip or entire finger may occur.

Step-by-step diagnostic approach

The work-up should include:

- Clinical symptoms compatible with Raynaud's phenomenon (RP)
- A history to determine the frequency/severity of the attacks
- Smoking history
- Review of systems
- Family history (FHx) of RP and other connective tissue disease
- Physical examination focusing on features of RP and associated connective tissue disease
- Investigations may include FBC, ESR, ANA, creatinine, and urinalysis
- Referral to a rheumatologist or other specialist if necessary (i.e., for determining if RP is secondary to a connective tissue disease and/or help with respect to treatment in severe RP).

History

RP is diagnosed following a thorough history eliciting features of pallor of digits with subsequent cyanosis and/or then rubor. It is normal for digits to turn mottled or cyanotic in the cold; pallor should be present to make the diagnosis. The history should focus on:

- The location (fingertips or tips of the toes)
- A clear demarcation of colour change
- Cyanosis and/or rubor on rewarming.

Indicators of increased severity of RP are attacks in warm weather (without exposure to cold or air conditioning), late onset RP (age >40 years), and the presence of complications such as digital ulcers.

A review of systems should rule out secondary causes such as connective tissue disease, which could include inflammatory arthritis, morning stiffness, rash, photosensitivity, alopecia, significant dry eyes/dry mouth, puffiness of fingers or tightness of the skin, or significant oesophageal dysmotility/GORD.

A FHx of RP and other connective tissue disease such as rheumatoid arthritis, SLE, scleroderma, Sjogren's syndrome, polymyositis, and juvenile idiopathic arthritis should be sought. Other causes of secondary RP may be obvious, such as malignancy, chemotherapeutic exposure, or severe peripheral vascular disease.

RP can be confused with other vascular diseases, but biphasic or triphasic colour change is not present in these conditions. Onset of primary RP is rare after 40 years of age and often begins in adolescence. If the patient is young and has no signs/symptoms of connective tissue disease, primary RP should be suspected. In this instance, no more than a good history and physical examination are necessary.

Examination

Physical examination should include:

- An overview of general health and BP
- Signs of connective tissue disease
- Peripheral vascular disease: peripheral pulse should be checked. If RP sounds atypical (e.g., older age of onset of symptoms compatible with systemic disease), then blood pressure should be checked in both arms to rule out major discrepancies between arms, and the presence of carotid bruits should be checked. Giant cell arteritis and Takayasu's arteritis, for example, can be accompanied by large vessel narrowing, which can affect blood pressure in a limb and can also produce carotid bruits.
- Magnification with an otoscope or ophthalmoscope to study the nailbeds of the fingers. A dermatoscope can be used and is a reliable technique for identifying abnormal capillaries and connective tissue disease. It has 10 times magnification and uses polarised light.[27]
- Evidence of complications, including digital ulcers, digital pits (fibrotic plugs from ischaemia), digital tuft resorption, threatened ischaemic digit, gangrene of the fingertip/entire finger, infection including osteomyelitis, or auto-amputation.
- Livedo reticularis may be associated with the antiphospholipid antibodies (e.g., anticardiolipin antibodies and lupus anticoagulant).

Management of concomitant connective tissue disease is crucial in improving outcomes in RP. The likelihood of underlying connective tissue disease increases when age of onset is more than 40 years. Strongly positive ANA and/or the presence of visible dilated capillaries at the nailbeds are also suggestive

of underlying connective tissue disease. Dilated capillaries result from dropout of capillaries with secondary hyperplasia and hypertrophy of the remaining blood vessels. On inspection, these capillaries can appear like discrete red pen marks and are often seen around the cuticle.

A referral to a rheumatologist should be considered if standard treatment is ineffective and/or if RP is severe and complications such as digital ulcers are present. The presence of digital ulceration is generally thought to exclude a diagnosis of primary RP, and so a secondary cause should be sought if ulceration occurs.

Secondary RP may pre-date a connective tissue disease such as limited systemic scleroderma by several years or may coincide with the onset of diffuse cutaneous systemic sclerosis or polymyositis. RP can occur at any stage in rheumatoid arthritis, SLE, or Sjogren's syndrome. Complications of secondary RP may be present, such as ulcers, digital pits, or digital tuft resorption.

Investigations

If the patient has new-onset RP, is more than 40 years old, and/or has features from history or physical examination that suggest secondary causes, the following may be carried out:

- ANA with titre and pattern
- FBC
- ESR
- Serum creatinine
- Urinalysis.

Follow-up should take place if a patient has:

- Strongly positive ANA
- Dilated capillaries at the nailbed
- An uncommon ANA pattern such as an anti-centromere pattern
- An elevated ESR (less predictive).

Follow-up should take place, as 30% will develop a connective tissue disease within the next 5 years. In particular, an anti-centromere antibody and/or dilated capillaries at the peri-ungual region are predictive for scleroderma.[28]

Rarely, RP can be caused by obstruction of blood flow by a cervical rib. This can be identified on CXR, although this investigation is not carried out routinely on patients with mild RP and is ordered only if there is a high index of suspicion.

No investigations are necessary if by history and physical examination there are no clues that a secondary cause of RP is present.

Risk factors

Strong

female

- Primary RP is more common in women than men.

- Secondary RP is more common in women (up to 9:1) in conditions such as SLE, scleroderma, and other connective tissue diseases.

FHx

- In primary or secondary RP, a family history of RP or connective tissue disease may be present.[9] [10] [11]

connective tissue disease

- RP occurs in 20% of patients with rheumatoid arthritis,[15] 40% to 45% with SLE,[16] 13% to 17% with Sjogren's syndrome,[17] [18] 10% with polymyositis,[19] >80% with mixed connective tissue disease,[20] and >90% with scleroderma.[21]

vibration injury

- Vibration injury is also called hand-arm vibration syndrome and occurs from repeated use of vibrating hand-held machinery. Jackhammer operation and other causes of vibration injury increase the risk of developing RP.[22] It can cause numbness, tingling, and pain and may persist even after the occupation ceases. It occurs more often with tools of a certain acceleration amplitude and if used for longer duration. There is no diagnostic test, so the history and observed RP can be helpful.[23]

Buerger's disease

- Buerger's disease is also known as thromboangiitis obliterans. There is repeated inflammation and thrombosis of digital arteries or arterioles. Smoking is a major risk factor, but even chewing tobacco is a risk. Accelerated atherosclerosis can cause RP, but often there is no Raynaud's but instead very cold fingers often with ulcers. It is more common in men and often between the ages of 20 and 40 years.[24] An angiogram may be needed to make the diagnosis, including use of MR angiography. The arteries can have a corkscrew appearance from vascular damage, especially at the wrist or ankle. It is often a diagnosis of exclusion (ruling out endocarditis, connective tissue diseases, and hypercoagulable states). There is probably an immunological risk as well, but smoking cessation is mandatory in the treatment. The treatment otherwise is not standardised but can include antiplatelet medications, vasodilators, and lipid-lowering drugs if ulcers are present, and there are studies with PGE1 given orally and streptokinase.[25]

Weak

prolonged cold exposure/frostbite

- There have been case reports of RP onset after frostbite.

colder climate

- The prevalence of RP is higher in colder climates.

smoking

- Smoking can exacerbate RP.[26]

ischaemia

- Vascular ischaemia (e.g., subclavian steal syndrome or peripheral vascular disease) can cause RP.

migraine

- RP may be more common in people with migraines.

glaucoma

- RP may be more common in people with glaucoma.

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Risk factors include female sex, family history of RP[11] and/or connective tissue disease, presence of connective tissue disease, vibration injury, prolonged cold exposure/frostbite, colder climate, smoking, ischaemia, Buerger's disease, glaucoma, and migraine.

digit pain/discomfort (common)

- Common presenting symptom.

digital paraesthesia (common)

- Paraesthesias can occur when the fingers are re-warming. However, paraesthesias are common and non-specific, so RP would not be considered in a patient with hand paraesthesias without a history of well-demarcated pallor of fingers.

pallor of digits (common)

- This must be present to diagnose primary and secondary RP.

red and/or blue discoloration of digits (common)

- At least one must be present to diagnose primary RP and secondary RP.

dilated capillaries at nailbeds (common)

- Occurs mainly in secondary RP; if present, secondary RP should be assumed until proven otherwise.

well-defined discoloration (common)

- In all cases of RP there are well-defined areas of pallor, which then display cyanosis followed by rubor.

magnification of nailbeds (common)

- Presence of dilated capillaries at the nailbeds that look like red pen marks are often seen at the cuticle. This finding is highly specific for secondary RP, although not sensitive. It helps to rule in secondary RP if positive.[29]

Other diagnostic factors

heartburn (uncommon)

- May indicate secondary RP.

dysphagia (uncommon)

- May indicate secondary RP.

puffy hands (uncommon)

- May indicate secondary RP.

tight skin (uncommon)

- May indicate secondary RP.

arthralgia (uncommon)

- May indicate secondary RP.

photosensitivity (uncommon)

- May indicate secondary RP.

oral/nasal ulcers (uncommon)

- May indicate secondary RP.

alopecia (uncommon)

- May indicate secondary RP.

butterfly rash (uncommon)

- May indicate secondary RP.

sclerodactyly (uncommon)

- May rarely be a complication of long-standing and frequent RP but if not in a patient with connective tissue disease, the tightening of the skin is usually distal to proximal interphalangeal joints (i.e., not entire fingers).

telangiectasia (uncommon)

- May indicate secondary RP.

pleuritic chest pain (uncommon)

- May indicate secondary RP.

digital ulcers (uncommon)

- A recognised complication of RP. The presence of digital ulceration is generally thought to exclude a diagnosis of primary RP, and so a secondary cause should be sought if ulceration occurs.

digital pits (uncommon)

- A recognised complication of RP.

digital tuft resorption (uncommon)

- A recognised complication of RP.

gangrene of fingertip/finger (uncommon)

- A recognised complication of RP.

raised painful red lesions on finger tips (uncommon)

- Sometimes RP's features are accompanied by chilblains (perniosis), but this is a separate condition with red raised areas on tips of toes or fingers in the cold, often like frostbite. They may heal with desquamation, may be painful, are often multiple, and may be cyclical.

auto-amputation (uncommon)

- A recognised complication of RP. Nearly only in secondary RP.

Diagnostic tests

1st test to order

Test	Result
clinical diagnosis • No investigations are necessary if by history and physical examination there are no clues that a secondary cause of RP is present.	**clinical features of RP**
ANA • Ordered if connective tissue disease, especially SLE, is suspected. • Normal in primary RP. • In secondary RP is often positive with a centromere pattern. • Thirty percent of RP patients with a positive, centromere pattern ANA will develop scleroderma in the following 5 years.[28]	**strongly positive ANA or uncommon pattern such as centromere or nucleolar are suggestive of secondary RP; however, a positive ANA is common in the general population**
FBC • Normal in primary RP, may be abnormal in secondary RP. Any connective tissue disease may cause anaemia. In SLE, cytopenias are often present.	**normal in primary RP; may show low WBC, anaemia, and low platelet count in secondary RP**
ESR • Normal in primary RP, may be elevated in secondary RP.	**normal in primary RP; may be elevated in secondary RP**
creatinine	**normal in primary RP; creatinine may be elevated in secondary RP**
urinalysis • Normal in primary RP; may show RBCs and/or protein in secondary RP such as in SLE or vasculitis with active glomerulonephritis.	**normal in primary RP; may show RBCs and/or protein in secondary RP**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Normal response to cold	• Normal hands can be mottled in cold. RP has classic pallor that is well demarcated.	• No differentiating tests.
Cyanosis/ cryoglobulinaemia	• Blue digits in cold but no distal digital pallor.	• Detection of circulating cryoglobulins.

Condition	Differentiating signs / symptoms	Differentiating tests
Chilblains (perniosis)	• Symptoms include pruritus, erythema, and ulceration. • An acute response to cold temperatures but can be chronic.	• No differentiating tests.
Acrocyanosis	• There is no ischaemia (no pallor in this condition), which is characterised by non-paroxysmal, in most cases persistent, painless bluish-red symmetrical discolorations of the hands and often the feet. History with lack of pallor (no well-demarcated white colour change).[1]	• No differentiating tests.
Erythromelalgia	• Usually provoked by heat. • Characterised by painful red extremities, burning, and increased skin temperature of affected area.[1]	• Thrombocytosis may be underlying cause.
Livedo reticularis	• Lacy purple appearance of skin at extremities. • Venous blood flow sluggish. • Usually found on legs.	• May be positive for antiphospholipid antibodies (e.g., anticardiolipin antibodies, lupus anticoagulant).
Carpal tunnel syndrome	• Numbness and tingling of fingertips, with no distal digital pallor. • Associated conditions may be present: pregnancy, hypothyroidism, diabetes, or rheumatoid arthritis. • Positive Tinel's or Phalen's test in carpal tunnel syndrome. Lack of colour change in carpal tunnel syndrome.	• Nerve conduction studies: focal slowing of conduction velocity in the median sensory nerves across the carpal tunnel (necessary only if symptoms are severe or there is wasting of the thenar eminence). • Elevated TSH, blood glucose, and serum abnormalities of other associated conditions may be present.
Cervical rib or other subclavian compression	• May develop RP, but ischaemia is often positional with the arm above the head.	• CXR may demonstrate cervical rib. Routine screening of mild RP would not require this investigation, as it would be performed only if there was a high index of suspicion.

Condition	Differentiating signs / symptoms	Differentiating tests
Subclavian steal syndrome	• Symptoms/signs of peripheral ischaemia usually present unilaterally. • Dizziness, syncope, and vertigo common.	• Duplex ultrasonography demonstrates retrograde blood flow and occlusive lesions of vascular architecture.

Step-by-step treatment approach

Many cases of Raynaud's phenomenon (RP) do not require pharmacological treatment unless symptoms become severe. Non-pharmacological interventions should be considered first: for example, keeping warm,1[C]Evidence and smoking cessation.2[C]Evidence Advice should be given about avoiding injury to the digits, moisturising dry skin, and avoiding drugs known to exacerbate RP, such as cocaine and ergotamine.

Systematic reviews of RP treatments have concluded that there is sufficient evidence for the use of calcium-channel blockers for RP, and for the use of intravenous iloprost for severe RP.[31] [32]There is also sufficient evidence for the use of phosphodiesterase-5 (PDE-5) inhibitors[33] and nitrates (oral or topical) for RP,3[B]Evidence but there is little or no high-level evidence for other treatments.

Primary RP is virtually never associated with irreversible tissue damage. Consequently, if RP is accompanied by digital tip ulceration or critical ischaemia, if usual treatment is ineffective, or if there is suspicion of connective tissue disease or other underlying condition, not only is treatment warranted but the patient should be referred to a rheumatologist.

First-line pharmacological treatments

The goals of pharmacological treatment are to decrease frequency, severity, and duration of attacks. Clinical trial data mainly support the first 2 treatment outcomes. The recommended first-line pharmacological treatment is calcium-channel blockers.[31] Studies have shown that these drugs decrease the frequency/severity of attacks, often by 30%.[38] Recommended agents include nifedipine,4[A]Evidence nicardipine,5[C]Evidence and less well-studied agents, including amlodipine6[C]Evidence or felodipine. Diltiazem should be offered as a third-line treatment in this class.7[B]Evidence Calcium-channel blockers do not work in everyone and may have side effects such as hypotension, lightheadedness, flushing, and ankle puffiness. Short-acting calcium-channel blockers may cause orthostatic hypotension, and many people with RP are young and have normal-to-low BP. However, if the drug is tolerated and efficacy is not obtained, then the dose can be increased. A Cochrane meta-analysis also demonstrated that dihydropyridine calcium-channel blockers are effective in primary RP.[32]

Second-line pharmacological treatments

When calcium-channel blockers have failed or are not tolerated, alternatives include the angiotensin-II receptor antagonist losartan,8[B]Evidence the selective serotonin-reuptake inhibitor (SSRI) fluoxetine,9[B]Evidence topical nitrates,3[B]Evidence alpha-blockers,10[C]Evidence or ganglion blockers. The angiotensin-converting enzyme (ACE) inhibitor captopril can also be used as an alternative to a calcium-channel blocker,11[B]Evidence but other ACE inhibitors, such as quinapril, may not be effective.[55] In the past, ganglion blockers were used to treat RP, but they are rarely used now as more effective and better tolerated treatments are available for RP. There is some weak evidence to support the use of naftidrofuryl in RP,12[C]Evidence but this drug is not widely used for RP.

Severe disease

Oral PDE-5 inhibitors (e.g.. sildenafil, tadalafil, vardenafil, and udenafil) can be used for patients with moderate to severe secondary RP, or when first- and second-line drug treatments have failed or are not tolerated.[33] Two trials have shown positive benefit with sildenafil in RP. One was a multi-centre trial that studied limited cutaneous systemic sclerosis patients with significant RP who were non-smokers, while the other was a single-site crossover trial in patients with RP.[57] [58] Tadalafil has also shown positive results in an RP trial in scleroderma and mixed connective tissue disease patients with at least

4 attacks per week. The medication was effective and also seemed to help digital ulcers, which was a secondary end point.[59] Similarly, when examining the results of vardenafil compared with placebo in a randomised crossover trial, there was a reduction in the number of attacks per week, the cumulative duration of attacks, and the Raynaud's Condition Score in 53 patients with either primary or secondary RP.[60] One PDE-5 inhibitor trial has shown negative data for RP.[61] A small crossover trial comparing the PDE-5 inhibitor udenafil (currently only available in a small number of countries) with amlodipine (a dihydropyridine calcium-channel blocker) in RP found no difference between the two drugs for primary and secondary outcomes.[62] However, it did show that digital blood flow was better with udenafil. This study was probably underpowered to show differences, but adds support to the approach that both dihydropyridine calcium-channel blockers and PDE-5 inhibitors may be effective in treating patients with RP who require medication. Long-acting PDE-5 inhibitors (e.g., tadalafil, udenafil) may be better tolerated than short-acting PDE-5 inhibitors, causing less hypotension and perhaps better adherence.

Intravenous prostacyclins (especially iloprost [31]) plus oral sildenafil13[B]Evidence are used to treat complications of severe RP, such as threatened digital loss due to ischaemia and digital ulcers. These drugs can be effective for several months after treatment. Treatment has been shown to decrease the frequency/severity of attacks and heals/prevents digital ulcers. Atorvastatin has also been found to decrease new ulcer formation in patients with secondary RP and should be used in patients with past or present digital ulcers.[63] Bosentan, an endothelial receptor antagonist, has also been used for the prevention of digital ulcers. Endothelin is up-regulated in the digital arteries and finger pulp in scleroderma. It has been found to reduce the incidence of new ulcers by 30% to 50%. However, it is not superior to usual care in healing current ulcers. It has no effect on RP in the systemic sclerosis digital ulcer trials.[64] [65] [66] Aspirin may be beneficial in helping prevent micro-thrombi formation, but there are no trials with aspirin in RP.

If there is a large fingertip ulcer, then secondary causes of RP are to be considered. For some digital ulcers, debridement by a surgeon may be necessary to remove necrotic tissue and/or infection and promote healing. Treatment with antibiotics is not necessary for most digital ulcers; however, antibiotics should be considered when ulcers are infected. Infections are often due to *Staphylococcus* species from the skin. Cloxacillin or cephalexin are used, and erythromycin or a fluoroquinolone may be considered in penicillin-allergic patients. If there is frank purulence, it is advisable to take a swab for culture and sensitivities prior to starting antibiotics. Topical antibacterials can be used if there is no evidence of a significant infection, but they may be working as a barrier and lubricant more than an antibacterial. If gangrene has progressed in spite of treatment, amputation of the digit may be required.

Intravenous iloprost is generally considered to be the first-line prostacyclin; however, the intravenous formulation is not available in several countries worldwide, and the inhaled formulation is generally not recommended for this indication. Intravenous epoprostenol can be used as an alternative to intravenous iloprost. Inhaled prostacyclins are not commonly used for RP; however, they have a role in treating pulmonary arterial HTN in connective tissue diseases and can improve RP symptoms. Oral prostacyclins are usually not stable and/or well absorbed and tend to be less effective than intravenous iloprost.[67] [68]

Other treatments

Surgical sympathectomy may be effective in the treatment of severe RP that has failed pharmacological treatment. Techniques available include stellate ganglion or lumbar sympathetic blocks, proximal cervical sympathectomies via endoscopic surgery, and selective palmar and/or digital sympathectomies.[69] Such techniques may not be available in all centres. If a stellate ganglion or lumbar sympathetic block is

successful, it may indicate that selective palmar or digital sympathectomy may be effective. Although this is rarely indicated, if successful it may help RP for years.

For many other treatments there is weak evidence or historical wisdom. However, some patients with complicated or severe secondary RP may warrant unproven therapies after failing the usual standard of care. Complementary and alternative therapies that have been investigated in randomised controlled trials include evening primrose oil,[39] 14[C]Evidence omega-3 fatty acids,[71] 15[C]Evidence *Ginkgo biloba* ,[72] [73] 16[C]Evidence biofeedback, acupuncture,[74] 17[C]Evidence low-level laser therapy,[75] 18[C]Evidence and ceramic-impregnated gloves.[30] 19[C]Evidence A review and meta-analysis of complementary and alternative medicines in the treatment of RP found most trials were negative, of poor quality, and done prior to 1990.[76] However, given the limited risks associated with these treatments, using them as an adjunctive therapy may be considered for patients at any stage of RP severity, but data are primarily negative or there is an overall lack of proof. Choice of treatment may depend on patient preference.

A study involving patients with RP who were deficient in vitamin D showed improvements on the visual analogue scale with use of oral vitamin D3 supplementation compared with placebo supplementation.[77]

Pain relief is an important component of symptom management. Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. NSAIDs, paracetamol, and anti-convulsants should be considered, and topical preparations may be suitable if pain is particularly localised. In severe cases of recalcitrant disease, oral/transdermal opioid analgesics may be required.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Acute (summary)

Patient group	Tx line	Treatment
severe secondary RP: critical ischaemia with digital ulcers or threatened digital loss	**1st**	**prostacyclin and/or phosphodiesterase-5 inhibitor**
	plus	**treatment of underlying condition**
	plus	**atorvastatin**
	adjunct	**analgesia**
	adjunct	**aspirin**
	adjunct	**surgical debridement**
	adjunct	**systemic antibiotics**
	adjunct	**topical antibacterial ointment**
	adjunct	**bosentan**

Acute (summary)

2nd	surgical sympathectomy
plus	treatment of underlying condition
plus	atorvastatin
adjunct	analgesia
adjunct	aspirin
adjunct	surgical debridement
adjunct	systemic antibiotics
adjunct	topical antibacterial ointment
adjunct	bosentan

Ongoing (summary)

Patient group	Tx line	Treatment
primary or mild secondary RP	1st	supportive treatment
	adjunct	analgesia
	adjunct	complementary and alternative therapies
	2nd	calcium-channel blocker + supportive treatment
	adjunct	analgesia
	adjunct	complementary and alternative therapies
	3rd	angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist + supportive treatment
	adjunct	analgesia
	adjunct	complementary and alternative therapies
	3rd	selective serotonin-reuptake inhibitor + supportive treatment
	adjunct	analgesia
	adjunct	complementary and alternative therapies
	3rd	topical nitrate or vasodilator + supportive treatment
	adjunct	analgesia
	adjunct	complementary and alternative therapies
	4th	alpha-blocker + supportive treatment

Ongoing		(summary)
	adjunct	analgesia
	adjunct	complementary and alternative therapies

Treatment options

Acute

Patient group	Tx line	Treatment
severe secondary RP: critical ischaemia with digital ulcers or threatened digital loss	**1st**	**prostacyclin and/or phosphodiesterase-5 inhibitor** » Trials have shown a positive benefit with sildenafil in RP.[57] [58] A prostanoid would not normally be combined with a phosphodiesterase-5 (PDE-5) inhibitor due to the potential for drug interactions. Also, combining a prostacyclin and PDE-5 inhibitor can cause significant hypotension. However, if a patient has severe enough RP to warrant prostanoid treatment, the patient would probably be referred to an expert centre where a combination treatment may be considered. In systemic sclerosis, after failure of calcium-channel blockers for severe and moderate RP, adding or switching to PDE-5 inhibitors would be considered by experts.[78] » Longer-acting PDE-5 inhibitors such as tadalafil are also used. Although once-a-day dosing for tadalafil is more convenient, it has shown positive findings in RP only in a small crossover study,[59] but not in combination with prostacyclins. A trial of vardenafil versus placebo in RP has shown that vardenafil is associated with a reduction in frequency and duration of RP attacks and Raynaud's Condition Score.[60] » Intravenous prostacyclins (particularly iloprost[31]), sometimes in combination with oral sildenafil,13[B]Evidence are used to treat complications of severe RP, such as threatened digital loss due to ischaemia and digital ulcers. These drugs can be effective for several months after treatment. » Treatment with prostacyclins alone has been shown to decrease the frequency/severity of attacks and heals/prevents digital ulcers. Intravenous iloprost is generally considered to be the first-line prostacyclin; however, the intravenous formulation is not available in several countries worldwide, and the inhaled formulation is generally not recommended for this indication. Intravenous epoprostenol can be used as an alternative to intravenous iloprost. » Inhaled prostacyclins are not commonly used for RP; however, they have a role in treating pulmonary arterial HTN in connective tissue

Acute

Patient group	Tx line	Treatment

diseases and can improve RP symptoms. Oral prostacyclins are usually not stable and/or well absorbed and tend to be less effective than intravenous iloprost.[67] [68]

Primary options

» iloprost: consult specialist for guidance on dose

OR

Primary options

» epoprostenol: 2 nanograms/kg/min intravenous infusion initially, increase by 2 nanograms/kg/min every 15 mins or longer according to response
Use permanent central line. Dose escalation dependent on tolerability.

OR

Primary options

» sildenafil: 12.5 mg orally twice daily initially, increase according to response, maximum 100 mg/day (given in 2-3 divided doses)

OR

Primary options

» tadalafil: 5-40 mg orally once daily

OR

Primary options

» vardenafil: consult specialist for guidance on dose

OR

Secondary options

» iloprost: consult specialist for guidance on dose
-or-
» epoprostenol: 2 nanograms/kg/min intravenous infusion initially, increase by 2 nanograms/kg/min every 15 mins or longer according to response
Use permanent central line. Dose escalation dependent on tolerability.

--AND--

Acute

Patient group	Tx line	Treatment
		» sildenafil: 12.5 mg orally twice daily initially, increase according to response, maximum 100 mg/day (given in 2-3 divided doses) **-or-** » tadalafil: 5-40 mg orally once daily **-or-** » vardenafil: consult specialist for guidance on dose
	plus	**treatment of underlying condition** » Treatment for the underlying condition that has resulted in secondary RP should be instigated after appropriate specialist consultation.
	plus	**atorvastatin** » Atorvastatin has been found to decrease new ulcer formation in patients with secondary RP and should be used in patients with past or present digital ulcers.[63] **Primary options** » atorvastatin: 40 mg orally once daily
	adjunct	**analgesia** » Pain relief is an important component of symptom management. Vasodilators treat the pain of RP if they are effective in reducing the frequency, severity, or duration of attacks. It is not common to use analgesics for RP; however, they may be required to treat pain from severe or prolonged ischaemia or complications such as gangrene or digital ulcers. » Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. Simple analgesics such as paracetamol and NSAIDs may be sufficient. Short- or long-acting narcotics may be required. Digital ulcers may be very painful, and codeine or oxycodone may be indicated. Rarely, transdermal fentanyl is used if other opioids are not effective or not tolerated, typically for patients with gangrene or osteomyelitis. Local palmar and/or digital sympathectomy is a last-line option. **Primary options** » paracetamol: 500-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day **OR**

Acute

Patient group	Tx line	Treatment
		Primary options » ibuprofen: 300-400 mg orally every 4-6 hours when required, maximum 2400 mg/day **OR** **Primary options** » naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day **OR** **Primary options** » diclofenac sodium: 50 mg orally (immediate-release) twice or three times daily when required; 100 mg orally (extended-release) once daily when required **OR** **Secondary options** » codeine phosphate: 15-60 mg orally (immediate-release) every 4-6 hours when required, maximum 360 mg/day **OR** **Secondary options** » oxycodone: 5-10 mg orally (immediate-release) every 4-6 hours when required; 10 mg orally (extended-release) every 12 hours when required **OR** **Tertiary options** » fentanyl transdermal: 12.5 micrograms/hour patch applied every 72 hours, increase to 25 micrograms/hour patch applied every 72 hours if required
	adjunct	**aspirin** » Aspirin may be beneficial in helping prevent micro-thrombi formation. **Primary options** » aspirin: 75 mg orally once daily
	adjunct	**surgical debridement** » If there is a large fingertip ulcer, debridement by a surgeon may be necessary to remove

TREATMENT

Acute

Patient group	Tx line	Treatment
		necrotic tissue and/or infection and to promote healing. If gangrene has progressed in spite of treatment, amputation of the digit may be required.
	adjunct	**systemic antibiotics**
		» Treatment with antibiotics is not necessary for most digital ulcers; however, antibiotics should be considered when ulcers are infected. Infections are often due to *Staphylococcus* species from the skin, and cloxacillin or cephalexin are common choices. In penicillin-allergic patients, erythromycin or a fluoroquinolone may be considered. If there is frank purulence, it is advisable to take a swab for culture and sensitivities prior to starting antibiotics.
		» If infection is not resolved after 7 days of treatment (e.g., continued discoloured purulence), treat for another 3 to 7 days.
		» If osteomyelitis is suspected, seek specialist advice from a microbiologist.
		Primary options
		» cloxacillin: 250-500 mg orally four times daily
		OR
		Primary options
		» cefalexin: 500 mg orally four times daily
		OR
		Secondary options
		» erythromycin: 250-500 mg orally four times daily
		OR
		Secondary options
		» ciprofloxacin: 250-500 mg orally twice daily
	adjunct	**topical antibacterial ointment**
		» Topical antibacterials can be used if there is no evidence of a serious infection, but these may be working as a barrier and lubricant more than an antibacterial.
		Primary options

Acute

Patient group	Tx line	Treatment
		» fusidic acid topical: apply ointment thinly to ulcer twice daily
		OR
		Primary options
		» mupirocin topical: apply ointment thinly to ulcer twice daily
		OR
		Primary options
		» bacitracin/polymyxin B topical: apply ointment thinly to ulcer twice daily
	adjunct	**bosentan**
		» Can be used to help prevent formation of new digital ulcers, particularly in patients with 4 or more existing digital ulcers. Liver function tests need to be checked monthly during treatment, and the duration of treatment required for prevention of digital ulcers is unknown but may be indefinitely.[64] [65] [66]
		Primary options
		» bosentan: 62.5 mg orally twice daily for 1 month, followed by 125 mg orally twice daily thereafter
	2nd	**surgical sympathectomy**
		» Surgical sympathectomy may be effective in the treatment of severe RP that has failed pharmacological treatment. Techniques available include stellate ganglion or lumbar sympathetic blocks, proximal cervical sympathectomies via endoscopic surgery, and selective palmar and/or digital sympathectomies.[69] Such techniques may not be available in all centres. If a stellate ganglion or lumbar sympathetic block is successful, it may indicate that selective palmar or digital sympathectomy may be effective. Although this is rarely indicated, if successful it may help RP for years.
	plus	**treatment of underlying condition**
		» Treatment for the underlying condition that has resulted in secondary RP should be instigated after appropriate specialist consultation.
	plus	**atorvastatin**
		» Atorvastatin has been found to decrease new ulcer formation in patients with secondary RP

Acute

Patient group	Tx line	Treatment
		and should be used in patients with past or present digital ulcers.[63]
		Primary options
		» atorvastatin: 40 mg orally once daily
	adjunct	**analgesia**
		» Pain relief is an important component of symptom management. Vasodilators treat the pain of RP if they are effective in reducing the frequency, severity, or duration of attacks. It is not common to use analgesics for RP; however, they may be required to treat pain from severe or prolonged ischaemia or complications such as gangrene or digital ulcers.
		» Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. Simple analgesics such as paracetamol and NSAIDs may be sufficient. Short- or long-acting narcotics may be required. Digital ulcers may be very painful, and codeine or oxycodone may be indicated. Rarely, transdermal fentanyl is used if other opioids are not effective or not tolerated, typically for patients with gangrene or osteomyelitis. Local palmar and/or digital sympathectomy is a last-line option.
		Primary options
		» paracetamol: 500-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day
		OR
		Primary options
		» ibuprofen: 300-400 mg orally every 4-6 hours when required, maximum 2400 mg/day
		OR
		Primary options
		» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day
		OR
		Primary options
		» diclofenac sodium: 50 mg orally (immediate-release) twice or three times daily

Acute

Patient group	Tx line	Treatment
		when required; 100 mg orally (extended-release) once daily when required
		OR
		Secondary options
		» codeine phosphate: 15-60 mg orally (immediate-release) every 4-6 hours when required, maximum 360 mg/day
		OR
		Secondary options
		» oxycodone: 5-10 mg orally (immediate-release) every 4-6 hours when required; 10 mg orally (extended-release) every 12 hours when required
		OR
		Tertiary options
		» fentanyl transdermal: 12.5 micrograms/hour patch applied every 72 hours, increase to 25 micrograms/hour patch applied every 72 hours if required
	adjunct	**aspirin**
		» Aspirin may be beneficial in helping prevent micro-thrombi formation.
		Primary options
		» aspirin: 75 mg orally once daily
	adjunct	**surgical debridement**
		» If there is a large fingertip ulcer, debridement by a surgeon may be necessary to remove necrotic tissue and/or infection and to promote healing. If gangrene has progressed in spite of treatment, amputation of the digit may be required.
	adjunct	**systemic antibiotics**
		» Treatment with antibiotics is not necessary for most digital ulcers; however, antibiotics should be considered when ulcers are infected. Infections are often due to *Staphylococcus* species from the skin, and cloxacillin or cephalexin are common choices. In penicillin-allergic patients, erythromycin or a fluoroquinolone may be considered. If there is frank purulence, it is advisable to take a swab

Acute

Patient group	Tx line	Treatment
		for culture and sensitivities prior to starting antibiotics. » If infection is not resolved after 7 days of treatment (e.g., continued discoloured purulence), treat for another 3 to 7 days. » If osteomyelitis is suspected, seek specialist advice from a microbiologist. **Primary options** » cloxacillin: 250-500 mg orally four times daily **OR** **Primary options** » cefalexin: 500 mg orally four times daily **OR** **Secondary options** » erythromycin: 250-500 mg orally four times daily **OR** **Secondary options** » ciprofloxacin: 250-500 mg orally twice daily
	adjunct	**topical antibacterial ointment** » Topical antibacterials can be used if there is no evidence of a serious infection, but these may be working as a barrier and lubricant more than an antibacterial. **Primary options** » fusidic acid topical: apply ointment thinly to ulcer twice daily **OR** **Primary options** » mupirocin topical: apply ointment thinly to ulcer twice daily **OR** **Primary options** » bacitracin/polymyxin B topical: apply ointment thinly to ulcer twice daily

Acute

Patient group	Tx line	Treatment
	adjunct	**bosentan**

» Can be used to help prevent formation of new digital ulcers, particularly in patients with 4 or more existing digital ulcers. Liver function tests need to be checked monthly during treatment, and the duration of treatment required for prevention of digital ulcers is unknown but may be indefinitely.[64] [65] [66]

Primary options

» bosentan: 62.5 mg orally twice daily for 1 month, followed by 125 mg orally twice daily thereafter

Ongoing

Patient group	Tx line	Treatment
primary or mild secondary RP	1st	**supportive treatment**

» Many patients with RP do not require treatment unless symptoms become severe.

» Non-pharmacological interventions should be considered first: for example, keeping warm,1[C]Evidence and smoking cessation.

» Advice should be given about avoiding injury to the digits, moisturising dry skin, and avoiding drugs known to exacerbate RP such as cocaine, ergotamine, clonidine, and ciclosporin.

» Smoking is likely to worsen RP.[79] 2[C]Evidence

	adjunct	**analgesia**

» Pain relief is an important component of symptom management. Vasodilators treat the pain of RP if they are effective in reducing the frequency, severity, or duration of attacks. It is not common to use analgesics for RP; however, they may be required to treat pain from severe or prolonged ischaemia or complications such as gangrene or digital ulcers.

» Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. Simple analgesics such as paracetamol and NSAIDs may be sufficient. Short- or long-acting narcotics may be required.

Ongoing

Patient group	Tx line	Treatment

Digital ulcers may be very painful, and codeine or oxycodone may be indicated. Rarely, transdermal fentanyl is used if other opioids are not effective or not tolerated, typically for patients with gangrene or osteomyelitis. Local palmar and/or digital sympathectomy is a last-line option.

Primary options

» paracetamol: 500-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day

OR

Primary options

» ibuprofen: 300-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

Primary options

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

Primary options

» diclofenac sodium: 50 mg orally (immediate-release) twice or three times daily when required; 100 mg orally (extended-release) once daily when required

OR

Secondary options

» codeine phosphate: 15-60 mg orally (immediate-release) every 4-6 hours when required, maximum 360 mg/day

OR

Secondary options

» oxycodone: 5-10 mg orally (immediate-release) every 4-6 hours when required; 10 mg orally (extended-release) every 12 hours when required

OR

Tertiary options

Ongoing

Patient group	Tx line	Treatment
		» fentanyl transdermal: 12.5 micrograms/hour patch applied every 72 hours, increase to 25 micrograms/hour patch applied every 72 hours if required
	adjunct	**complementary and alternative therapies**
		» Complementary and alternative therapies that have been investigated in randomised controlled trials include evening primrose oil,[39] 14[C]Evidence omega-3 fatty acids,[71] 15[C]Evidence *Ginkgo biloba* ,[72] [73] 16[C]Evidence biofeedback, acupuncture,[74] 17[C]Evidence low-level laser therapy,[75] 18[C]Evidence and ceramic-impregnated gloves,[30] 19[C]Evidence but most trials have shown no difference from placebo.
		» One study has shown that oral vitamin D3 supplementation may be beneficial (as measured on the visual analogue scale) in patients with RP who are deficient in vitamin D when compared with placebo.[77]
		» A review and meta-analysis of complementary and alternative medicines in the treatment of RP found most trials were negative, of poor quality, and done prior to 1990.[76] However, given the limited risks associated with these treatments, using them as an adjunctive therapy may be considered for patients at any stage of RP severity. Choice of treatment may depend on patient preference.
	2nd	**calcium-channel blocker + supportive treatment**
		» Non-pharmacological interventions should be considered first: for example, keeping warm,1[C]Evidence and smoking cessation.
		» Advice should be given about avoiding injury to the digits, moisturising dry skin, and avoiding drugs known to exacerbate RP such as cocaine, ergotamine, clonidine, and ciclosporin.
		» Smoking is likely to worsen RP.[79] 2[C]Evidence
		» The recommended first-line pharmacological treatment is a calcium-channel blocker.[31] Studies of calcium-channel blockers have shown that these drugs decrease the frequency/severity of attacks, often by 30%.[38] The dihydropyridine calcium-channel blockers are the most studied, particularly long- or short-acting nifedipine4[A]Evidence or

Ongoing

Patient group	Tx line	Treatment
		nicardipine.5[C]Evidence There is less evidence of efficacy with other calcium-channel blockers. » Most randomised controlled trials showed no improvement in severity of attacks, but the doses used were quite low.[38] » Calcium-channel blockers can be prescribed on an 'as required' basis, such as in cold weather. They do not work for every patient, and there are side effects associated with them (e.g., hypotension, flushing, lightheadedness, peripheral oedema), which may make other drug treatment necessary. **Primary options** » nifedipine: 10 mg orally (immediate-release) three times daily, titrate according to response, maximum 180 mg/day; 30-60 mg orally (extended-release) once daily **OR** **Primary options** » nicardipine: 20 mg orally three times daily, maximum 120 mg/day **OR** **Secondary options** » felodipine: 2.5 mg orally once daily, titrate according to response, maximum 10 mg/day **OR** **Secondary options** » amlodipine: 2.5 mg orally once daily, titrate according to response, maximum 10 mg/day **OR** **Tertiary options** » diltiazem: 30 mg orally (immediate-release) four times daily, maximum 360 mg/day
	adjunct	**analgesia** » Pain relief is an important component of symptom management. Vasodilators treat the pain of RP if they are effective in reducing the frequency, severity, or duration of attacks. It is not common to use analgesics for RP; however, they may be required to treat pain from severe or

Ongoing

Patient group

Tx line

Treatment

prolonged ischaemia or complications such as gangrene or digital ulcers.

» Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. Simple analgesics such as paracetamol and NSAIDs may be sufficient. Short- or long-acting narcotics may be required. Digital ulcers may be very painful, and codeine or oxycodone may be indicated. Rarely, transdermal fentanyl is used if other opioids are not effective or not tolerated, typically for patients with gangrene or osteomyelitis. Local palmar and/or digital sympathectomy is a last-line option.

Primary options

» paracetamol: 500-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day

OR

Primary options

» ibuprofen: 300-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

Primary options

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

Primary options

» diclofenac sodium: 50 mg orally (immediate-release) twice or three times daily when required; 100 mg orally (extended-release) once daily when required

OR

Secondary options

» codeine phosphate: 15-60 mg orally (immediate-release) every 4-6 hours when required, maximum 360 mg/day

OR

Secondary options

Ongoing

Patient group	Tx line	Treatment
		» oxycodone: 5-10 mg orally (immediate-release) every 4-6 hours when required; 10 mg orally (extended-release) every 12 hours when required
		OR
		Tertiary options
		» fentanyl transdermal: 12.5 micrograms/hour patch applied every 72 hours, increase to 25 micrograms/hour patch applied every 72 hours if required
	adjunct	**complementary and alternative therapies**
		» Complementary and alternative therapies that have been investigated in randomised controlled trials include evening primrose oil,[39] 14[C]Evidence omega-3 fatty acids,[71] 15[C]Evidence *Ginkgo biloba* ,[72] [73] 16[C]Evidence biofeedback, acupuncture,[74] 17[C]Evidence low-level laser therapy,[75] 18[C]Evidence and ceramic-impregnated gloves,[30] 19[C]Evidence but most trials have shown no difference from placebo.
		» One study has shown that oral vitamin D3 supplementation may be beneficial (as measured on the visual analogue scale) in patients with RP who are deficient in vitamin D when compared with placebo.[77]
		» A review and meta-analysis of complementary and alternative medicines in the treatment of RP found most trials were negative, of poor quality, and done prior to 1990.[76] However, given the limited risks associated with these treatments, using them as an adjunctive therapy may be considered for patients at any stage of RP severity. Choice of treatment may depend on patient preference.
	3rd	**angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist + supportive treatment**
		» Non-pharmacological interventions should be considered first: for example, keeping warm,1[C]Evidence and smoking cessation.
		» Advice should be given about avoiding injury to the digits, moisturising dry skin, and avoiding drugs known to exacerbate RP, such as cocaine, ergotamine, clonidine, and ciclosporin.

Ongoing

Patient group	Tx line	Treatment
		» Smoking is likely to worsen RP.[79] 2[C]Evidence » ACE inhibitors or angiotensin-II receptor antagonists are used second line when calcium-channel blockers have failed or are not tolerated. **Primary options** » losartan: 25-100 mg orally once daily **OR** **Primary options** » captopril: 25-150 mg orally three times daily
	adjunct	**analgesia** » Pain relief is an important component of symptom management. Vasodilators treat the pain of RP if they are effective in reducing the frequency, severity, or duration of attacks. It is not common to use analgesics for RP; however, they may be required to treat pain from severe or prolonged ischaemia or complications such as gangrene or digital ulcers. » Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. Simple analgesics such as paracetamol and NSAIDs may be sufficient. Short- or long-acting narcotics may be required. Digital ulcers may be very painful, and codeine or oxycodone may be indicated. Rarely, transdermal fentanyl is used if other opioids are not effective or not tolerated, typically for patients with gangrene or osteomyelitis. Local palmar and/or digital sympathectomy is a last-line option. **Primary options** » paracetamol: 500-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day **OR** **Primary options** » ibuprofen: 300-400 mg orally every 4-6 hours when required, maximum 2400 mg/day **OR** **Primary options**

Ongoing

Patient group	Tx line	Treatment
		» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day
		OR
		Primary options
		» diclofenac sodium: 50 mg orally (immediate-release) twice or three times daily when required; 100 mg orally (extended-release) once daily when required
		OR
		Secondary options
		» codeine phosphate: 15-60 mg orally (immediate-release) every 4-6 hours when required, maximum 360 mg/day
		OR
		Secondary options
		» oxycodone: 5-10 mg orally (immediate-release) every 4-6 hours when required; 10 mg orally (extended-release) every 12 hours when required
		OR
		Tertiary options
		» fentanyl transdermal: 12.5 micrograms/hour patch applied every 72 hours, increase to 25 micrograms/hour patch applied every 72 hours if required
	adjunct	**complementary and alternative therapies**
		» Complementary and alternative therapies that have been investigated in randomised controlled trials include evening primrose oil,[39] 14[C]Evidence omega-3 fatty acids,[71] 15[C]Evidence *Ginkgo biloba* ,[72] [73] 16[C]Evidence biofeedback, acupuncture,[74] 17[C]Evidence low-level laser therapy,[75] 18[C]Evidence and ceramic-impregnated gloves,[30] 19[C]Evidence but most trials have shown no difference from placebo.
		» One study has shown that oral vitamin D3 supplementation may be beneficial (as measured on the visual analogue scale) in patients with RP who are deficient in vitamin D when compared with placebo.[77]
		» A review and meta-analysis of complementary and alternative medicines in the treatment of

Ongoing

Patient group	Tx line	Treatment
		RP found most trials were negative, of poor quality, and done prior to 1990.[76] However, given the limited risks associated with these treatments, using them as an adjunctive therapy may be considered for patients at any stage of RP severity. Choice of treatment may depend on patient preference.
	3rd	**selective serotonin-reuptake inhibitor + supportive treatment** » Non-pharmacological interventions should be considered first: for example, keeping warm,1[C]Evidence and smoking cessation. » Advice should be given about avoiding injury to the digits, moisturising dry skin, and avoiding drugs known to exacerbate RP such as cocaine, ergotamine, clonidine, and ciclosporin. » Smoking is likely to worsen RP.[79] 2[C]Evidence » Selective serotonin-reuptake inhibitors may be used third line when other drugs have failed or are not tolerated. **Primary options** » fluoxetine: 20-60 mg orally once daily
	adjunct	**analgesia** » Pain relief is an important component of symptom management. Vasodilators treat the pain of RP if they are effective in reducing the frequency, severity, or duration of attacks. It is not common to use analgesics for RP; however, they may be required to treat pain from severe or prolonged ischaemia or complications such as gangrene or digital ulcers. » Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. Simple analgesics such as paracetamol and NSAIDs may be sufficient. Short- or long-acting narcotics may be required. Digital ulcers may be very painful, and codeine or oxycodone may be indicated. Rarely, transdermal fentanyl is used if other opioids are not effective or not tolerated, typically for patients with gangrene or osteomyelitis. Local palmar and/or digital sympathectomy is a last-line option. **Primary options**

Ongoing

Patient group	Tx line	Treatment
		» paracetamol: 500-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day
		OR
		Primary options
		» ibuprofen: 300-400 mg orally every 4-6 hours when required, maximum 2400 mg/day
		OR
		Primary options
		» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day
		OR
		Primary options
		» diclofenac sodium: 50 mg orally (immediate-release) twice or three times daily when required; 100 mg orally (extended-release) once daily when required
		OR
		Secondary options
		» codeine phosphate: 15-60 mg orally (immediate-release) every 4-6 hours when required, maximum 360 mg/day
		OR
		Secondary options
		» oxycodone: 5-10 mg orally (immediate-release) every 4-6 hours when required; 10 mg orally (extended-release) every 12 hours when required
		OR
		Tertiary options
		» fentanyl transdermal: 12.5 micrograms/hour patch applied every 72 hours, increase to 25 micrograms/hour patch applied every 72 hours if required
	adjunct	**complementary and alternative therapies**
		» Complementary and alternative therapies that have been investigated in randomised controlled trials include evening primrose oil,[39] 14[C]Evidence omega-3 fatty acids,[71] 15[C]Evidence *Ginkgo biloba* ,[72] [73]

Ongoing

Patient group	Tx line	Treatment
		16[C]Evidence biofeedback, acupuncture,[74] 17[C]Evidence low-level laser therapy,[75] 18[C]Evidence and ceramic-impregnated gloves,[30] 19[C]Evidence but most trials have shown no difference from placebo. » One study has shown that oral vitamin D3 supplementation may be beneficial (as measured on the visual analogue scale) in patients with RP who are deficient in vitamin D when compared with placebo.[77] » A review and meta-analysis of complementary and alternative medicines in the treatment of RP found most trials were negative, of poor quality, and done prior to 1990.[76] However, given the limited risks associated with these treatments, using them as an adjunctive therapy may be considered for patients at any stage of RP severity. Choice of treatment may depend on patient preference.
	3rd	**topical nitrate or vasodilator + supportive treatment** » Non-pharmacological interventions should be considered first: for example, keeping warm,1[C]Evidence and smoking cessation. » Advice should be given about avoiding injury to the digits, moisturising dry skin, and avoiding drugs known to exacerbate RP such as cocaine, ergotamine, clonidine, and ciclosporin. » Smoking is likely to worsen RP.[79] 2[C]Evidence » Topical glyceryl trinitrate may be used third line when other drugs have failed or are not tolerated. » Topical phosphodiesterase-5 inhibitors may also be used; however, they are not widely available at present and may need to be specially compounded. **Primary options** » glyceryl trinitrate topical: (2%) apply to the affected area(s) twice daily
	adjunct	**analgesia** » Pain relief is an important component of symptom management. Vasodilators treat the pain of RP if they are effective in reducing the frequency, severity, or duration of attacks. It is

Ongoing

Patient group	Tx line	Treatment

not common to use analgesics for RP; however, they may be required to treat pain from severe or prolonged ischaemia or complications such as gangrene or digital ulcers.

» Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. Simple analgesics such as paracetamol and NSAIDs may be sufficient. Short- or long-acting narcotics may be required. Digital ulcers may be very painful, and codeine or oxycodone may be indicated. Rarely, transdermal fentanyl is used if other opioids are not effective or not tolerated, typically for patients with gangrene or osteomyelitis. Local palmar and/or digital sympathectomy is a last-line option.

Primary options

» paracetamol: 500-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day

OR

Primary options

» ibuprofen: 300-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

Primary options

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

Primary options

» diclofenac sodium: 50 mg orally (immediate-release) twice or three times daily when required; 100 mg orally (extended-release) once daily when required

OR

Secondary options

» codeine phosphate: 15-60 mg orally (immediate-release) every 4-6 hours when required, maximum 360 mg/day

OR

Ongoing

Patient group	Tx line	Treatment
		Secondary options » oxycodone: 5-10 mg orally (immediate-release) every 4-6 hours when required; 10 mg orally (extended-release) every 12 hours when required **OR** **Tertiary options** » fentanyl transdermal: 12.5 micrograms/hour patch applied every 72 hours, increase to 25 micrograms/hour patch applied every 72 hours if required
	adjunct	**complementary and alternative therapies** » Complementary and alternative therapies that have been investigated in randomised controlled trials include evening primrose oil,[39] 14[C]Evidence omega-3 fatty acids,[71] 15[C]Evidence *Ginkgo biloba* ,[72] [73] 16[C]Evidence biofeedback, acupuncture,[74] 17[C]Evidence low-level laser therapy,[75] 18[C]Evidence and ceramic-impregnated gloves,[30] 19[C]Evidence but most trials have shown no difference from placebo. » One study has shown that oral vitamin D3 supplementation may be beneficial (as measured on the visual analogue scale) in patients with RP who are deficient in vitamin D when compared with placebo.[77] » A review and meta-analysis of complementary and alternative medicines in the treatment of RP found most trials were negative, of poor quality, and done prior to 1990.[76] However, given the limited risks associated with these treatments, using them as an adjunctive therapy may be considered for patients at any stage of RP severity. Choice of treatment may depend on patient preference.
	4th	**alpha-blocker + supportive treatment** » Non-pharmacological interventions should be considered first: for example, keeping warm,1[C]Evidence and smoking cessation. » Advice should be given about avoiding injury to the digits, moisturising dry skin, and avoiding drugs known to exacerbate RP such as cocaine, ergotamine, clonidine, and ciclosporin.

Ongoing

Patient group	Tx line	Treatment
		» Smoking is likely to worsen RP.[79] 2[C]Evidence » Alpha-blockers may be used fourth line when all other drugs have failed or are not tolerated. **Primary options** » prazosin: 1 mg orally twice daily
	adjunct	**analgesia** » Pain relief is an important component of symptom management. Vasodilators treat the pain of RP if they are effective in reducing the frequency, severity, or duration of attacks. It is not common to use analgesics for RP; however, they may be required to treat pain from severe or prolonged ischaemia or complications such as gangrene or digital ulcers. » Local pain management algorithms should be followed, and treatment should be tailored to medical history and any relative/absolute contraindications. Simple analgesics such as paracetamol and NSAIDs may be sufficient. Short- or long-acting narcotics may be required. Digital ulcers may be very painful, and codeine or oxycodone may be indicated. Rarely, transdermal fentanyl is used if other opioids are not effective or not tolerated, typically for patients with gangrene or osteomyelitis. Local palmar and/or digital sympathectomy is a last-line option. **Primary options** » paracetamol: 500-1000 mg orally/rectally every 4-6 hours when required, maximum 4000 mg/day **OR** **Primary options** » ibuprofen: 300-400 mg orally every 4-6 hours when required, maximum 2400 mg/day **OR** **Primary options** » naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day **OR** **Primary options**

Ongoing

Patient group	Tx line	Treatment
		» diclofenac sodium: 50 mg orally (immediate-release) twice or three times daily when required; 100 mg orally (extended-release) once daily when required
		OR
		Secondary options
		» codeine phosphate: 15-60 mg orally (immediate-release) every 4-6 hours when required, maximum 360 mg/day
		OR
		Secondary options
		» oxycodone: 5-10 mg orally (immediate-release) every 4-6 hours when required; 10 mg orally (extended-release) every 12 hours when required
		OR
		Tertiary options
		» fentanyl transdermal: 12.5 micrograms/hour patch applied every 72 hours, increase to 25 micrograms/hour patch applied every 72 hours if required
	adjunct	**complementary and alternative therapies**
		» Complementary and alternative therapies that have been investigated in randomised controlled trials include evening primrose oil,[39] 14[C]Evidence omega-3 fatty acids,[71] 15[C]Evidence *Ginkgo biloba* ,[72] [73] 16[C]Evidence biofeedback, acupuncture,[74] 17[C]Evidence low-level laser therapy,[75] 18[C]Evidence and ceramic-impregnated gloves,[30] 19[C]Evidence but most trials have shown no difference from placebo.
		» One study has shown that oral vitamin D3 supplementation may be beneficial (as measured on the visual analogue scale) in patients with RP who are deficient in vitamin D when compared with placebo.[77]
		» A review and meta-analysis of complementary and alternative medicines in the treatment of RP found most trials were negative, of poor quality, and done prior to 1990.[76] However, given the limited risks associated with these treatments, using them as an adjunctive therapy may be considered for patients at any stage of

Ongoing

Patient group	Tx line	Treatment
		RP severity. Choice of treatment may depend on patient preference.

Emerging

Botulinum toxin type A

There are no large randomised controlled trials. One small trial assessed the efficacy of local injections of botulinum toxin type A versus placebo in improving blood flow to the hands of patients with RP secondary to scleroderma. It found some short-term benefit though it questioned its clinical meaningfulness, and blood flow was not significantly different at 4 months.[80] One review found 5 studies with botulinum toxin A to treat RP.[81] These were case series or case reports showing improvement in pain and decreased number of digital ulcers. The following is an example of the papers reviewed. There is a case series of treating RP with injections of 50 to 100 units of onabotulinumtoxinA (botulinum toxin A) near the digital artery areas or perineurovascular tissue of the wrist or the distal palm.[82] The injections helped blood flow as measured by Dopplers before and after injection and relieved pain in 85%. Another small pilot was also performed using botulinum toxin A.[83] There need to be more data such as an RCT to see whether botulinum toxin injections are superior to placebo. Another study of a topical agent (NXCL-4950) showed improved Raynaud's Condition Score in those with a high baseline score and improved blood flow.[84]

Ketanserin

Trials of ketanserin in RP have not demonstrated improvement consistently, so there is insufficient evidence to recommend its use.[85]

Fasudil

A study was performed using a RhoA/Rho kinase inhibitor (fasudil); it did not affect skin temperature or digital blood flow.[86]

Recommendations

Monitoring

RP should be monitored by regular symptom review and physical examination. If underlying connective tissue disease is suspected, capillary microscopy at the nailbeds should be arranged. Patients with abnormally dilated capillaries are at increased risk of developing a connective tissue disease (especially scleroderma) over the following 3 to 5 years.[28]

Patient instructions

Advice should include:

- Staying warm (wear hat, mittens in cold weather rather than gloves, use warming devices such as pocket hand warmer)
- Stopping smoking
- Avoiding stress
- Doing regular exercise, although there is no evidence to suggest that this improves RP.

Many pharmacological treatments for RP cause lightheadedness, flushing, or more rarely peripheral oedema (puffy feet) and palpitations. Medical attention should be sought if side effects are severe.

Complications

Complications	Timeframe	Likelihood
necrosis with gangrene	**long term**	**medium**
Necrosis may occur in secondary RP but not in primary RP. This complication results from the progression of digital ulcers and ischaemia and may lead to auto-amputation or require surgical amputation. In digital ulcers with scleroderma, only 60% of ulcers heal by 6 months, with 1% to 2% requiring amputation.[66] [89]		
auto-amputation	**long term**	**low**
May result from severe digital ischaemia and tissue necrosis.		
ischaemic digital ulcers	**variable**	**medium**
The likelihood of developing digital ulcers increases with disease duration, probably due to worsening obliterative vasculopathy. The presence of digital ulceration is generally thought to exclude a diagnosis of primary RP, and so a secondary cause should be sought if ulceration occurs. Ischaemic digital ulcers are found on the digit tips. Treatment of digital ulcers includes prostacyclins and phosphodiesterase-5 (PDE-5) inhibitors.[58] [67] Prevention of digital ulcers has also been studied using bosentan, an endothelin receptor blocker. This treatment is not yet widely available. A negative study has been completed with macicentan, so only bosentan has proven data about decreasing the number of new digital ulcers compared with placebo.[88] Atorvastatin has been found to yield a reduction in the number of new digital ulcers (prevention of ulcers but not healing) in systemic sclerosis (SSc).[63]		
traumatic digital ulcers	**variable**	**medium**

Complications	Timeframe	Likelihood
Traumatic ulcers (particularly in scleroderma) are often located on the extensor surfaces of the fingers. Creased areas with little underlying subcutaneous tissue (such as the extensor surfaces of the proximal interphalangeal joints) are particularly vulnerable. Treating traumatic ulcers with vasodilator therapy is not appropriate. Treatment should be targeted at protecting the digits from further trauma and treating superimposed infection as it arises; analgesia is often required.		
digital tuft resorption	**variable**	**medium**
Moderate risk in secondary RP; does not occur in primary RP. Ischaemia causes loss of tissue pulp and should be treated with prostacyclins and PDE-5 inhibitors.		
threatened ischaemic digit	**variable**	**medium**
Patients with severe ischaemia should be treated with intravenous prostacyclins such as iloprost or epoprostenol, and sildenafil or other PDE-5 inhibitors such as tadalafil and vardenafil. If necessary, a sympathetic block should be considered. Techniques available include stellate ganglion blockage, proximal cervical sympathectomies via endoscopic surgery, and local palmar and/or digital sympathectomies. Such techniques may not be available in all centres.		
digital pits	**variable**	**medium**
Fibrotic plugs due to ischaemia occur in RP and should be treated with prostacyclins and PDE-5 inhibitors.		
cellulitis/osteomyelitis	**variable**	**medium**
Digital ulcers can become infected and may require topical or oral antibiotics and appropriate wound care.		

Prognosis

Prognosis

The course may fluctuate in both primary and secondary Raynaud's phenomenon (RP). Symptoms worsen in cold weather and during seasonal changes with the absolute daily change in temperature and on cold, wet days. Not keeping warm and trauma to the affected areas may precipitate attacks. Attacks may last from several minutes to a few hours. In many people with primary RP, their symptoms may become more mild or even disappear over time. Thirteen percent of long-term patients later develop an underlying disorder such as scleroderma.[87] 20[C]Evidence

Treatment guidelines

Europe

Update of EULAR recommendations for the treatment of systemic sclerosis

Published by: European League Against Rheumatism **Last published:** 2016

Summary: European League Against Rheumatism (EULAR) guidelines that include information on the treatment of RP in patients with systemic sclerosis.

North America

Treatment of systemic sclerosis complications: what to use when first-line treatment fails

Published by: Scleroderma Clinical Trials Consortium; Canadian Scleroderma Research Group **Last published:** 2012

Summary: Experts from the Scleroderma Clinical Trials Consortium (SCTC) recommend nifedipine or other similar calcium-channel blockers as first-line treatment. In severe RP, adding or switching to a phosphodiesterase-5 (PDE-5) inhibitor is described. If poorly tolerated, or an increased risk of hypotension is seen, then prostanoid treatment would be considered. This guidance differs from the EULAR guidelines but is more recent and highlights the use of PDE-5 inhibitors as second-line treatment, and considers combination treatment for RP if tolerated in severe cases.

Evidence scores

1. Keeping warm and RP: most clinicians recommend avoiding the cold, if possible, to prevent RP attacks, but there are no trials assessing its effects.[30]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

2. Smoking and risk of developing RP: there is no evidence of the relationship between smoking and developing RP, but it makes clinical sense. There are no randomised controlled trials of smoking cessation in RP, but vasoconstrictive substances in cigarette smoke are likely to worsen RP. The confounding influence of atherosclerosis in smokers (especially in the older population) is likely to adversely impact the up-regulated factors already occurring in RP.
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

3. RP severity/frequency: there is medium-quality evidence that topical nitrates decrease the frequency and severity of attacks in primary and secondary RP, and may improve digital ulcers. Oral, transdermal, or topical nitrates may cause side effects such as headaches, which could limit their use.[34] [35] [36] [37]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

4. RP severity and nifedipine: there is good-quality evidence that nifedipine reduces the frequency and severity of attacks over 4 to 12 weeks compared with placebo.[39] [40] [41] [42] [43] [44] [45] It also improves overall symptoms.
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

5. RP severity/frequency: there is poor-quality evidence that nicardipine decreased the frequency of RP attacks over 8 weeks after crossover when compared with placebo, but a randomised trial found no significant difference in the severity of attacks.[46] Another trial found no significant difference in frequency, severity, or duration of attacks with nicardipine when compared with placebo. This trial was insufficiently powered to detect a clinically important difference in outcomes.[47]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

6. RP severity/frequency and amlodipine: there is poor-quality evidence that amlodipine significantly reduced the number of acute attacks per week from baseline at 7 weeks (from 11.8 attacks/week at baseline to 8.6 attacks/week after treatment; P <0.001) and reduced the severity of attacks from baseline (from a discomfort score of 7.8 at baseline to 5.1 after treatment). However, methodological flaws were evident in this trial.[48]

Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

7. RP severity/frequency and diltiazem: there is medium-quality evidence that diltiazem significantly reduced the number of attacks compared with placebo (mean reduction in attacks from baseline 22.9/month with diltiazem vs 4.6/month with placebo; P <0.01) and reduced the duration of attacks (mean reduction from baseline 444 minutes/month with diltiazem vs 160 minutes/month with placebo; P <0.01) over an 8-week period. Methodological flaws included a lack of intention-to-treat analysis.[49]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

8. RP severity/frequency: there is medium-quality evidence for the benefit of losartan as a therapy for RP. This drug is approved for HTN but has been found to work well in RP and is well tolerated.[50] [51]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

9. RP severity/frequency: there is medium-quality evidence for the benefit of fluoxetine. There are positive trial data for the treatment of RP using fluoxetine, an SSRI approved for the treatment of depression and some anxiety disorders.[52]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

10. RP severity/frequency: there is poor-quality evidence that prazosin reduced the number and duration of attacks over 6 weeks after crossover compared with placebo, but the small crossover trial found no significant difference in the severity of attacks.[53]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

11. RP severity/frequency: there is medium-quality evidence for the benefit of captopril treatment, with data from a positive trial of captopril in primary RP.[51] [54] However, a meta-analysis found no benefit in primary RP for vasodilators other than calcium-channel blockers including enalapril, buflomedil, beraprost, dazoxiben, and ketanserin.[45]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

12. RP severity/frequency: there is poor-quality evidence that naftidrofuryl oxalate reduced the duration and intensity of RP attacks over 2 months, and reduced the impact of attacks on daily activities. However, evidence is limited for this drug.[56]

Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

13. Healing of digital ulcers: there is medium-quality evidence that sildenafil heals digital ulcers. Two trials in severe RP noted that sildenafil had a higher chance of healing digital ulcers than placebo, and one trial with tadalafil.[59] However, these were not primary outcomes in the PDE-5 studies.[58] [59]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

14. RP severity/frequency: there is poor-quality evidence that evening primrose oil showed a decrease in the frequency of RP attacks in one small study (n = 21).[70]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

15. Omega-3 fatty acids and RP: there is poor-quality evidence for the benefit of this treatment. Fish oil has shown an increase in digital systolic pressure and an increase in the time to onset of symptoms after exposure to cold in patients with primary and secondary RP.[71]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

16. RP severity/frequency: there is poor-quality evidence that the use of *Ginkgo biloba* , a herbal antioxidant, led to a reduction in the number of events per week in primary RP.[72]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

17. RP severity/frequency: there is poor-quality evidence for the benefit of acupuncture. Only one small positive trial has been conducted in primary RP.[74]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

18. RP severity/frequency: there is poor-quality evidence for the use of low-level laser therapy. Only one small trial (n = 47) in primary and secondary RP has been conducted with low-level laser therapy.[75]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

19. RP severity/frequency: there is poor-quality evidence for the use of ceramic-impregnated gloves.[30]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

20. Scleroderma following RP: there is poor-quality evidence that supports this finding. One systematic review of 10 prospective observational studies, totalling 639 subjects with primary RP, found that 13% subsequently developed scleroderma.[87]
Evidence level C: Poor quality observational (cohort) studies or methodologically flawed randomized controlled trials (RCTs) of <200 participants.

Key articles

- Brand FN, Larson MG, Kannel WB, et al. The occurrence of Raynaud's phenomenon in a general population: the Framingham Study. Vasc Med. 1997;2:296-230. Abstract
- Walker KM, Pope J; participating members of the Scleroderma Clinical Trials Consortium (SCTC), Canadian Scleroderma Research Group (CSRG). Treatment of systemic sclerosis complications: what to use when first-line treatment fails - a consensus of systemic sclerosis experts. Semin Arthritis Rheum. 2012;42:42-55. Abstract

References

1. Herrick A. Pathogenesis of Raynaud's phenomenon. Rheumatology (Oxford). 2005;44:587-596. Full text Abstract
2. White CR, Haidekker MA, Stevens HY, et al. Extracellular signal-regulated kinase activation and endothelin-1 production in human endothelial cells exposed to vibration. J Physiol. 2004;555(Pt 2):565-572. Full text Abstract
3. Brand FN, Larson MG, Kannel WB, et al. The occurrence of Raynaud's phenomenon in a general population: the Framingham Study. Vasc Med. 1997;2:296-230. Abstract
4. Rodriguez Garcia JL, Saban Ruiz J. Raynaud's phenomenon [in Spanish]. Rev Clin Esp. 1989;184:311-321. Abstract
5. Riera G, Vilardell M, Vaque J, et al. Prevalence of Raynaud's phenomenon in a healthy Spanish population. J Rheumatol. 1993;20:66-69. Abstract
6. Inaba R, Maeda M, Fujita S, et al. Prevalence of Raynaud's phenomenon and specific clinical signs related to progressive systemic sclerosis in the general population of Japan. Int J Dermatol. 1993;32:652-655. Abstract
7. Flavahan NA, Flavahan S, Liu Q, et al. Increased alpha2-adrenergic constriction of isolated arterioles in diffuse scleroderma. Arthritis Rheum. 2000;43:1886-1890. Full text Abstract
8. Wigley FM. Raynaud's phenomenon. Curr Opin Rheumatol. 1993;5:773-784. Abstract
9. Pistorius MA, Planchon B, Schott JJ, et al. Heredity and genetic aspects of Raynaud's disease. J Mal Vasc. 2006;31:10-15. Abstract
10. Smyth AE, Hughes AE, Bruce IN, et al. A case-control study of candidate vasoactive mediator genes in primary Raynaud's phenomenon. Rheumatology (Oxford). 1999;38:1094-1098. Full text Abstract
11. Freedman RR, Mayes MD. Familial aggregation of primary Raynaud's disease. Arthritis Rheum. 1996;39:1189-1191. Abstract

12. Eliasson K, Danielson M, Hylander B, et al. Raynaud's phenomenon caused by beta-receptor blocking drugs. Improvement after treatment with a combined alpha- and beta-blocker. Acta Med Scand. 1984;215:333-339. Abstract

13. Brotzu G, Falchi S, Mannu B, et al. The importance of presynaptic beta receptors in Raynaud's phenomenon. J Vasc Surg. 1989;9:767. Abstract

14. Herrick A. Treatment of Raynaud's phenomenon: new insights and developments. Curr Rheumatol Rep. 2003;5:168-174. Abstract

15. Pope JE, Al-Bishri J, Al-Azem H, et al. The temporal relationship of Raynaud's phenomenon and features of connective tissue disease in rheumatoid arthritis. J Rheumatol. 2008;35:2329-2333. Abstract

16. Lalani S, Pope J, de Leon F, et al. Clinical features and prognosis of late-onset systemic lupus erythematosus: results from the 1000 faces of lupus study. J Rheumatol. 2010;37:38-44. Abstract

17. Ramos-Casals M, Anaya JM, García-Carrasco M, et al. Cutaneous vasculitis in primary Sjögren syndrome: classification and clinical significance of 52 patients. Medicine (Baltimore). 2004;83:96-106. Abstract

18. García-Carrasco M, Sisó A, Ramos-Casals M, et al. Raynaud's phenomenon in primary Sjögren's syndrome. Prevalence and clinical characteristics in a series of 320 patients. J Rheumatol. 2002;29:726-730. Abstract

19. Parodi A, Caproni M, Marzano AV, et al. Dermatomyositis in 132 patients with different clinical subtypes: cutaneous signs, constitutional symptoms and circulating antibodies. Acta Derm Venereol. 2002;82:48-51. Abstract

20. Grader-Beck T, Wigley FM. Raynaud's phenomenon in mixed connective tissue disease. Rheum Dis Clin North Am. 2005;31:465-481. Abstract

21. Hong P, Pope JE, Ouimet JM, et al. Erectile dysfunction associated with scleroderma: a case-control study of men with scleroderma and rheumatoid arthritis. J Rheumatol. 2004;31:508-513. Abstract

22. Taylor W. Hand-arm vibration syndrome: a new clinical classification and an updated British standard guide for hand transmitted vibration. Br J Ind Med. 1988;45:281-282. Abstract

23. Harada N, Mahbub MH. Diagnosis of vascular injuries caused by hand-transmitted vibration. Int Arch Occup Environ Health. 2008;81:507-518. Abstract

24. Małecki R, Zdrojowy K, Adamiec R. Thromboangiitis obliterans in the 21st century - a new face of disease. Atherosclerosis. 2009;206:328-334. Abstract

25. Paraskevas KI, Liapis CD, Briana DD, et al. Thromboangiitis obliterans (Buerger's disease): searching for a therapeutic strategy. Angiology. 2007;58:75-84. Abstract

26. Suter LG, Murabito JM, Felson DT, et al. Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. Am J Med. 2007;120:264-267. Abstract

27. Moore TL, Roberts C, Murray AK, et al. Reliability of dermoscopy in the assessment of patients with Raynaud's phenomenon. Rheumatology (Oxford). 2010;49:542-547. Abstract

28. Boin F, Wigley FM. Understanding, assessing and treating Raynaud's phenomenon. Curr Opin Rheumatol. 2005;17:752-760. Abstract

29. Baron M, Bell M, Bookman A, et al. Office capillaroscopy in systemic sclerosis. Clin Rheumatol. 2006;26:1268-1274. Abstract

30. Ko GD, Berbrayer D. Effect of ceramic-impregnated "thermoflow" gloves on patients with Raynaud's syndrome: randomized, placebo-controlled study. Altern Med Rev. 2002;7:328-335. Full text Abstract

31. Huisstede BM, Hoogvliet P, Paulis WD, et al. Effectiveness of interventions for secondary Raynaud's phenomenon: a systematic review. Arch Phys Med Rehabil. 2011;92:1166-1180. Abstract

32. Ennis H, Hughes M, Anderson ME, et al. Calcium channel blockers for primary Raynaud's phenomenon. Cochrane Database Syst Rev. 2016 Feb 25;2:CD002069. Full text Abstract

33. Roustit M, Blaise S, Allanore Y, et al. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. Ann Rheum Dis. 2013;72:1696-1699. Abstract

34. Teh LS, Manning J, Moore T, et al. Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. Br J Rheumatol. 1995;34:636-641. Abstract

35. Franks AG Jr. Topical glyceryl trinitrate as adjunctive treatment in Raynaud's disease. Lancet. 1982;1:76-77. Abstract

36. Chung L, Shapiro L, Fiorentino D, et al. MQX-503, a novel formulation of nitroglycerin, improves the severity of Raynaud's phenomenon: a randomized, controlled trial. Arthritis Rheum. 2009;60:870-877. Full text Abstract

37. Hummers LK, Dugowson CE, Dechow FJ, et al. A multi-centre, blinded, randomised, placebo-controlled, laboratory-based study of MQX-503, a novel topical gel formulation of nitroglycerine, in patients with Raynaud phenomenon. Ann Rheum Dis. 2013;72:1962-1967. Abstract

38. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. Rheumatology (Oxford). 2005;44:145-150. Full text Abstract

39. Challenor VF, Waller DG, Hayward RA, et al. Vibrotactile sensation and response to nifedipine dose titration in primary Raynaud's phenomenon. Angiology. 1989;40:122-128. Abstract

40. Raynaud's Treatment Study Investigators. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon: results from a randomized clinical trial with 1-year follow-up. Arch Intern Med. 2000;160:1101-1108. Full text Abstract

41. Sarkozi J, Bookman AA, Mahon W, et al. Nifedipine in the treatment of idiopathic Raynaud's syndrome. J Rheumatol. 1986;13:331-336. Abstract

42. Corbin DO, Wood DA, Macintyre CC, et al. A randomized double blind cross-over trial of nifedipine in the treatment of primary Raynaud's phenomenon. Eur Heart J. 1986;7:165-170. Abstract

43. Gjorup T, Kelbaek H, Hartling OJ, et al. Controlled double-blind trial of the clinical effect of nifedipine in the treatment of idiopathic Raynaud's phenomenon. Am Heart J. 1986;111:742-745. Abstract

44. Waller DG, Challenor VF, Francis DA, et al. Clinical and rheological effects of nifedipine in Raynaud's phenomenon. Br J Clin Pharmacol. 1986;22:449-454. Full text Abstract

45. Stewart M, Morling JR. Oral vasodilators for primary Raynaud's phenomenon. Cochrane Database Syst Rev. 2012;(7):CD006687. Full text Abstract

46. French Cooperative Multicenter Group for Raynaud Phenomenon. Controlled multicenter double-blind trial of nicardipine in the treatment of primary Raynaud phenomenon. Am Heart J. 1991;122:352-355. Abstract

47. Wollersheim H, Thien T. Double-blind placebo-controlled crossover study of oral nicardipine in the treatment of Raynaud's phenomenon. J Cardiovasc Pharmacol. 1991;18:813-818. Abstract

48. La Civita L, Pitaro N, Rossi M, et al. Amlodipine in the treatment of Raynaud's phenomenon. A double-blind placebo-controlled crossover study. Clin Drug Invest. 1997;13:126-131. Abstract

49. Rhedda A, McCans J, Willan AR, et al. A double blind controlled crossover randomized trial of diltiazem in Raynaud's phenomenon. J Rheumatol. 1985;12:724-727. Abstract

50. Dziadzio M, Denton CP, Smith R, et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. Arthritis Rheum. 1999; 42:2646-2655. Full text Abstract

51. Wood HM, Ernst ME. Renin-angiotensin system mediators and Raynaud's phenomenon. Ann Pharmacother. 2006;40:1998-2002. Abstract

52. Coleiro B, Marshall SE, Denton CP, et al. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. Rheumatology (Oxford). 2001;40:1038-1043. Full text Abstract

53. Wollersheim H, Thien T, Fennis J, et al. Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. Clin Pharmacol Ther. 1986;40:219-225. Abstract

54. Rustin MH, Almond NE, Beacham JA, et al. The effect of captopril on cutaneous blood flow in patients with primary Raynaud's phenomenon. Br J Dermatol. 1987;117:751. Abstract

55. Gliddon AE, Doré CJ, Black CM, et al. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. Arthritis Rheum. 2007;56:3837-3846. Full text Abstract

56. Davinroy M, Mosnier M. Double-blind clinical evaluation of naftidrofuryl in Raynaud's phenomenon [in French]. Sem Hop Paris. 1993;69:1322-1326.

57. Herrick AL, van den Hoogen F, Gabrielli A, et al. Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. Arthritis Rheum. 2011;63:775-782. Full text Abstract

58. Fries R, Shariat K, von Wilmowsky H, et al. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. Circulation. 2005;112:2980-2985. Full text Abstract

59. Shenoy PD, Kumar S, Jha LK, et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. Rheumatology (Oxford). 2010;49:2420-2428. Abstract

60. Caglayan E, Axmann S, Hellmich M, et al. Vardenafil for the treatment of Raynaud phenomenon: a randomized, double-blind, placebo-controlled crossover study. Arch Intern Med. 2012;172:1182-1184. Abstract

61. De LaVega AJ, Derk CT. Phosphodiesterase-5 inhibitors for the treatment of Raynaud's: a novel indication. Expert Opin Investig Drugs. 2009;18:23-29. Abstract

62. Lee EY, Park JK, Lee W, et al. Head-to-head comparison of udenafil vs amlodipine in the treatment of secondary Raynaud's phenomenon: a double-blind, randomized, cross-over study. Rheumatology (Oxford). 2014;53:658-664. Abstract

63. Abou-Raya A, Abou-Raya S, Helmii M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. J Rheumatol. 2008;35:1801-1808. Abstract

64. Varga J. New hope for systemic sclerosis patients with digital ulcers. Curr Rheumatol Rep. 2005;7:127. Abstract

65. Korn JH, Mayes M, Matucci Cerinic M, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum. 2004;50:3985-3993. Full text Abstract

66. Seibold JR, Matucci-Cerinic M, Denton CP, et al. Bosentan reduces the number of new digital ulcers in patients with systemic sclerosis. Ann Rheum Dis. 2006;65(suppl II):90.

67. Wigley FM, Seibold JR, Wise RA, et al. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. J Rheumatol. 1992;19:1407-1414. Abstract

68. Wigley FM, Wise RA, Seibold JR, et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. Ann Intern Med. 1994;120:199-206. Abstract

69. Wasserman A, Brahn E. Systemic sclerosis: bilateral improvement of Raynaud's phenomenon with unilateral digital sympathectomy. Semin Arthritis Rheum. 2010;40:137-146. Abstract

70. Belch JJ, Shaw B, O'Dowd A, et al. Evening primrose oil (Efamol) in the treatment of Raynaud's phenomenon: a double blind study. J Thromb Haemost. 1985;54:490. Abstract

71. DiGiacomo RA, Kremer JM, Shah DM. Fish-oil dietary supplementation in patients with Raynaud's: a double-blind, controlled, prospective study. Am J Med. 1989;68:158-164. Abstract

72. Muir AH, Robb R, McLaren M, et al. The use of Ginkgo biloba in Raynaud's disease: a double-blind placebo controlled trial. Vasc Med. 2002;7:265-267. Abstract

73. Bredie SJ, Jong MC. No significant effect of ginkgo biloba special extract EGb 761 in the treatment of primary Raynaud phenomenon: a randomized controlled trial. J Cardiovasc Pharmacol. 2012;59:215-221. Abstract

74. Appiah R, Hiller S, Caspary L, et al. Treatment of primary Raynaud's syndrome with traditional Chinese acupuncture. J Intern Med. 1997;241:119. Abstract

75. Al-Awami M, Schillinger M, Maca T, et al. Low-level laser therapy treatment of primary and secondary Raynaud's phenomenon. Vasa. 2004;33:25-29. Abstract

76. Malenfant D, Catton M, Pope JE. The efficacy of complementary and alternative medicine in the treatment of Raynaud's phenomenon: a literature review and meta-analysis. Rheumatology (Oxford). 2009;48:791-795. Abstract

77. Hélou J, Moutran R, Maatouk I, et al. Raynaud's phenomenon and vitamin D. Rheumatol Int. 2013;33:751-755. Abstract

78. Walker KM, Pope J; participating members of the Scleroderma Clinical Trials Consortium (SCTC), Canadian Scleroderma Research Group (CSRG). Treatment of systemic sclerosis complications: what to use when first-line treatment fails - a consensus of systemic sclerosis experts. Semin Arthritis Rheum. 2012;42:42-55. Abstract

79. Pope JE, Black C, Matucci-Cerinic M, et al. Functional correlates of reduction of digital ulcers by bosentan therapy in patients with systemic sclerosis (SSc). Arthritis Rheum. 2006;54(suppl):S740. Full text

80. Bello RJ, Cooney CM, Melamed E, et al. The therapeutic efficacy of botulinum toxin in treating scleroderma-associated Raynaud's phenomenon: a randomized, double-blind, placebo-controlled clinical trial. Arthritis Rheumatol. 2017;69:1661-1669. Abstract

81. Iorio ML, Masden DL, Higgins JP. Botulinum toxin A treatment of Raynaud's phenomenon: a review. Semin Arthritis Rheum. 2012;41:599-603. Abstract

82. Neumeister MW, Chambers CB, Herron MS, et al. Botox therapy for ischemic digits. Plast Reconstr Surg. 2009;124:191-201. Abstract

83. Jenkins SN, Neyman KM, Veledar E, et al. A pilot study evaluating the efficacy of botulinum toxin A in the treatment of Raynaud phenomenon. J Am Acad Dermatol. 2013;69:834-835. Full text Abstract

84. Kim DC, Lee CE. NXCL-4950, a novel composite applicable to peripheral skin, is capable of increasing skin temperature by enhancing capillary circulation. Clin Exp Dermatol. 2013;38:244-250. Abstract

85. Pope J, Fenlon D, Thompson A, et al. Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev. 2000;(2):CD000954. Full text Abstract

86. Fava A, Wung PK, Wigley FM, et al. Efficacy of Rho kinase inhibitor fasudil in secondary Raynaud's phenomenon. Arthritis Care Res (Hoboken). 2012;64:925-929. Abstract

87. Spencer-Green G. Outcomes in primary Raynaud phenomenon: a meta-analysis of the frequency, rates, and predictors of transition to secondary diseases. Arch Intern Med. 1998;158:595-600. Full text Abstract

88. Khanna D, Denton C, Merkel PA, et al. Macitentan in systemic sclerosis associated with ischemic digital ulcers: results from two large randomized controlled trials. JAMA. In press.

89. Black C, Denton CP, Furst DE, et al. Bosentan reduces the number of new digital ulcers in patients with systemic sclerosis: open-label extension to a double-blind trial. Ann Rheum Dis. 2006;65(suppl II):384.

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