CME CREDIT *LEARNING OBJECTIVE:* Readers will follow a stepwise approach to assessing and treating Raynaud phenomenon

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Treating Raynaud phenomenon: Beyond staying warm

ABSTRACT

Raynaud phenomenon is an overactive vascular response to cold and emotional stress that results in cutaneous color changes and sensory symptoms in the digits. It can be idiopathic (primary) or secondary to another condition; the latter can be more severe and more apt to lead to ischemic complications such as digital ulceration and even loss of digits. If nonpharmacologic interventions prove inadequate, then vasodilator agents are used.

KEY POINTS

Primary Raynaud phenomenon occurs in the absence of any underlying disease process. Secondary Raynaud phenomenon occurs in concert with another disease, frequently rheumatic.

Young patients with mild Raynaud phenomenon, normal nailfold capillaries, and no additional symptoms or signs to suggest a rheumatic or other underlying disease can be followed carefully by the primary care doctor and do not require further serologic workup or referral to a specialist.

Nonpharmacologic interventions, ie, cold avoidance and stress management, are first-line for all patients.

Calcium channel blockers are first-line drugs and should be titrated to the maximum tolerated dose before adding or switching to other agents.

The goal of treatment should not be to eliminate Raynaud attacks completely but to improve quality of life and prevent ischemic complications.

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RAYNAUD PHENOMENON is an overactive vascular response to cold and emotional stress that results in cutaneous color changes and sensory symptoms of the digits (**Figure 1**). It can occur in isolation as primary Raynaud phenomenon or secondary to another disease process. It is thought to be triggered by a heightened sympathetic vasoconstrictive response of small arteriovenous anastomoses in the fingers, toes, ears, and tip of the nose. These structures play a key role in maintaining a stable core body temperature by cutaneous thermoregulation.[1]

Secondary Raynaud phenomenon can be seen with a wide array of systemic conditions as well as environmental and drug exposures. It is a frequent feature of autoimmune rheumatic conditions such as systemic sclerosis, mixed connective tissue disease, systemic lupus erythematosus, and dermatomyositis. Less commonly, cryoproteinemias, paraneoplastic syndromes, hypothyroidism, and carpal tunnel syndrome can be associated with or cause Raynaud phenomenon. Vibratory trauma (eg, from using a jackhammer) and drugs (eg, vasopressors, stimulants, ergots, chemotherapeutic agents) can also cause Raynaud phenomenon.[1]

A variety of disorders that cause vasospasm or vascular occlusion of the peripheral circulation can mimic typical Raynaud phenomenon, including peripheral nerve injury,[2] complex regional pain syndrome,[3] occlusive vascular disease, vasculitis, acrocyanosis,[4] and thoracic outlet syndrome.

The prevalence of Raynaud phenomenon is not exactly known, in part due to geographic differences in climate and variation in methods of assessment. However, a 2015 systematic review and meta-analysis of primary Raynaud

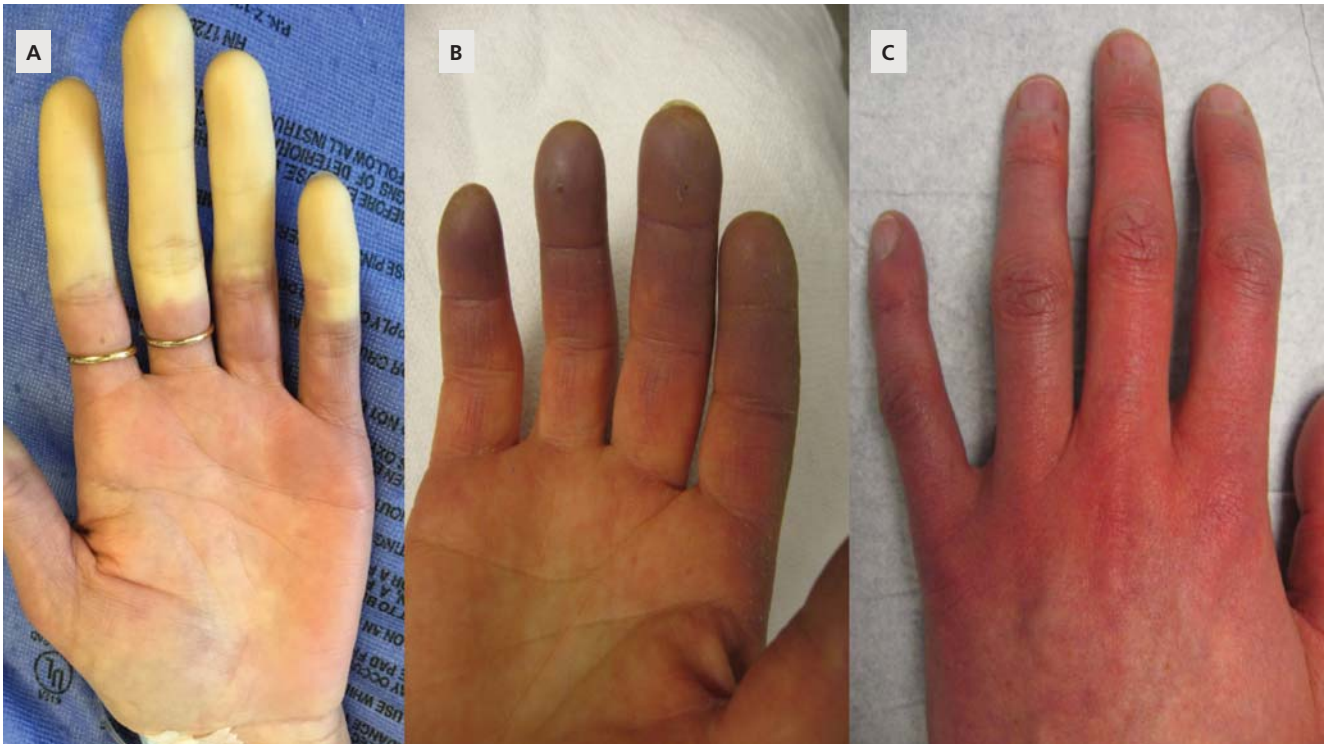

FIGURE 1. (A) White digits with intense vasoconstriction in Raynaud phenomenon; (B) blue digits with hypoxemic venous stasis; (C) red digits with hyperemic reperfusion.

Nearly 5% of the general population may have primary Raynaud phenomenon

phenomenon determined a pooled prevalence of 4.85% (95% confidence interval [CI] 2.08%–8.71%) in the general population.[5] Accordingly, accurate identification and management of this condition is a useful skill for the internist.

COLD SENSITIVITY AND COLOR CHANGES

Because there are no confirmatory diagnostic tests for this condition, there are no formal diagnostic criteria. However, many experts agree that Raynaud phenomenon can be diagnosed clinically when patients report:

- Unusual sensitivity of the fingers to cold, manifesting as pain or paresthesia (eg, tingling, pricking, numbness), and
- Color changes of the fingers when exposed to cold, specifically pale white or blue-black, or both.[6]

Provocative testing such as submerging patients' hands in cold water is not recommended, as it is distressing to the patient and inconsistent in triggering an event.

Pain is a symptom of critical digital ischemia. The skin color changes are due to rapid alterations in blood flow in digital skin. The pale white is due to markedly reduced or absent flow secondary to intense vasoconstriction, the blue-black is due to hypoxemic venous stasis, and the red blush is due to hyperemic reperfusion (**Figure 1**). However, not all patients have all 3 phases of the classic triphasic color changes, and color changes may not follow a set sequence.

Raynaud phenomenon can also occur in other areas of the body that have thermoregulatory vessels, such as the toes, ears, nipples, tongue, and nose. While some patients with Raynaud phenomenon have a finger that is more sensitive than the others, repeated isolated single-digit or asymmetric events without typical progression to all fingers suggest a secondary local structural disease requiring further investigation (see below).

Symptoms related to Raynaud often mimic sensory changes including paresthesias, numbness, aching, and clumsiness of the hand. Abnormal vascular reactivity has been implicated as a causative factor in several disorders, such as migraine headache, preeclampsia, and variant angina. While case reports, case series,

and some controlled studies have linked Raynaud phenomenon and these conditions, there is no solid evidence of a systemic vasospastic disorder in patients with primary Raynaud phenomenon.

Raynaud phenomenon is triggered by more than just a cold ambient temperature. Provocation can occur during movement from warmer to relatively cooler temperatures, as well as during episodes of elevated sympathetic activity (eg, emotional distress or fear). In fact, maintaining full body warmth as well as emotional equilibrium are the most important strategies to reduce the frequency of attacks.

PRIMARY VS SECONDARY RAYNAUD PHENOMENON

To distinguish between primary and secondary Raynaud phenomenon, a careful history and physical examination are paramount.

Primary Raynaud phenomenon

In uncomplicated primary Raynaud phenomenon, the episodes typically last 15 to 20 minutes after rewarming and usually start in a single finger and spread to other digits symmetrically and bilaterally.[7] The thumb is often spared, and ischemic digital ulcers do not occur. Vasoconstrictive episodes are mild.

Females under age 20 are most commonly affected. In our experience, a young woman with the above clinical picture, no signs or symptoms suggestive of connective tissue disease (see below), and normal nailfold capillaries can be diagnosed as having primary Raynaud phenomenon without any further workup.

Careful clinical follow-up is recommended, because if an occult secondary process is indeed present, most patients will begin to show additional symptoms or signs of it within 2 years of the onset of Raynaud phenomenon.

Should a clinician be unfamiliar with nailfold capillary examination, or if symptoms (eg, fatigue or arthralgia) or signs (eg, rash, arthritis) suggestive of connective tissue disease are present, referral to a rheumatologist for further evaluation is appropriate. Results of further diagnostic testing dictated by the history and physical such as a screening antinuclear antibody test can be sent before referral.

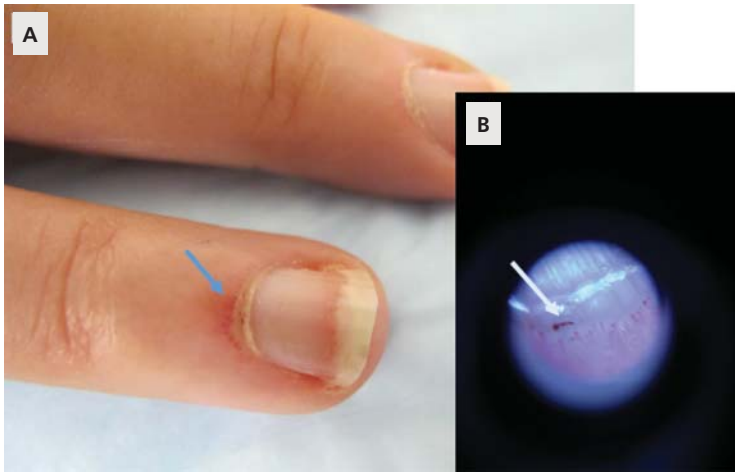

FIGURE 2. (A) Dilated nailfold capillaries in a patient with scleroderma (blue arrow); (B) dilation and dropout of nailfold capillaries (white arrow) viewed with a magnifier.

Secondary Raynaud phenomenon

Several clinical features suggest secondary Raynaud phenomenon and warrant referral to a rheumatologist:

- Age 20 or older at onset
- Frequent severe vasoconstrictive episodes
- Male sex
- Thumb involvement
- Signs of an autoimmune rheumatic disease, eg, sclerodactyly, cutaneous or mucosal matted telangiectasia, inflammatory arthritis, an abnormal lung examination, severe digital ischemia with ulceration or gangrene, or nailfold capillary dilation or dropout (**Figure 2**)[8]
- Isolated single-limb or 1-finger ischemic events, seen in macrovascular occlusive disease or inflammatory disease mimicking Raynaud phenomenon (eg, atherosclerosis, vasculitis); when isolated acute ischemic events occur in the upper or lower extremity, a further workup is necessary.

Patients with primary Raynaud tend to be younger and female

Figure 3 shows our approach to evaluation.

NONPHARMACOLOGIC THERAPY

Cold avoidance and stress management are first-line therapies for preventing Raynaud attacks and must be part of any treatment strategy. Digital arteries and thermoregulatory vessels of the skin are predominantly under sympathetic adrenergic control, so temperature changes and emotional stressors trigger vaso-

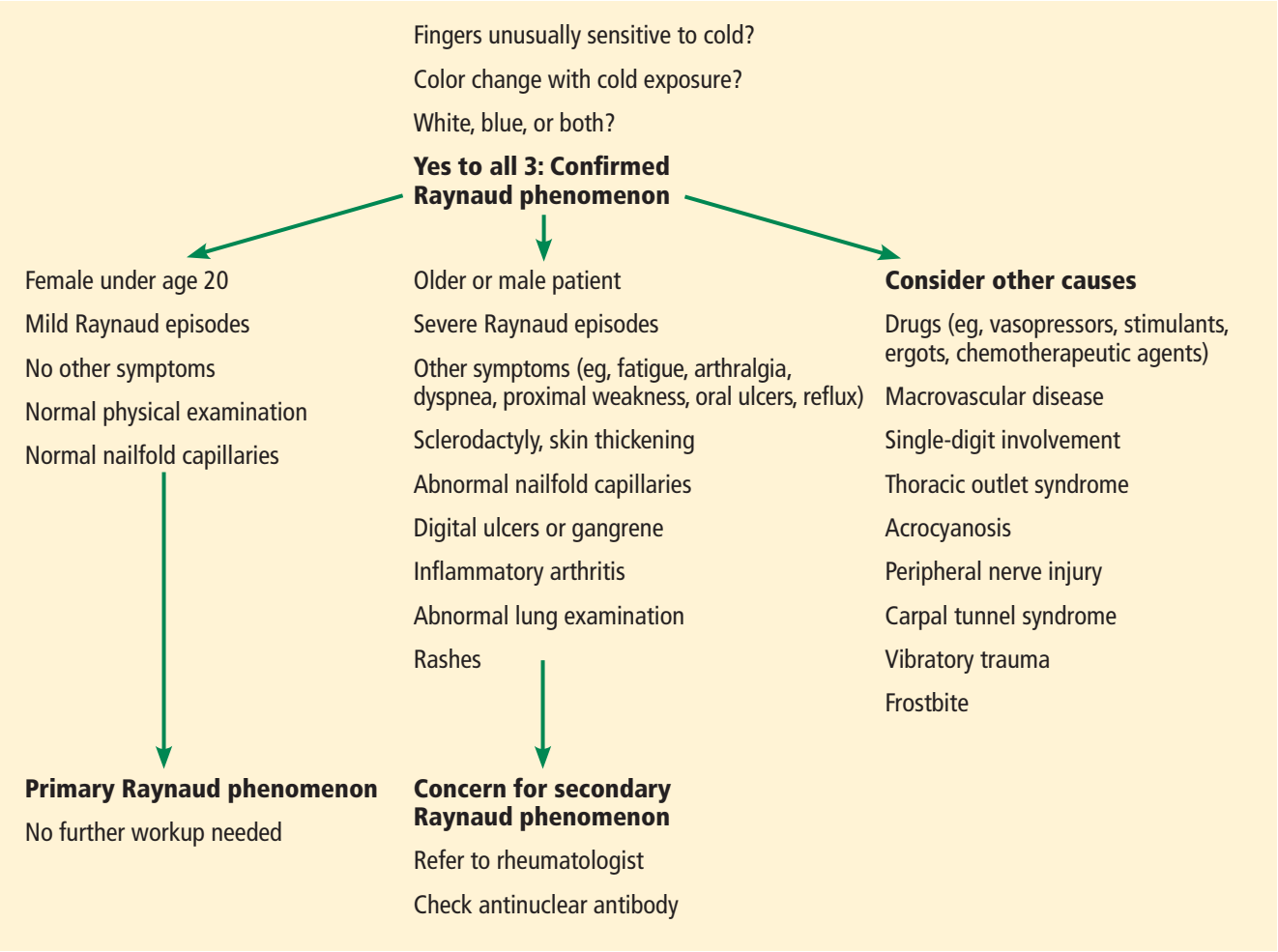

FIGURE 3. Our approach to diagnosis of Raynaud phenomenon and differentiating primary from secondary Raynaud phenomenon.

constriction. Patients should be counseled to:

Keep the whole body warm. Patients should wear multiple layers of clothing, a hat, warm gloves, and warm socks. Commercially available hand-warmers can help, especially for patients who live in cold climates.

Learn to avoid or manage stress. Good communication, attention to the patient's needs, and regular follow-up for reassurance are paramount. For some patients, psychotropic medications to manage mood may help. Behavioral approaches have been suggested for acute stress management. One approach, autogenic training, is a form of relaxation with temperature biofeedback in which finger temperature data are provided to patients to help them learn to relax by monitoring their internal states and changes in temperature. However, there are no strong data to support the routine use of this technique or the use of one behavioral approach over another. Trials have generally been of low quality and limited by small sample size.[9]

Stop smoking![10]

Stop a Raynaud attack should one occur, eg, place the hands under warm water or in a warm part of the body, such as under legs when sitting. This can help speed recovery.

In addition, the physician should:

Eliminate vasoconstricting agents such as nonselective beta-blockers, ergots, triptans, and amphetamines.

PHARMACOLOGIC THERAPY

For many patients, nonpharmacologic interventions are enough to decrease the severity

and frequency of attacks. However, if Raynaud phenomenon continues to negatively affect quality of life, drug therapy can be added (**Table 1**).

Calcium channel blockers

Calcium channel blockers are first-line agents for both primary and secondary Raynaud phenomenon that does not adequately respond to nonpharmacologic interventions. These agents are effective, available, and reasonably inexpensive.

Dihydropyridine calcium channel blockers such as nifedipine and amlodipine are commonly used. Both drugs are acceptable options, though some patients may respond better to one than the other in terms of symptoms and side effects. Nondihydropyridines such as diltiazem can also be used, but they have less potent vasodilatory effects because they are less selective for vascular smooth muscle.

These medications should be started at the lowest dose and titrated up over several weeks as tolerated to achieve their maximal effect. Intermittent therapy (eg, during the winter months only) is reasonable for primary Raynaud without risk of digital ulceration, as relief of symptoms and improvement in quality of life are the main indications for therapy in this circumstance.

A 2016 Cochrane review and meta-analysis of the use of calcium channel blockers to treat primary Raynaud phenomenon included 7 randomized controlled trials with 296 patients treated with either nifedipine or nicardipine.[11] There was moderate-quality evidence that these drugs minimally decreased the frequency of attacks (standardized mean difference of 0.23; 95% CI 0.08–0.38, P = .003). This translated to 1.72 fewer attacks per week with treatment than with no pharmacologic therapy (95% CI 0.60–2.84). When analyzed individually, only nifedipine was effective; nicardipine did not decrease the frequency of attacks.

Unfortunately, calcium channel blockers failed to decrease the severity of attacks (according to unvalidated severity scoring systems) or make any differences in physiologic measurement outcomes. Attacks were not completely eliminated, just less frequent than before treatment.[11]

TABLE 1

Stepwise therapy for Raynaud phenomenon

Step 1	Cold avoidance
	Emotional regulation
Step 2	Dihydropyridine calcium channel blocker in maximum tolerated dose
	Phosphodiesterase type 5 (PDE5) inhibitor substituted for or added to a calcium channel blocker
Step 3	Topical nitrate (contraindicated in a patient already taking a PDE5 inhibitor due to risk of hypotension)
	Prazosin
	Fluoxetine
	Pentoxifylline
	Atorvastatin
For acute digital crisis	Calcium channel blocker plus topical nitrate or calcium channel blocker plus PDE5 inhibitor
	Intravenous prostacyclin
	Localized digital sympathectomy

Most commonly reported side effects included headache, flushing, hypotension, edema, and, rarely, gastrointestinal reflux. Use of these medications may be limited by hypotension.

The review was limited by the small sample size, short duration of treatment, and relatively low doses of calcium channel blockers used in the available studies.[11]

A 2005 meta-analysis also indicated a statistically significant decrease of 2.8 to 5 attacks per week with nifedipine treatment, though this study also included some patients with secondary Raynaud phenomenon.[12]

If an occult secondary process is present, most patients begin to have symptoms or signs of it within 2 years

Phosphodiesterase type 5 inhibitors

When calcium channel blockers do not adequately control symptoms, phosphodiesterase type 5 (PDE5) inhibitors can be added or substituted. These medications work by preventing breakdown of cyclic guanosine monophosphate, which induces relaxation in vascular smooth muscle and vasodilation.

Sildenafil can be started at a low dose (20

mg daily) and up-titrated to the maximum dose (20 mg 3 times daily) as tolerated.

A 2014 meta-analysis of 6 randomized controlled trials included 244 patients with secondary Raynaud phenomenon treated with sildenafil, tadalafil, or vardenafil.[13] These drugs decreased the daily frequency of attacks by about 0.5 per day vs placebo (–0.49, 95% CI –0.71 to –0.28, $P < .0001$). PDE5 inhibitors also decreased the severity of attacks (based on the Raynaud's Condition Score, a popular scoring system) and the duration of attacks by a statistically significant amount.

Almost all patients in these 6 trials were on PDE5 monotherapy. Data on the cumulative benefit of calcium channel blocker and PDE5 inhibitor combination therapy are not yet available. Not all patients tolerate combination therapy, as it can cause symptomatic hypotension, but it can be a successful option in some.

There are also no data showing that either calcium channel blockers or PDE5 inhibitors are superior, though the former are less expensive. A small double-blind, randomized, crossover study of udenafil vs amlodipine in the treatment of secondary Raynaud phenomenon showed that both medications significantly decreased the frequency of attacks and had comparable efficacy.[14]

No drug is approved for use in Raynaud phenomenon

Cost and insurance coverage. We have generally been successful in obtaining coverage for this off-label use of PDE5 inhibitors, though additional effort may be required. No drug (not even a calcium channel blocker) is approved by the US Food and Drug Administration for use in Raynaud phenomenon. In our experience, a letter of appeal outlining the rationale for use and citing supporting publications can lead to successful coverage of a medication. If the drug is still not approved, the patient either pays for it out of pocket or another agent is selected. In certain circumstances, pharmaceutical companies may provide prescription assistance for compassionate use of these drugs in Raynaud phenomenon, although this also takes letter-writing, phone calls, or both on the part of the physician.

Topical nitrates

Patients who have an unsatisfactory response to calcium channel blockers with or without PDE5 inhibitors can try topical nitrates, available as sustained-release transdermal patches, tapes, creams, gels, and ointments.

Small trials have noted slight improvement in the Raynaud Condition Score[15] and finger temperature[16] with these therapies. Another trial noted decreased frequency of attacks and symptoms with the use of sustained-release glyceryl trinitrate patches, but use was limited by intolerable headache.[17]

In our experience, topical nitrates are most helpful for patients who have 1 or a few digits that are more severely affected than the others, and we reserve these drugs for this indication. Localized vasodilation can provide targeted rapid relief of more ischemic areas.

Topical nitroglycerin can be applied to the base of the ischemic digit for 6 to 12 hours. Preparations vary, and patients should be closely monitored for dose response and tolerance.

Combining a topical nitrate with a calcium channel blocker is safe, but the use of a nitrate with a PDE5 inhibitor is contraindicated due to the risk of hypotension. The use of topical nitrates may be limited by systemic side effects such as headache and flushing and a lack of benefit over time.

Other therapies

If the aforementioned agents are not tolerated or not effective, there is limited evidence that other therapies reduce the frequency and sometimes the severity of attacks. These are not first-line agents but may be tried when other options have been exhausted and symptoms persist. There are no data to support combining these therapies, but in our experience doing so may help some patients in whom drug-drug interactions are not prohibitive.

Prazosin, an alpha-1-adrenergic receptor antagonist, was reported to improve Raynaud phenomenon in 2 small studies in the 1980s, but we do not use it since better options are available. In addition, the vasoactive blood vessels involved do not have alpha-1 receptors, so there is no theoretical basis for using prazosin.[18,19]

Fluoxetine, a selective serotonin reuptake inhibitor, reduced the frequency and severity of attacks in a 6-week crossover study with nifedipine.[20]

Losartan, an angiotensin II receptor blocker, also reduced the severity and frequency of attacks when compared with nifedipine.[21]

Pentoxifylline, a nonselective phosphodiesterase inhibitor, showed some benefit in a trial in 11 patients with primary Raynaud.[22]

Atorvastatin, a lipid-lowering drug, reduced the number of digital ulcers in patients with secondary Raynaud already on first-line vasodilatory therapy, and might be added in this situation.[23]

Botulinum toxin A injections have some data to support their use, but evidence is based on uncontrolled case series.[24] A controlled trial in scleroderma patients with severe Raynaud phenomenon found botulinum toxin to be no better than placebo.[25]

Prostacyclin preparations are available. Intermittent intravenous doses of prostacyclin analogues over several days can be used in resistant cases. Oral prostacyclin agents have not shown consistent benefit. New prostacyclin receptor agonists are under investigation.

Overall, we move to other options only in patients with persistent symptoms that impair quality of life, or in patients with recurrent digital ischemic lesions that have not responded to calcium channel blockers and PDE5 inhibitors or nitrates, either alone or in combination.

DIGITAL ULCERATION AND ACUTE DIGITAL ISCHEMIC CRISIS

Patients with secondary Raynaud phenomenon may be at risk of recurrent digital ulceration and acute digital ischemia with gangrene. These patients should be comanaged with a rheumatologist so that the underlying disease process is fully addressed. Digital ulcers should be inspected closely for signs of infection, which may require treatment with antibiotics.

Acute digital ischemia is a medical emergency and should prompt inpatient admission with warming, emotional regulation, and pain control (often with narcotics) to decrease sympathetic vasoconstriction. These patients require aggressive vasodilatory therapy to reverse the ischemic event.

A short-acting calcium channel blocker or combination therapy with a calcium channel blocker and a PDE5 inhibitor or topical nitrate should be started. If there is no benefit, then transient intravenous vasodilatory therapy with a prostacyclin (epoprostenol) or localized digital sympathectomy is used to prevent digital loss.

The endothelin receptor inhibitor bosentan has been shown to decrease recurrent digital ulcers in patients with scleroderma, and while bosentan does not decrease the frequency of Raynaud attacks, it can be used in this select group to prevent new digital ulcers.

Treatment options may be limited by insurance coverage or access to intravenous infusions.

TAKE-HOME RECOMMENDATIONS

For many patients with primary or secondary Raynaud phenomenon, nonpharmacologic interventions are all that are required to decrease the frequency of attacks and improve quality of life. The goal should not be to eliminate attacks completely, as aggressive drug treatment may cause more harm than benefit. From our perspective, the goals of treatment should be to improve quality of life and prevent ischemic complications.

Pharmacologic therapies should be added only if attacks remain poorly controlled with incapacitating symptoms, or if the patient has digital ischemic ulcers. Calcium channel blockers are first-line therapy, given proven efficacy and low cost, and should be titrated to the maximum tolerated dose before adding or substituting other agents.

Acute digital ischemia is a medical emergency and should prompt inpatient admission

REFERENCES

1. **Wigley FM, Flavahan NA**. Raynaud's phenomenon. N Engl J Med 2016; 375:556–565.
2. **Irwin MS, Gilbert SE, Terenghi G, Smith RW, Green CJ**. Cold intolerance following peripheral nerve injury. Natural history and factors predicting severity of symptoms. J Hand Surg Br 1997; 22:308–316.
3. **Wasner G**. Vasomotor disturbances in complex regional pain syndrome—a review. Pain Med 2010; 11:1267–1273.
4. **Kurklinsky AK, Miller VM, Rooke TW**. Acrocyanosis: the Flying Dutchman. Vasc Med 2011; 16:288–301.
5. **Garner R, Kumari R, Lanyon P, Doherty M, Zhang W**. Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. BMJ Open 2015; 5:e006389.
6. **Wigley FM**. Clinical practice. Raynaud's phenomenon. N Engl J Med 2002; 347:1001–1008.
7. **Chikura B, Moore TL, Manning JB, Vail A, Herrick AL**. Sparing of the thumb in Raynaud's phenomenon. Rheumatology (Oxford) 2008; 47:219–221.
8. **Kallenerg CG**. Early detection of connective tissue disease in patients with Raynaud's phenomenon. Rheum Dis Clin North Am 1990; 16:11–30.
9. **Kwakkenbos L, Thombs BD**. Non-drug approaches to treating Raynaud's phenomenon. In: Wigley FM, Her-

rick AL, Flavahan NA, editors. Raynaud's Phenomenon. A Guide to Pathogenesis and Treatment. New York: Springer Science+Business Media, 2015:299–313.
10. **Goodfield MJ, Hume A, Rowell NR**. The acute effects of cigarette smoking on cutaneous blood flow in smoking and non-smoking subjects with and without Raynaud's phenomenon. Br J Rheumatol 1990; 29:89–91.
11. **Ennis H, Hughes M, Anderson ME, Wilkinson J, Herrick AL**. Calcium channel blockers for primary Raynaud's phenomenon. Cochrane Database Sys Review 2016; 2:CD002069.
12. **Thompson AE, Pope JE**. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. Rheumatology (Oxford) 2005; 44:145–150.
13. **Roustit M, Blaise S, Allanore Y, Carpentier P, Caglayan E, Cracowski J**. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomized trials. Ann Rheum Dis 2013; 72:1696–1699.
14. **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.
15. **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.
16. **Kan C, Akimoto S, Abe M, Okada K, Ishikawa O**. Preliminary thermographic evaluation of a new nitroglycerine tape on the peripheral circulatory disturbance in systemic sclerosis. Ann Rheum Dis 2002; 61:177–179.
17. **Teh LS, Manning J, Moore T, Tully MP, O'Reilly D, Jayson MI**. Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. Br J Rheumatol 1995; 34:636–641.
18. **Russell IJ, Lessard JA**. Prazosin treatment of Raynaud's phenomenon: a double blind single crossover study. J Rheumatol 1985; 12:94–98.
19. **Wollersheim H, Thien T, Fennis J, van Elteren P, van 't Laar A**. Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. Clin Pharmacol Ther 1986; 40:219–225.
20. **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.
21. **Didazio 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.
22. **Neirotti M, Longo F, Molaschi M, Macchione C, Pernigotti L**. Functional vascular disorders: treatment with pentoxifylline. Angiology 1987; 38:575–580.
23. **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.
24. **Iorio ML, Masden DL, Higgins JP**. Botulinum toxin A treatment of Raynaud's phenomenon: a review. Semin Arthritis Rheum 2012; 41: 599–603.
25. **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. Epub ahead of print.

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