



# ESVM guidelines – the diagnosis and management of Raynaud’s phenomenon

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**Summary:** Regarding the clinical diagnosis of Raynaud’s phenomenon and its associated conditions, investigations and treatment are substantial, and yet no international consensus has been published regarding the medical management of patients presenting with this condition. Most knowledge on this topic derives from epidemiological surveys and observational studies; few randomized studies are available, almost all relating to drug treatment, and thus these guidelines were developed as an expert consensus document to aid in the diagnosis and management of Raynaud’s phenomenon. This consensus document starts with a clarification about the definition and terminology of Raynaud’s phenomenon and covers the differential and aetiological diagnoses as well as the symptomatic treatment.

**Keywords:** Raynaud’s, systemic sclerosis, vasospasm, hand arm vibration

## The European Society for Vascular Medicine (ESVM)

This society aims to further develop the specialty of vascular medicine in Europe in order to improve the vascular health of the population and the overall quality of life and health status of vascular patients. ESVM engages in promotion of scientific exchanges, education, cooperative research, and quality of care in the field of arterial, venous, lymphatic, and microvascular diseases. As part of the endeavour to improve the medical care of vascular patients, a series of guidelines, filling gaps in the literature, are being formulated. Each of the ESVM member country’s society endorses the guideline after review and comment. The European Society for Vascular Medicine is an excellent opportunity to bring together experts from 16 different countries who regularly manage patients with Raynaud’s phenomenon, in order to propose a consensual approach to the practical problems encountered by patients with Raynaud’s phenomenon and their attending physicians.

## The need for guidelines for the diagnosis and management of Raynaud’s phenomenon

Raynaud’s phenomenon (RP) is highly prevalent in the general population (prevalence 3–21% depending on the climate) [1]. The literature regarding its clinical diagnosis, associated conditions, investigations, and treatment is substantial, and yet no international consensus has been published regarding the medical management of patients presenting with this condition. For example, the use of syndrome, phenomenon, and disease appears arbitrary in terms of the nomenclature, systematic diagnostic investigations proposed in the literature vary from nil to extensive work-ups, and the therapeutic strategies also vary tremendously [2].

Most knowledge on this topic derives from epidemiological surveys and observational studies; few randomized studies are available, almost all relating to drug treatment and thus these guidelines were developed as an expert consensus document to aid in the diagnosis and management of Raynaud’s phenomenon. This consensus document starts with a clarification about the definition and terminology of Raynaud’s phenomenon and covers the differential and aetiological diagnoses as well as the symptomatic treatment.

## Aims and goals

The aim of this guideline is not to replace expert opinion on individual cases but to give the general practitioner (GP) in primary care insight into the different types of Raynaud’s, the mechanisms for diagnosis/differential diagnosis, and early management. As patients with primary Raynaud’s may be managed in primary care/family practice, a guideline, which clarifies these points, will allow appropriate referral to secondary care for the small but significant, proportion of Raynaud’s patients who require this (see below for recommendations for referral). This guideline aims to help such staff make appropriate onward referrals where appropriate. It aims to inform GPs about associated conditions in secondary Raynaud’s and alert the GP about early symptoms/signs/markers of secondary Raynaud’s to ensure appropriate referral to secondary care.

We hope also that the guideline will be useful for non-specialist secondary care staff, who might be referred such patients to general clinics. It should be noted that this guideline deals only with the management of Raynaud’s and not with any disorder to which RP is secondary; e.g. connective tissue disorders (CTDs).

We hope to inform about investigations in primary care for the Raynaud’s itself and importantly, for exclusion/confirmation of secondary Raynaud’s. The issue of management in secondary care will be covered in the Raynaud’s phenomenon guideline II.

## Methods of assessment and strength of recommendations

The following provides a key to levels of evidence and grades of recommendations that were used in this guideline (modified from the two other European vascular societies for consistency i.e. European Society of Cardiology, (ESC) [3] and European Society of Vascular Surgery (ESVS).

### Levels of evidence

**Level A:** Data derived from many randomised controlled trials (RCTs) or from meta-analyses.

**Level B:** Data derived from one RCT or from large non-randomised clinical trials.

**Level C:** Consensus from experts or data from small studies, registries or retrospective studies.

### Grades of recommendation

Note: The grade of recommendation relates to the strength of the evidence. It is not a measure of the clinical importance of the recommendation.

**Grade I:** Evidence that a treatment or procedure is beneficial, and effective.

**Grade II:** Conflicting evidence and/or differences in opinion of experts regarding the benefit/efficacy of the treatment/procedure.

**Grade IIa:** The weight of evidence or opinion is in favour of benefit/efficacy.

**Grade IIb:** Benefit/efficacy is less well established.

**Grade III:** Evidence or agreement that the treatment is not beneficial nor is it efficacious, and in some cases may even be harmful.

## Definition and nomenclature

In 1862, Maurice Raynaud described a phenomenon of transient and reversible attacks of colour changes triggered by cold exposure, associated with various conditions leading to different outcomes, which he ascribed to an ischaemic mechanism [4]. However, even from the beginning the nomenclature used was not standardized. The title of his thesis “*De l’asphyxie locale et de la gangrène symétrique des extrémités*”, and the focus on the trophic changes in its first English shortened translation led to many workers naming conditions such as digital gangrene, digital ischaemia and digital ulcerations after Maurice Raynaud. Over the last twenty years, however, clarification has been progressively observed in the literature, restricting the use of the name ‘Raynaud’ to its initial clinical description of cold induced ischaemic attacks of the extremities, manifested by transient reversi-

ble digital colour changes. Thus, Raynaud’s phenomenon (RP) is the overarching term for the condition of digital vasospasm producing blanching.

Further clarification is needed regarding the terms “Raynaud disease” and “Raynaud syndrome”. These terms were coined in order to differentiate the two main aetiological subsets of Raynaud’s phenomenon: Raynaud disease, where there is no associated or underlying disorder and Raynaud syndrome, where there is. Unfortunately, both these denominations have drawbacks:

- Raynaud disease is used as a synonym for primary RP. However, it is a benign condition, affecting 3 to 21% of the general population [1] and is not associated with any tissue loss or progression under normal circumstances; as clinicians, we would like to reassure those patients and avoid an unnecessary medicalization. The use of the word “disease” is thus misleading and not helpful.
- When the Raynaud’s is associated with other disorders, it is indeed a syndrome, since it associates several signs and symptoms and may be related to many aetiologies. The usual classification of RP as a vascular acrosyndrome is consistent with this view. Raynaud syndrome (RS) may occur with many other conditions and takes on the prognosis from them rather than from the RS itself.

However, as there is no additional value in the use of these terms, we propose to avoid any other denomination but primary or secondary Raynaud’s phenomenon. Such consistency of terminology is crucial, because of the need for standardisation to allow epidemiology and therapeutic trials of defined populations.

## Epidemiology and symptoms

There is an initial blanching of the skin resulting from vasospasm, usually followed by cyanosis due to deoxygenation of the static venous blood and lastly, by rubor as a consequence of reactive hyperaemia after return of flow, producing the classical ‘triphasic colour change’. However, this classical triphasic colour change is not always present (occurring in about one-third of primary RP patients and two thirds of secondary RP associated with systemic sclerosis [5]) but blanching must be a feature in order for the diagnosis of RP to be made. As cyanosis and rubor are not always present, it should be remembered that blanching alone can also allow for the diagnosis of RP to be made.

### Recommendation 1:

Raynaud’s phenomenon is the correct term for this disorder. It may take the form of primary Raynaud’s phenomenon or secondary Raynaud’s phenomenon.

The colour changes start at the tip of the finger and spread to one, two or three phalanges, or more fingers.

- The demarcation of the colour changes is usually clear-cut and involves both volar and dorsal aspects i.e. it is circumferential.
- There is almost always associated transient numbness of the affected finger tips, often with paraesthesia on re-warming.
- Vasospasm may be systemic, affecting other extremities e.g. nose, ears, tongue, and may be associated with other vasospastic disorders such as a migraine, irritable bowel, and microvascular chest pain [6].

### Primary Raynaud's phenomenon (PRP)

Classically PRP presents as symmetrical vasospasm, usually affecting both hands, brought on by a number of stimuli including cold and emotion, but also carrying objects. The thumbs are often spared. It tends to begin at a younger age than secondary RP. Trophic changes are not seen in primary RP. If trophic changes are seen, the search for an underlying condition must be thorough.

PRP is nine times more common in women than men and has an overall prevalence of 10%, although it may affect as many as 20–30% of women in the younger age groups [2]. The proportion affected within a population depends on the local climate [1]. In addition to digital vessel involvement, patients with RP may experience symptoms in the tongue, ear lobes, tip of the nose, and the nipples, and there is a high incidence of migraine in these patients. By far the largest group of patients presenting to their primary care physician are those with primary RP, which typically occurs in young women in their teens and twenties, with a familial predisposition; they account for the vast majority of all cases of RP.

### Secondary Raynaud's phenomenon (SRP)

In contrast, more than 50% of the patients with RP referred to secondary or tertiary care will have an associated underlying systemic disease. Trophic changes are seen in secondary RP, particularly in RP associated with CTDs. There may also be symptoms of the associated disorder at the time of presentation.

The predictors for the RP attack rate, severity, and pain are low average daily temperature, stress, anxiety, older age, and female gender. Recent studies have shown that the RP may predate systemic illness by up to two decades. The occurrence of certain clinical features may suggest a greater likelihood of disease progression to CTD (Table I). For instance, sclerodactyly (puffy fingers with skin tightening) and pitting scars over the finger pulp are associated with later development of other features of CTD and may allow fulfilment of the 2013 ACR-EULAR classification criteria for systemic sclerosis [7].

### Other vascular acrosyndromes/differential diagnoses

Vascular acrosyndromes define any condition either primary or secondary, vasospastic or obstructive, that induces disturbances in the cutaneous microcirculatory network of the extremities. They include RP, acrocyanosis, livedo, and erythromelalgia. Differential diagnosis has also to be made with related conditions including chilblains, cold injuries and paroxysmal digital haematoma.

- **Primary acrocyanosis** is a benign condition often found in young women with low body mass index, often with anorexia, which associates painless distal symmetrical cyanosis of the upper limbs or all four extremities, with coldness and sometimes palmar or palmo-plantar hyperhidrosis due to sympathetic overdrive. The degree

**Table I.** The conditions which may be associated with secondary RP.

<b>Connective tissue disorders</b>
– Systemic sclerosis (SSc)
– Systemic lupus erythematosus
– Mixed CTD
– Sjögren's syndrome
– Dermatomyositis/polymyositis
– Primary biliary cirrhosis (often with underlying SSc)
<b>Occupational</b>
– Hand arm vibration syndrome and hypothenar hammer syndrome
– Vinyl chloride monomer exposure
– Silica and solvents (causing systemic sclerosis)
<b>Drugs</b>
– Anti-migraine drugs e.g. ergot derivatives
– Non-selective $\beta$ blockers, including eye drops
– Some cytotoxic drugs
– Cyclosporin (though may be obstructive especially in transplant patients)
– Bromocriptine
– Interferon $\alpha$ and $\beta$
– Cocaine or amphetamine abuse, cannabis
– Estrogen replacement therapy without progesterone
– Ephedrine e. g. in ear nose and throat preparations
<b>Endocrine</b>
– Hypothyroidism
– Pheochromocytoma
<b>Paraneoplastic (e.g. carcinoid)</b>
<b>Miscellaneous</b>
– Buerger's disease (thromboangiitis obliterans)
– Low body mass index
– Following bariatric surgery
– Complex regional pain syndrome
– Frostbite sequelae
– Digital injury sequelae

#### Recommendation 2

The terms primary Raynaud's phenomenon and secondary Raynaud's phenomenon should be used and the terms 'syndrome' and 'disease' discarded.

*Grade IIa – Level C*

of cyanosis worsens in winter and during cold exposure and decreases in summer, but there is no attack, no demarcation, and no numbness [8]. However, this benign condition can be associated with a genuine primary RP, most often a white only RP, due to the common thermoregulation-related risk factors they share. The lack of fat insulation augments the normal vasoconstrictive response to cold in the digital vessels.

- **Livedo** is a relatively common physical finding consisting of a red to blue mottled netlike discoloration of the skin of the lower (more frequent) and upper limbs, potentially of the whole body. The literature is often confusing because different synonyms are reported such as livedo reticularis (complete rings), livedo racemosa (incomplete rings), purpura retiform (incomplete rings and subcutaneous local necrosis), cutis marmorata, reticular cyanosis, and livedo annularis. Livedo is secondary to organic or functional disorders of the efferent dermo-hypodermal arterioles that will induce deoxygenation in the superficial venous plexus. Possible causes include: vasospasm caused by cold (primary/idiopathic livedo), arterial embolism, increased blood viscosity, Sneddon's syndrome, some drugs including phenylbutazone, and vasculitis (secondary livedo) [9]. The idiopathic form affects especially young women and is benign. Only the primary/idiopathic form fades when lifting or warming limbs. A complete work-up is needed when a secondary form is suspected.
- **Chilblains** (Pernio) often occur in patients with acrocyanosis, as oedematous papules of deeper hue in the extremities, such as the finger or toe pads, but also the nail folds, and the skin of dorsum of the feet and hand at the level of the small digital joints. They are pruriginous and can be painful. Their location on the finger pads could be confused with a permanent area of digital ischaemia associated with a secondary RP rather than with a benign RP, but the pain is much milder and the itch pronounced. They are more frequent in association with RP. They consist of inflammatory cutaneous lesions in patients exposed to non-freezing weather (and damp conditions) during late winter or early spring. The lesions typically present as painful erythematous or purple lesions with associated swelling or itching (sometimes with cutaneous necrosis, ulceration or blistering) of the fingers or toes (or both): They are frequently misdiagnosed as vasculitis or embolic events. Chilblains are a self-limiting process that usually resolves within 1 to 3 weeks [10].
- **Erythromelalgia** (= Erythermalgia) (EM) is a symptom complex characterised by: 1) burning pain in the extremities, 2) pain worsened by warming, 3) pain relieved by cooling, 4) erythema of affected skin, and 5) increased temperature of affected skin [11]. The symptoms and findings are most often intermittent and may not present during physical examination. Two forms exist: Primary and secondary. Primary is a true primary vasodilatory disorder, secondary EM may be related to two broad causes: a) Vasospastic in origin, where the blanching is absent and the burning erythema is due to a reactive hyperaemia. This latter occurs most commonly in association with risk factors for atherosclerosis; and b) in myeloproliferative syndromes. These symptoms are more often improved by aspirin and sometimes referred to as erythromelalgia.
- **Paroxysmal digital haematoma** (synonyms: Achenbach syndrome, orange ecchymotique, digital venous apoplexy, spontaneous digital haematoma, haemorrhagic phlebotonia). It presents with a sudden acute pain in a finger, rarely in the palm or a toe. The onset is spontaneous or after a minor mechanical stimulus. A painful tension persists for hours and an ecchymosis appears in the affected area. The concomitant oedema may impair movements of the finger. The second, third, and fourth fingers are commonly affected. Symptoms and signs fade spontaneously over a few days. Very rarely, a digital venous thrombosis may complicate the clinical picture. Pathogenesis can be ascribed to spasm and rupture of a venule. The syndrome mostly affects women in the fourth to sixth decades. Frequently, another vascular primary acrosyndrome coexists [12] (acrocyanosis, chilblains, primary RP).
- **Non-freezing cold injuries** (NFCI) occur when tissue fluids do not freeze (usually at about  $-0.5^{\circ}\text{C}$ ), but local temperatures remain low for several hours or days. NFCI are probably often unreported and under-diagnosed. There is often a history of having been cold and wet for a sustained period and having been unable to dry out fully. On rewarming, the affected limb shows a localised sensory neuropathy. There are generally few other objective clinical signs. In severe cases, there is cold sensitisation so that individuals are unable to work outside developing oedema, hyperhidrosis and/or chronic pain resembling algoneurodystrophy [13].
- **Frostbite** is true tissue freezing caused by heat loss sufficient to cause ice crystal formations in superficial or deep tissues: There is evidence of the role of thromboxanes and prostaglandins in the tissue damage [13]. The spectrum of injury varies from minimal tissue loss with mild long term sequelae to major necrosis of the distal limbs with subsequent major amputations and phantom limb pain.

## Associated conditions in SRP

The early diagnosis is important as RP is often the presenting feature of CTD and therefore provides an opportunity for early diagnosis. Early management might prevent morbidity and might save lives. Introduction of organ screening early in associated diseases has been shown to be associated with reduced disease progression and better outcomes [14]. Most cases of severe RP are associated with CTDs. RP occurs in 90 % of patients with systemic sclerosis (SSc) and is often perceived to be their most pressing clinical problem. It also occurs in the other CTDs: in 85 % of patients with mixed CTD, in

between 10% and 45% of patients with systemic lupus erythematosus, in 33% of patients with Sjögren's syndrome, and in 20% of those with dermatomyositis/poly-myositis. Patients with rheumatoid arthritis have a similar overall prevalence of RP as compared with the general population (10%); however, symptomatology tends to be more severe.

Patients presenting for the first time in their third to fifth decade are at high risk of developing CTDs. In RP occurring in very young children, an underlying CTD should be considered, especially if the symptoms include blanching and are severe. In patients with the limited cutaneous subtype of SSc, RP commonly precedes the diagnosis of CTD by several years, conversely rapid appearance of skin changes around the same time as the onset of RP is suggestive of diffuse cutaneous SSc. Systemic enquiry should concentrate on the presence of migraine (or a family history of migraine), and the presence of a family history of Raynaud's (usually markers of primary RP) and musculo-skeletal symptoms associated with CTD.

A full physical examination should be directed to look for any obstructive vascular disease and for signs of associated autoimmune conditions. Simple blood pressure measurement in both arms will help to detect significant occlusive vascular disease above the brachial artery. Live-do reticularis could point to cold agglutinin disease or underlying CTD. Patients with abnormal nail fold microscopy are more likely to progress to a CTD (see below).

Various drugs can precipitate or exacerbate RP. Of these, B-blockers are the most frequently prescribed culprits. The newer generation of vasodilating B-blockers, however, seem to be safer in RP sufferers. In the older age group, obstructive vascular disease is the most common cause of RP and it has been reported that 60% of RP occurring in individuals older than 60 years is atherosclerotic in origin. In workers exposed to vibration, hand-hammer syndrome must be considered. Hand arm vibration syndrome (HAVS), previously known as vibration white finger syndrome is the most common form of occupational RP with a prevalence of 50% in all workers using vibrating tools for any significant period of time.

Other conditions associated with RP are listed in Table I. Table II list conditions which might worsen already an established tendency for RP, and Table III is where microvascular obstruction mimics RP.

Again it is important to note that research is needed to clarify progressively what is associated with SRP and to be sure that some PRP are true PRP. For example, bariatric surgery, in the opinion of some experts, could be associated with the development of RP because of an important loss of weight and thermoregulation dysfunction. However, no study has been done to assess this association. Moreover, it is possible that some RP considered as PRP could be SRP, if future studies confirm the possible role of cryofibrinogenaemia [15].

However, it should be noted that there are a large number of historically 'associated conditions' but they often have different aetiologies:

**Table II.** Conditions that may worsen existing Raynaud's.

<b>Anatomical</b>
– Thoracic outlet syndrome
– Carpal tunnel syndrome
<b>Drugs</b>
As for Table I
<b>Atherosclerosis</b>
<b>Cigarette smoking</b>

**Table III.** Conditions where microvascular occlusion may mimic Raynaud's and should be excluded.

<b>Occlusive vascular disease</b>
– Embolism (e.g. from thoracic outlet syndrome)
<b>Haematological</b>
– Malignancies
– Cryo diseases (cryoglobulinaemia, cryofibrinogenaemia and cold agglutinin disease)
– Hyperviscosity syndromes
<b>Infection</b>
– Hepatitis associated vasculitis

- A large subgroup of these listed conditions (such as some drug-induced necrosis, cancer and haematological disorders associated with thrombosis or vasculitis of any cause, or even frostbite) are digital necrosis, often due to small vessel occlusion, not RP, their presence in the list being remnants of the nosological confusion explained above. It should be noted that cold injury, however, can result in RP in the damaged area afterwards and this includes frostbite. Rarely, a true RP can be associated with these conditions, but only as sequelae of previous ischaemic trophic changes, and in the exact location of these trophic changes. They do not need to be considered in patients with isolated RP and with no history of such changes.
- Any condition increasing vasoconstriction can worsen a pre-existing RP (vasoconstrictive drugs, hypothyroidism and pheochromocytoma). In these cases, as in other instances, there is an underlying true RP aetiology, which is worsened by the additional disease or drug. And sometimes several associated factors can be found in the same patient (e.g. a patient with hypothyroidism and carpal tunnel syndrome, and an underlying limited systemic sclerosis). Indeed, a multifactorial RP is not uncommon and the detection of one factor should not conclude the aetiological evaluation.
- RP was once thought to be a rare condition. However, its real prevalence is quite substantial in the general population, yet some conditions often associated with RP are not but still more prevalent in RP subjects than in the general population. This has been shown at least for carpal tunnel syndrome and for thoracic outlet syndrome. However, the pattern of the attacks is often influenced by the associated condition (asymmetrical RP predominant in the medial nerve territory for carpal tunnel syn-

drome, in C8-D1 territory for the thoracic outlet syndrome). As they do not influence the prevalence from an epidemiological point of view, these factors cannot be considered true aetiologies, but only worsening factors and again, their detection in RP patients should not conclude the aetiological evaluation.

## Diagnosis in primary care

### History taking in the patient with RP

- A history of Raynaud's symptoms will diagnose RP if there is a clear history of well demarcated blanching (+/- cyanosis/rubor). Ask age of patient at onset of RP, about frequency of attacks, whether associated with numbness, paraesthesia on rewarming or pain. Asking patients to photograph their fingers during an attack can often help secure the diagnosis. As PRP is an augmentation of the vascular response to temperature, such patients may also have 'excessive' vasodilatory responses to warmth, alcohol, and spicy food affecting not only the fingers but face and chest wall.
- Taking a clear history will help to diagnose CTD or other associated causes. Important symptoms to elucidate are photosensitivity, mouth ulcers, tightening of the skin, and dryness of eyes or mouth. Drug history should be taken, as should occupational history to look for hand arm vibration syndrome. In PRP a family history is often present.
- A history of migraine, irritable bowel, anorexia i.e. systemic vasospasm symptoms elsewhere is more likely to be PRP.

### Examination of the patient with RP

- On examination, check for colour change, but note that the time the patient has been in the warm waiting room may have attenuated an attack (thus the usefulness of a photograph), and rubor alone may be witnessed as the hands rewarm. Check the peripheral pulses to exclude obstructive vascular disease.
- Look for signs of poor tissue nutrition such as trophic changes in the nails, digital pitting, hacks or ulcers. Chilblains can co-exist in PRP. Digital ulcers are not seen in PRP and are a strong pointer to SRP.
- Look for signs of an associated disorder. Key signs include widespread telangiectasia, sclerodactyly, tighten-

ing of the skin elsewhere, especially around the mouth, malar rash, synovitis, and patchy alopecia.

- Blood pressure should be checked in both arms where there is asymmetrical RP.
- Allen's test is mandatory for the detection of distal arterial disease of the upper limbs. The hand is elevated and the patient is asked to clench their fist for about 30 seconds. Pressure is applied over the ulnar and the radial arteries so as to occlude both of them. The occlusion is released one artery at a time. If colour returns quickly as described above, the Allen's test is considered to demonstrate normal circulation. If the pallor persists for some time after the patient opens their fingers, this suggests a degree of occlusion of the uncompressed artery

### Recommended primary care tests in the patient with RP

- Blood tests: Where there is any suspicion at all of a secondary RP, some basic blood tests can be helpful. Antinuclear antibody (ANA) titres, should be measured [16]. If the ANA screen is positive, an ENA may be helpful. The ENA screen may turn up anti-topoisomerase antibodies associated with diffuse systemic sclerosis, anti-centromere antibody with limited systemic sclerosis, anti Ro or La with Sjögrens, and a positive anti DNA titre is suggestive of SLE. A full blood count will exclude many disorders, thyroid function should be checked. A CRP will detect inflammation (note: a normal CRP does not exclude CTD). Plasma viscosity or ESR will also measure inflammation. Unless symptoms or signs direct otherwise, this is usually a sufficient primary care screen.
- Urine: A Dipslide urinalysis can be useful in picking up renal involvement in conditions such as SLE.
- Capillary microscopy: Abnormalities of the nailfold vessels as detected by capillaroscopy is one of the most sensitive ways to detect early CTD [17]. However, this is not usually performed in primary care, although a number of clinicians do use dermatoscopy for skin lesions such as differentiating mole from melanoma and this can be used to visualise the nail fold vessels. Though, low power (x10) can miss early changes. An early referral to a secondary care physician practising capillaroscopy is recommended. Capillaroscopy plus more selective immunopathology tests can help the secondary care physician to exclude or confirm CTD rapidly in most cases [18].

#### Recommendation 3

Conditions associated with RP should be divided into true associated disorders with aetiological links, those which worsen RP or precipitate its appearance, and those which do not cause vasospasm but digital necrosis.

*Grade IIb – Level C*

#### Recommendation 4

A thorough history and examination should be taken from all patients presenting in primary care to ensure correct diagnosis of any underlying condition, as early diagnosis and organ screening in CTD improves outcome.

*Grade IIa – Level C*

- Other tests: Secondary care may carry out additional tests, predominantly blood tests for underlying diseases but also vascular tests such as plethysmography, cold challenge, etc. However, these are neither possible, nor desirable for all patients in primary care and are therefore not covered in this guideline.

## Referral to secondary care

- The majority of patients seen in primary care will have PRP; however, missing early CTD or other associated causes can have serious consequences, as organ involvement in CTD can be asymptomatic until extensively progressed.
- Any symptom, sign or blood test that raises suspicion of an SRP should prompt the physician to refer to secondary care.
- RP associated with vibration requires referral to a vascular clinician with expertise in this area or an occupational physician.
- Referral is recommended, if there is any suspicion of an SRP, if any isolated signs of SRP are detected (such as digital ulcer), the patient has an abnormal ESR/CRP/blood count, and an abnormal ANA and ENA screen. However, RP can be the precursor of CTD by many years and any worsening symptoms should trigger a referral.
- Recommendation of referral to secondary or tertiary care should also be considered, if the RP is severely symptomatic and unresponsive to standard treatments.
- Consideration should be given to secondary referral of children under the age of 12, as PRP may be less common in the younger age groups. A high index of suspicion should be applied.

## Management of RP

Not all patients experiencing digital vasospasm require drug treatment, but potential prescribers should be aware that the severity of the pain produced by vasospastic attacks and the degree of interruption that patients may experience in their normal daily routine can be profound. The aim of therapy is to provide symptom relief and improve quality of life. Management of RP depends on severity, for example management of a patient with mild primary RP will be very different from that of a patient with severe RP secondary to systemic sclerosis that has progressed to digital ulceration.

### General measures including lifestyle changes

Education and avoidance of triggers are key. It is important to advise patients about protecting themselves from the cold. Lifestyle measures such as wearing gloves when

handling frozen food should be adopted. Simple suggestions such as keeping the trunk warm and providing occupational therapy aids such as key holders to use when the fingers are numb can all help. Education is important and an occupational therapist can provide useful advice, as can patient self-help groups. It is essential that patients with RP stop smoking and, where applicable, avoid vibration exposure. Initial treatment in mild disease is conservative and drug treatment reserved for those patients who do not respond to these conservative measures. Electrically heated gloves and socks and chemical hand warmers are helpful in some patients.

In the case of HAVS, early diagnosis and early discontinuation of vibration exposure may resolve the problem. Withdrawal of vasoconstrictor drugs should be considered when possible. Although the contraceptive pill has been linked anecdotally to the development of Raynaud's phenomenon, this has never been conclusively proven. In

#### Recommendation 5

All patients presenting with RP should undergo blood tests including full blood count, ESR or CRP, and ANA testing, and capillaroscopy when available.

*Grade IIa – Level C*

#### Recommendation 6

Capillaroscopy should only be carried out using equipment of good optical quality and by an experienced operator, usually in secondary or tertiary care.

*Grade IIa – Level C*

#### Recommendation 7

Capillary microscopy is a useful diagnostic tool. Abnormal capillary patterns are strong predictors of CTD and should be employed by secondary care.

*Grade IIa – Level B*

#### Recommendation 8

Children under the age of 12 should be referred to secondary care as PRP is less common in these age groups

*Grade IIa – Level C*

#### Recommendation 9

Patients with RP should be referred to secondary care when

- there is evidence of an associated disorder or of occlusive vascular disease,
- symptoms are severe or progressing despite first line lifestyle and drug treatment

*Grade IIa – Level C*



the management of digital ulceration in patients with severe RP, it is essential to treat any digital infection aggressively and quickly.

## Drug treatment

Patients whose symptoms interfere with either their social or working lives and who have not responded adequately to ‘general’ measures, should be considered for drug therapy.

**Calcium channel blockers:** Calcium channel blockers, for example nifedipine, are the first line drug treatment for RP. A meta-analysis of RCTs showed that nifedipine reduced both the number and severity of RP attacks [19]. A recent Cochrane review of calcium channel blockers in primary PRP [20], which included 296 patients in seven clinical trials, found that calcium channel blockers were only minimally effective, with 1.72 (95% confidence intervals 0.60 to 2.84) fewer RP attacks per week on calcium channel blockers compared to placebo. However, this was in the context of small sample sizes, and ‘variable data quality’. Many clinicians prefer long acting/delayed release preparations, as the short-acting preparations are more likely to produce vasodilatory adverse effects and their action lasts only a few hours. The recommended dosage for nifedipine retard ranges from 10 to 20 mg two or three times a day. Starting at a low dose, minimises side-effects, however, the 10 mg preparation is not available in all European countries. Better tolerance of side effects can be obtained by introducing the drug slowly e.g. 10 mg at night for two weeks, then in the morning for two weeks then twice daily etc. Adverse effects may disappear after a few weeks of treatment and patients should be encouraged to remain on therapy unless the vasodilatory side effects are intolerable. If adverse effects force discontinuation of nifedipine retard, then other calcium channel blockers can be used [21]. These include amlodipine, lercanidipine or diltiazem. It should be noted that nifedipine retard has not been passed for use in children <18 years of age or in pregnancy.

**Other vasodilators:** Treatment with other vasodilators remains controversial, as most studies have been uncontrolled or contain very few patients. A Cochrane review of vasodilators other than calcium channel blockers for primary RP [22] highlighted the lack of evidence base to support the use of any of other vasodilators, and calcium channel blockade is the main pillar of treatment in primary care. Nonetheless, if a patient does not respond to a calcium channel blocker, because of either inefficacy or intolerance, then it seems reasonable to try another vasodilator [23]. Some clinicians favour the angiotensin receptor antagonist losartan, which showed benefit in a head to head open label trial against nifedipine; however, no further studies have yet been published. Fluoxetine [24], an SSRI, was compared to nifedipine in an open-label cross-over study including patients with both primary and secondary RP and conferred benefit in terms of frequency and severity of attacks. Fluoxetine may

### Recommendation 10

Lifestyle change is an effective means of controlling RP attacks and should include dressing warmly, ceasing smoking, avoiding triggers such as cold, and an occupational therapy assessment for aids if difficulties are reported.

*Grade IIa – Level C*

### Recommendation 11

Calcium channel blockers are the recommended first line drug treatment for RP, if lifestyle modification alone has failed.

*Grade I – Level A*

### Recommendation 12

Nifedipine in slow release form should be used to minimise debilitating vasodilatory side effects and short duration of action. Care should be taken to increase dosage by increments to avoid side effects. If side effects are not severe, patients should be encouraged to tolerate them for two to three weeks as they may subside.

*Grade IIa – Level C*

be beneficial in patients intolerant to other therapies which are more likely to cause vasodilatory side effects.

Newer vasodilatory drugs are being studied but evidence is not yet available to support their use in primary RP. These include phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil) [25] and phosphodiesterase-3 inhibitors such as cilostazol. However, phosphodiesterase-5 inhibitors are being increasingly used in systemic sclerosis-related RP, with a number of recent trials [26–29] and a meta-analysis [25] suggesting benefit, although the trials were all of short duration and large, long duration controlled trials are required. Topical nitrates have recently been revisited. A multicentre, placebo-controlled trial (which included patients with both primary RP and secondary RP, most of whom had systemic sclerosis) demonstrated benefit from a novel formulation of glyceryl trinitrate (GTN), MQX-503, in terms of improvement in Raynaud’s Condition Score. MQX-503 gel was applied to the fingers immediately before or within five minutes of onset of a Raynaud’s attack over a four-week period, and was applied for its local (as opposed to its systemic) effect [30].

**Prostaglandins:** Prostaglandins (PGs) have potent vasodilatory and antiplatelet properties. Intravenous treatment with PGI<sub>2</sub>, its analogues such as iloprost [31], and PGE<sub>1</sub> [32] have been shown to be beneficial; however, intravenous administration is a drawback. Oral PGs have been shown to be ineffective in their current form [34]. A recent multicentre study of oral treprostinil in patients with systemic sclerosis-related digital ulcers [35] showed a small but statistically insignificant reduction in net ulcer burden

compared to placebo after 20 weeks treatment. A meta-analysis [36] and RCTs have shown benefit with IV iloprost and treatment with PGs is recommended if nifedipine fails. However, these treatments must be performed in secondary care due to the need for IV infusion and monitoring of vasodilatory side effects such as hypotension, and so tend to be reserved for patients with severe RP secondary to connective tissue diseases, often with digital ulceration. Compared to nifedipine PGs are as effective at symptom resolution, and better at ulcer healing.

**Other medical therapies [37]:** Endothelin-1 receptor antagonists also have been investigated. Bosentan has been evaluated as a treatment of digital ulceration secondary to SSC and conferred benefit in two multicentre RCTs [38, 39] in terms of prevention of new ulcers, although it had no effect on healing of existing ulcers. However its use for pure (uncomplicated) RP has as yet no evidence base and cannot be recommended.

**Surgery:** This has no role to play in primary RP but may be indicated in patients with secondary RP who have progressed to digital ulceration and/or gangrene. Surgical debridement/operations to remove some of the terminal phalanx and occasionally amputation [40] are necessary in Secondary Care for digital necrosis, but with iloprost treatment this is rare. Upper limb sympathectomy is no longer recommended due to observational studies failing to show any benefit. Localized digital sympathectomy has attracted increasing interest in recent years, especially in patients with digital ulceration (often in the context of systemic sclerosis) and a number of case series and observational studies have now been reported [41]. Digital sympathectomy is a highly specialised procedure, performed only in specialist centres. Although a systematic review indicated that there is no good evidence base for surgical procedures (including sympathectomy) for RP [35], this is unsurprising given the small numbers of patients coming to surgery and the difficulties inherent in running clinical trials of surgical procedures.

As can be seen in this guideline there are few areas of robust evidence in this field [42]. Further areas for study include large RCTs of the novel therapies described above, validation of nifedipine in a slow release preparation as a useful treatment. All surgical procedures should be subjected to RCTs (if feasible) or well-designed observational studies.

#### Recommendation 13

No good evidence exists in support of surgical management of RP, but this may be indicated in certain situations, for example systemic sclerosis-related digital ulceration.

*Grade IIb – Level C*

Areas where evidence lacking/areas for further study

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