

MANAGEMENT OF RAYNAUD'S PHENOMENON

1. Establish diagnosis and identify any underlying cause amenable to treatment (1)

Establish whether primary or secondary

If secondary, establish underlying cause, possibilities including:

- Connective tissue disease e.g. systemic sclerosis (SSc)-spectrum disorder
- Hand-arm-vibration syndrome
- Extrinsic vascular compression e.g. cervical rib
- Intravascular problems e.g. paraproteinaemia
- Drugs or chemicals (e.g. beta-blockers, vinyl chloride)

Determine severity: summer as well as winter, functional impairment, current or previous digital ulcers?

Establishing the diagnosis will be informed by:

- a. History (including full systems enquiry, drug, family and occupational history)
- b. Examination (especially of the hands and face)
- c. Investigations:
 1. Minimal list (when history and examination strongly suggest primary Raynaud's phenomenon): full blood count (FBC), erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), antinuclear antibody (ANA) and capillaroscopy
 2. 'Usual' list: in addition to 'minimal' list urea and electrolytes (U&Es), liver function tests (LFTs), bone biochemistry, thyroid function tests (TFTs), creatine kinase (CK), immunoglobulins (Igs), C3 and C4, chest (or thoracic outlet) X-ray
 3. Other investigations when index of suspicion high, may include:
 - Autoantibodies: anticentromere, anti-topoisomerase, anticardiolipin, anti-beta2-glycoprotein
 4. Fasting lipid profile
 5. Thermography (specialist centres only)

2. General/lifestyle measures

a. Patient education. Includes:

- Avoid cold exposure and changes in temperature
- Keep warm: wear layers of clothes, hand warmers, gloves (including electrically heated, silver)
- Paraffin wax
- Stop smoking

b. Complementary therapies

Many patients elect to try a number of complementary therapies for Raynaud's phenomenon, including vitamin C, vitamin E, gamolenic acid, ginkgo biloba, acupuncture and biofeedback (2). Physicians need to be aware of this and actively enquire about these: there may be potential pharmacological interactions with some of these therapies.

c. Useful sources of information:

<http://www.raynauds.org.uk/>

<http://www.sclerodermasociety.co.uk>

3. Drug therapy: first line

First line drugs are the calcium channel blockers (CCB), angiotensin receptor blockers (ARB) and selective serotonin re-uptake inhibitors (SSRI). Alpha blockers, angiotensin converting enzyme (ACE) inhibitors and topical nitrate therapy should also be considered.

Some examples, with usual adult dose ranges, are as follows:

CCBs: Nifedipine SR 10mg bd → 40mg bd, amlodipine 5mg od → 10mg od, diltiazem 60mg bd → 120mg bd (3,4)

ARBs: Losartan 25mg od → 100mg od (5)

SSRIs: fluoxetine 20mg od (especially useful in patients prone to vasodilatory side effects) (6)

Alpha-blockers: Prazosin 500 micrograms bd → 2mg bd (7)

ACE inhibitors: Lisinopril 5mg od → 20mg od (8)

4. Antiplatelet and/or statin therapy

These may be considered as adjunctive therapy, especially in patients with concomitant risk factors (e.g. positive anticardiolipin antibodies, cardiovascular risk factors) (9).

5. Drug therapy: refractory

IV prostanoid therapy should be considered especially in patients with SSc-spectrum disorders, and particularly in cold weather/onset of winter. Iloprost (10,11) and epoprostenol (12) are most commonly used:

IV iloprost. 3-5 days 0.5ng-2ng/kg/min for 6 hours

Oral vasodilators prescribed for Raynaud's phenomenon are generally discontinued for duration of infusion.

6. Phosphodiesterase (PDE)5 inhibitor

May be indicated in refractory disease.

Some examples, with usual adult dose ranges, are as follows:

Sildenafil 20mg / 25mg tds → 50mg tds (13,)

Tadalafil 10mg alternate days → 20mg od (14)

MANAGEMENT OF DIGITAL ULCERATION

1. Establish diagnosis early

Patients should be asked to report ulcers early to allow prompt intervention before the ulcer has enlarged and/or become secondarily infected.

2. Treat any contributory cause

Any contributory cause/complicating factor should be identified and treated, the main examples being:

Infection (including osteomyelitis): Systemic antibiotics (oral or IV depending on severity). Flucloxacillin appropriate first choice, but depends on swab sensitivities. Osteomyelitis requires long term antibiotics – MR scanning may detect osteomyelitis at an early stage.

Underlying calcinosis: Rarely this may require debridement if other digital ulcer healing measures are unsuccessful.

Large (proximal) vessel problems: Angioplasty/surgical revascularisation may be required

Vasculitis/coagulopathy e.g. antiphospholipid syndrome. These are rare, but if present require specific treatment.

Smoking: Smoking cessation.

Exacerbating therapies e.g. beta-blockade: These should be discontinued where possible.

3. Optimal wound care and analgesia

This depends on severity of the ulcer: strive for balance in dry / wet for best wound healing.

If wet, strive to dry e.g. alginates (e.g. Suprasorb), antimicrobials (e.g. Aquacel Ag)

If dry, strive to wet e.g. hydrogel (e.g. Intrasite gel), hydrocolloids (e.g. Duoderm)

Analgesia: opiates may be required in the short term.

4. Optimise oral vasodilators or IV prostanoids

Choice of treatment depends on severity.

If outpatient management is appropriate, then oral vasodilator therapy should be optimised either by increasing the dose or substituting/adding alternative vasodilator therapy (see Raynaud's phenomenon algorithm).

In severe cases admit patients for IV prostanoid treatment – consider continuous / extended courses in refractory cases.

5. Consider surgical debridement in patients with necrotic tissue or underlying calcinosis

Surgical debridement should be considered if the ulcerated area is extremely painful / tender or if there is necrotic tissue.

6. Antiplatelet and/or statin therapy

These may be considered as adjunctive therapy (9). Clopidogrel may be preferable to aspirin as many patients have upper gastrointestinal problems.

7. Repeat IV prostanoids or PDE5 inhibitor or endothelin-1 receptor antagonist (ERA)

Repeat IV prostanoid and/or PDE 5 inhibitor may be beneficial in patients with non-healing, recalcitrant ulcers (11, 12, 15).

In patients with recurrent ulcers, bosentan is licensed to reduce the number of new ulcers: 62.5mg bd for 4 weeks then 125mg bd (requires blood monitoring) (16).

8. Consider surgical sympathectomy

Digital (palmar) sympathectomy may benefit patients unresponsive to the above measures, although this is performed only in certain centres. Rarely digital amputation may be required, for the patient unresponsive to all the above measures.

MANAGEMENT OF CRITICAL DIGITAL ISCHAEMIA

1. Establish diagnosis and identify any treatable contributory cause

Patients should be asked to report any permanent finger/toe discolouration *early* to allow prompt intervention before progression to irreversible ischaemia/gangrene.

Any concomitant pathology which could be contributory should be identified, specifically: large (proximal) vessel disease, vasculitis, coagulopathy, thromboembolism, smoking. Investigations may include echocardiogram, angiography, cryoglobulins, immunoglobulins and protein electrophoresis.

2. Treat any contributory cause

Large (proximal) vessel disease: Angioplasty/surgical revascularisation may be required.

Vasculitis/coagulopathy/thromboembolism. These are rare, but if present require specific treatment.

Smoking: Smoking cessation (17).

3. Admit for IV prostanoid and analgesia

IV prostanoid treatment: Consider continuous / extended courses.

Analgesia: Opiates will most likely be required in the short term.

4. Antiplatelet therapy

Most clinicians prescribe antiplatelet therapy in this acute setting. Clopidogrel may be preferable to aspirin as many patients have upper gastrointestinal problems.

5. Consider statin

Consider short term high dose statin therapy (as is prescribed for other acute vascular events e.g. acute coronary syndrome) (18).

6. Antibiotic if any possibility of infection

Critically ischaemic digits are often infected, and so there should be a low threshold for giving antibiotics.

7. Optimise oral vasodilator therapy (consider PDE5 inhibitor)

Maximise oral vasodilator therapy, including vasodilators in combination. PDE5 inhibitor therapy should be used where first line therapy is inadequate.

8. Consider digital sympathectomy

Digital (palmar) sympathectomy may confer benefit, especially if there is a concern that ischaemia is progressing or may be extending to involve other digits.

9. Surgical debridement if necrotic tissue

Surgical debridement or amputation should be considered if the ischaemic area has progressed to necrosis. However, gangrene of the finger-tips may autoamputate.

10. Short-term anticoagulation

Consider heparinisation if ischaemia progresses despite all other measures and/ or other digits become involved.

References:

1. Herrick AL, Cutolo M. Clinical implications from capillaroscopic analysis in patients with Raynaud's phenomenon and systemic sclerosis. *Arthritis Rheum.* 2010 Sep;62(9):2595-604. *This review emphasises the distinction of primary RP that does not progress to digital ischaemia from secondary RP in particular with a focus on capillaroscopy that helps in early detection of microvascular changes that characterise secondary RP. The article also explores the recent advances in the understanding of RP in particular the vascular abnormalities.*
2. Simonini G, Pignone A, Generini S, Falcini F, Cerinic MM. Emerging potentials for an antioxidant therapy as a new approach to the treatment of systemic sclerosis. *Toxicology.* 2000 Nov 30;155(1-3):1-15. *The review discusses the rationale for the potential use of antioxidants in RP with a discussion of the effect of oxygen free radicals and reactive nitrogen species have on the endothelium dysfunction and disease progression in SSc.*
3. Thompson AE, Shea B, Welch V, Fenton D, Pope JE. Calcium channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum.* 2001 Aug; 44(8): 1841-7 *This meta-analysis showed a decrease of four attacks per week and a 35% reduction in severity of RP in response to calcium channel blockers in patients with SSc-related RP.*
4. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford).* 2005 Feb;44(2):145-50. *The same authors reviewed 18 randomised, placebo-controlled and double-blinded trials which evaluated the efficacy of CCBs in patients with primary RP with a mean reduction of 2.6-5.0 attacks over a week period and a 33% decrease in severity compared to those receiving placebo therapy*
5. Dziadzio M, Denton CP, Smith R, Howell K, Blann A, Bowers E, Black CM. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. *Arthritis Rheum.* 1999 Dec;42(12):2646-55. *Patients with secondary RP treated with losartan for 12 weeks had 45% and 36% reduction in the frequency and severity of RP attacks from baseline. The authors concluded that the therapeutic effect of losartan was greater than that of nifedipine. A reduction of serum VCAM-1 levels was also demonstrated. It was suggested that losartan also improved endothelial function.*
6. Coleiro B, Marshall SE, Denton CP, Howell K, Blann A, Welsh KI, Black CM. Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford).* 2001 Sep;40(9):1038-43. *A comparative study of fluoxetine and nifedipine in patients with primary or secondary RP showed that 6 weeks' treatment with fluoxetine significantly ($p < 0.01$) reduced RP attack severity, but not frequency, in patients with secondary RP, while nifedipine had no effect.*

7. Harding SE, Tingey PC, Pope J, Fenlon D, Furst D, Shea B, Silman A, Thompson A, Wells GA. Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev.* 2000;(2):CD000956 *Prazosin was modestly effective in reducing the frequency of attacks and producing overall disease improvement in patients with RP secondary to scleroderma.*
8. Wood HM, Ernst ME. Renin-angiotensin system mediators and Raynaud's phenomenon. *Annals of Pharmacotherapy* 2006; 40:1998–2002. *Systematic analysis of available data from several small and short-term studies suggested that the use of ACE inhibitors in the treatment of Raynaud's phenomenon demonstrated conflicting results with variable response to different ACE inhibitors.*
9. Abou-Raya, A. *et al.* Statins: potentially useful therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. *J. Rheumatol.* 35, 1801–1808 (2008). *In this pilot cross-sectional study, Atorvastatin 40 mg daily reduced the mean number of digital ulcers over four months. The effect was not attributable to other standard vasodilators but none of the patients received either prostanoids or endothelin receptor antagonists.*
10. Wigley FM, Wise RA, Seibold JR, et al. Intravenous iloprost infusion in patients with Raynaud's phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Annals of Internal Medicine* 1994; 120: 199-206. *The frequency and severity of RP attacks were significantly reduced with intravenous iloprost delivered over a 5-day period with a 9-week follow-up period.*
11. Pope J, Fenlon D, Thompson A, et al., Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database of Systematic Reviews*, 2000: CD000953. *Review of seven randomised controlled trials in RP secondary to SSc found modest efficacy favouring iloprost with regards to attack frequency and severity and improvement in digital lesions. In most studies iloprost was administered for 6-8 hours at the dose of 0.5-3ng/kg/min.*
12. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. *Annals of Internal Medicine* 2000; 132:425–434. *The benefit of epoprostenol in RP secondary to SSc was demonstrated in this RCT with 111 SSc patients in which epoprostenol reduced the severity of RP and frequency of digital ulcers.*
13. Shenoy PD, Kumar S, Jha LK, Choudhary SK, Singh U, Misra R, Agarwal V. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheumatology (Oxford).* 2010 Dec;49(12):2420-8. *In this eight week study, addition of tadalafil, a PDE5 inhibitor with a longer half life of 17.5 hours compared to 3.8 hours for sildenafil, led to symptomatic improvement with reduction of daily frequency and daily duration of RP. In addition, tadalafil also healed existing digital ulcers and prevented formation of new ulcers in patients with SSc.*
14. Fries R, Shariat K, von Wilmowsky H, Bohm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; 112:2980–2985. *In this crossover study with 16 patients, patients receiving sildenafil 50 mg twice daily for four weeks had significant improvement from baseline in attack frequency, duration with improvement in capillary flow velocity. Partial healing of digital ulcerations was also*

demonstrated in a subset of patients who received sildenafil and these ulcers reappeared after sildenafil was discontinued. By contrast, healing of ulceration did not occur among those who received placebo.

15. Bruecker CS, Becker MO, Kroencke T, Huscher D, Scherer HU, Worm M, Burmester G, Riemekasten G. Effect of sildenafil on digital ulcers in systemic sclerosis: analysis from a single centre pilot study. *Ann Rheum Dis.* 2010 Aug;69(8):1475-8. *In this open-label study, patients who received a maximal tolerated dose of sildenafil up to six months demonstrated a reduction of digital ulcers from 3.1 ulcers per patient at baseline to 1.1 ulcer per patient at the end of study period.*

16. 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; 50:3985–3893. *The effect of bosentan on prevention of DU was demonstrated in this double-blind, placebo-controlled trial in SSc patients who were treated for a period of 16 weeks (RAPIDS-1 study).*

17. Harrison BJ, Silman AJ, Hider SL, Herrick AL. Cigarette smoking as a significant risk factor for digital vascular disease in patients with systemic sclerosis. *Arthritis Rheum.* 2002 Dec;46(12):3312-6. *Current smokers are at least 3 times more likely than non-smokers to require treatment for digital ischaemia including admission for intravenous vasodilators, surgical intervention such as debridement or amputation for digital vasculopathy. This provides strong evidence to promote smoking cessation in patients with SSc.*

18. Kim JS, Kim J, Choi D, Lee CJ, Lee SH, Ko YG, Hong MK, Kim BK, Oh SJ, Jeon DW, Yang JY, Cho JR, Lee NH, Cho YH, Cho DK, Jang Y. Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the STATIN STEMI trial. *JACC Cardiovasc Interv.* 2010 Mar;3(3):332-9. *This study suggests that short-term high dose Atorvastatin 80 mg daily prior to primary percutaneous coronary intervention may improve microvascular coronary perfusion and ST-segment recovery rates compared with low-dose Atorvastatin.*