

Raynaud's & Scleroderma

A Guide for Health Professionals



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Actelion sponsored the production and printing of this booklet and had the opportunity to comment on the medical content and accuracy. However, final editorial control resides with the Raynaud's & Scleroderma Association.

HELP AND SUPPORT

Before the Raynaud's & Scleroderma Association (RSA) existed, sufferers could find little information, help or advice. By raising awareness of Raynaud's and scleroderma in a variety of ways, the Association has helped patients put a name to their symptoms and eased their path through diagnosis and into treatment.

The communication between a patient and health professionals is pivotal when providing optimum care. The RSA has empowered patients to better understand their condition. This in turn allows patients to have an informed, and so improved dialogue with their treating healthcare team.

The RSA has worked hand in hand with medical practitioners and researchers. This work has led to a better understanding of the development of the disease, which has led to improved treatment.

As treatments have advanced and become more complex, there has been an increase of expert, interdisciplinary medical collaboration. Specialist expert centres have evolved in which treatment of the many complications of the disease is best delivered. The pooling of this expert knowledge continues to push the boundaries of current understanding. This work is supported by the RSA.

The RSA would like to thank
Professor Chris Denton, Professor of Experimental Rheumatology,
Centre for Rheumatology, Royal Free Hospital, London.
for the preparation of this booklet.

Further information on Health Professional booklets
and patient literature is available from:



www.raynauds.org.uk

Raynaud's & Scleroderma Association (RSA)

112 Crewe Road, Alsager

Cheshire ST7 2JA

Tel: 01270 872776 Fax: 01270 883556

e-mail: info@raynauds.org.uk website: www.raynauds.org.uk

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INTRODUCTION

Connective tissue diseases comprise a clinically heterogeneous group of chronic disorders within the family of autoimmune rheumatic diseases. They share clinical and pathological features and comprise an important cause of chronic ill health. Although the constituent conditions are uncommon, the conditions together contribute significantly to health burden and are important in the differential diagnosis of commoner medical conditions. Many have high mortality and are associated with severe organ-based complications. It is therefore important to recognise these diseases early and treat promptly.

Approximate frequency of Raynaud's and scleroderma and related connective tissue diseases:

Primary Raynaud's Phenomenon (RP) - effects up to 1 in 20 of the UK population

Secondary RP - overall around 1% of cases of isolated RP have an associated rheumatic disease.

This is most often systemic lupus erythematosus (SLE) or undifferentiated connective tissue disease (UCTD) but systemic sclerosis, myositis or dermatomyositis are important.

Approximate frequency of systemic sclerosis in the UK is 1 in 10,000

Sources: Herrick AL. Rheumatology 2005 44: 587-96.

Denton CP. and Black CM. Ballieres Clinical Rheum 2000; 14: 17-35

WHAT IS RAYNAUD'S?

Raynaud's phenomenon describes episodic vasospasm of the extremities triggered by cold or emotional stress. Many of the connective tissue diseases are associated with Raynaud's and it often precedes the development of other manifestations and provides an important warning sign. However, Raynaud's is common and it is important to focus on associated "red flag" features that point to an associated connective tissue disease.

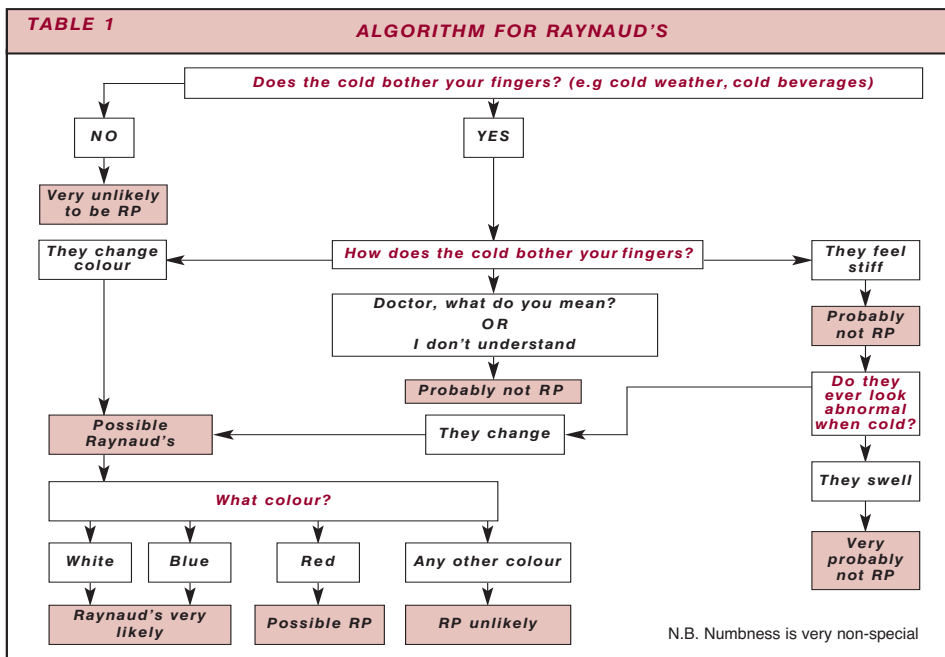
Connective Tissue Diseases associated with Raynaud's include the following:

- Antiphospholipid Syndrome
- Dermatomyositis
- Overlap connective tissue disease
- Polymyositis
- Rheumatoid Arthritis
- Sjögren's Syndrome
- Systemic lupus erythematosus
- Systemic Sclerosis
- Undifferentiated connective tissue diseases
- Vasculitis

Key features of associated conditions:

- Alopecia
- Arthralgia
- Arthritis
- Breathlessness
- Carpal tunnel syndrome
- Indigestion/GORD
- Mouth ulcers
- Rashes
- Severe digital ischemia
- Sun sensitivity
- Weight loss

- Raynaud's phenomenon (RP) is a common, episodic circulatory disorder. Raynaud's is most usually found in females. It affects between 3 and 20% of the adult population worldwide and there may be as many as ten million sufferers in the UK. It is different from chilblains, acrocyanosis or permanently cold, blue or white hands.
- The hallmark of Raynaud's is a biphasic or triphasic colour change of the extremities. The digits turn white, and/or blue and red. This happens on exposure to the cold, or to sudden but slight temperature changes, stress, or sometimes with exercise. The extremities mostly affected are the fingers and toes, whilst the ears and nose may also be affected. In addition the patient may complain of pain, numbness or tingling. It can affect children, adolescents and adults.
- It is generally a benign, primary condition, patients needing advice only on ways of maintaining a constant body temperature. Primary Raynaud's usually begins in the teens and early 20s and represents an exaggerated response to cold and other stimuli. However, the condition may also be severe and indicative of an underlying disorder. The development of the first symptoms of RP at an older age (35+), in males or associated with other symptoms and signs, suggests that it is secondary to another condition.
- Secondary Raynaud's, although less common, is being increasingly recognised and is associated with an underlying medical condition (see Table 3). Because many of these associations are serious, a careful history and examination should be taken on each patient so that referral to a specialist centre can be made if necessary.
- Prompt recognition and treatment of underlying problems can do much to modify the condition and improve the quality of life for sufferers who, in very severe cases may have severe pain, persistent ulcers, infection and ultimately gangrene, with the possibility of amputation.



RAYNAUD'S – PRIMARY OR SECONDARY?

90% of Raynaud's patients have primary Raynaud's - a benign condition but 10% have an underlying disease. Some of these are serious disorders. The causes of Raynaud's other than associated with a connective tissue disease are listed below in Table 2.

TABLE 2	
SECONDARY RAYNAUD'S PHENOMENON	
CHEMICAL OR DRUG EXPOSURE	INTRAVASCULAR
β-blockers	Polycythaemia vera
Vinyl chloride	Leukaemia
Erogotamines	Thrombocytosis
Oral contraceptives	Cold agglutinin disease
Bleomycin	Monoclonal gammopathies
Vinblastine	
Cisplatin	
Cancer chemotherapy	
Gemcitabine	
OCCCLUSIVE ARTERIAL DISORDERS	MISCELLANEOUS
External compression	Malignancy
(Carpal tunnel syndrome, thoracic outlet syndrome)	Hypothyroidism
Thrombosis	Anorexia nervosa
Thromboanglitis obliterans	Reflex sympathetic dystrophy
Embolisation	Fibromyalgia
Buerger's Disease	Arterial trauma
OCCUPATIONAL	
Vibrating machinery	
Cold	

Some causes such as β blockers, Hypothyroidism and Buerger's Disease have clear cut therapeutic implications, whilst other diagnoses are not so obvious but may be very important diagnoses not to miss e.g. underlying malignancy.

TABLE 3	
SYMPTOMS AND SIGNS OF UNDERLYING DISEASE	
IN PATIENTS PRESENTING WITH RAYNAUD'S	
CHECKLIST FOR CLINICAL ASSESSMENT	
<input type="checkbox"/> Arthralgia/arthritis	<input type="checkbox"/> Alopecia
<input type="checkbox"/> Myalgia	<input type="checkbox"/> Cerebral symptoms
<input type="checkbox"/> Skin rashes	<input type="checkbox"/> Increased blood pressure
<input type="checkbox"/> Bruising	<input type="checkbox"/> Oesophageal symptoms
<input type="checkbox"/> Absent pulses	<input type="checkbox"/> Dry eyes/mouth
<input type="checkbox"/> Changes in skin texture	<input type="checkbox"/> Muscle weakness
<input type="checkbox"/> Photosensitivity	<input type="checkbox"/> Weight loss
<input type="checkbox"/> Finger ulcers	<input type="checkbox"/> Weight gain
<input type="checkbox"/> Oral ulceration	<input type="checkbox"/> Lymphadenopathy
<input type="checkbox"/> Respiratory/cardiac problems	<input type="checkbox"/> Vascular events
<input type="checkbox"/> Depression	(M I, stroke at early age)
<input type="checkbox"/> Fever	<input type="checkbox"/> Recurrent unexplained miscarriages

TABLE 4 **MANAGEMENT OF RAYNAUD'S PHENOMENON**

Simple short attacks	→	Warmth, heating appliances Thermal clothing No smoking No β-blockers
Frequent prolonged attacks interfering with daily life often accompanied by digital infarcts	→	Drugs, oral or i.v. or selective surgery
Secondary infection	→	Antibiotics (Debridement if necessary)
Gangrene	→	Prostacyclins Auto amputation Sympathectomies

TESTS

What to do if you are presented with a patient with Raynaud's.

Take a careful history and perform an examination, looking for signs of underlying disease: Table 3 lists some of the important symptoms and signs to look for.

The two most important tests to perform in the context of RP:

Determining the presence and significance of Raynaud's phenomenon depends upon careful clinical assessment and when RP is present, two investigations are essential:

Autoantibody testing - particularly looking for ANA

- A blood test for anti nuclear antibodies (ANAs). The ANAs and their associated diseases are listed in Table 5.

Nailfold capillaroscopy

- Nailfold Capillaries looking for an abnormal pattern. This examination may, with practice, be done in the surgery with an ophthalmoscope. Abnormal patterns include dilatation of many loops or 'giant' loops and/or vascular areas with no visible capillaries.

You may wish to arrange them yourself or simply refer the patient to a specialist to pursue the matter. These tests have predictive value and are of great importance.

Four results are likely:

1. Both tests are negative. If so, the patient is highly unlikely to develop a CTD. These patients can be reassured and treated symptomatically.
2. If the ANA is positive but is not a disease associated antibody, the patient should be kept under regular review as they may develop a connective tissue disease.
3. If the ANA is a disease specific one they need close review, as disease development is much more likely.
4. If the capillary pattern is abnormal then patients should stay under review as they are at increased risk.

NB. Laboratory tests must be interpreted in the light of the clinical context. Approximately 5% of the general population have a clinically irrelevant positive ANA in the serum so a positive ANA in isolation may have no diagnostic significance. Its significance relates to the associated Raynaud's and other symptoms. Likewise abnormal nailfold capillaries are often present in healthy individuals and outside the context of RP.

TABLE 5 ANA SPECIFICITIES IN DIAGNOSIS AND DISEASE EXPRESSION			
INTERPRETATION OF AUTOIMMUNE SEROLOGY RESULTS IS VITALLY DEPENDENT ON CLINICAL CORRELATION			
Disease	Antibody	Frequency	Clinical Association
SYSTEMIC SCLEROSIS	Anticentromere	40%	Limited cutaneous disease, micro/macrovacular disease, telangiectasia
	Anti-topoisomerase-1	25%	Diffuse cutaneous disease, interstitial lung disease in both subsets
	Anti-RNA-polymerases	20%	Diffuse cutaneous disease, renal disease
	Anti-U3RNP	5%	Diffuse cutaneous disease, pulmonary hypertension
	Anti-PM-Scl	5%	Scleroderma/Polymyositis overlap
SYSTEMIC LUPUS ERYTHEMATOSUS	Anti-nDNA	70%	Lupus nephritis
	Anti-Sm	10-25%	Vasculitis; CNS lupus
	Anti-U1RNP	30%	Raynaud's swollen fingers, arthritis, myositis, MCTD
	Anti-Ro	40%	Photosensitive rash, SCLE#, neonatal lupus, CHB, Sjögren's
	Anti-La	15%	As for anti-Ro
	Anti-rRNP	15%	CNS lupus (psychosis, depression)
SJÖGREN'S SYNDROME	Anti-Ro	60-90%	Extraglandular disease, vasculitis, lymphoma
	Anti-La	35-85%	As for anti-Ro
DERMATO/POLYMYOSITIS	Anti-Jo01	30%	Antisynthetase syndrome
	Anti-Mi2	10%	Dermatomyositis

TREATMENT REGIMES FOR RAYNAUD'S

Many treatments are available. Only one drug, nifedipine, is licensed for Raynaud's. Patients sometimes find the side effects of this drug intolerable. Therefore one has to, as in other uncommon conditions, use drugs off license. It is important to have a variety of drugs with which to alleviate the symptoms.

Many patients with Raynaud's like to try natural products before using conventional drugs. Table 6 lists treatment options. There is a network of helplines around the country staffed by very knowledgeable nurses. A phone call to the Raynaud's & Scleroderma Association will find you the nurse closest to your area. These helplines are useful to both doctors and patients.

TABLE 6**TREATMENT OPTIONS**

The response to any individual therapy for Raynaud's varies with respect to how well a drug works and side effects and it is always worth trying one or more of the drugs within each of the groups listed below. Each drug should be taken for at least 2 weeks and then stop for 3 days before changing from one drug to another. To avoid side effects, try starting with a low dose, taken at night for a few days, then build up steadily to the full dose.

Calcium channel blockers

- Nifedipine retard (Adalat) 10mg twice a day increasing to 20mg twice a day
- Nifedipine LA 30mg daily
- Amlodipine 5-10mg daily
- Diltiazem 60mg three times a day

Angiotensin converting enzyme inhibitors

Usually started at low doses to prevent any blood pressure problems

- Captopril 6.25mg (test dose very small), then starting at a dose of 12.5mg twice a day (max 25mg twice a day)
- Enalapril 5mg starting dose, increasing to 10mg-20mg daily
- Lisinopril 2.5mg starting dose, increasing to 10mg-20mg daily

Angiotensin II receptor antagonists

- Losartan 25mg daily, increasing to 50mg daily
- Valsartan 40mg daily, increasing to 80mg daily

Serotonin re-uptake antagonists

- Fluoxetine 20-40mg daily. Note this drug is also used to treat depression in other patients. Its use in Raynaud's is to dilate the peripheral blood vessels.

Other members of the group that can be tried are:

- Sertaline 50mg daily increasing to a maximum of 200mg (doses of 150mg or greater should not be used for more than 8 weeks)
- Paroxetine 20mg daily increasing by 10mg per week to a max of 40mg daily

Other drugs and alternative treatments

- GTN patches: for the acute situation. A dose of 0.2mg/hr (5mg patch) to start with, increasing to 0.4mg/hr (10mg patch) if required. There must be a 12 hour period each day, free of drug to prevent nitrate tolerance (the drug no longer working).
- Sildenafil and related drugs are occasionally used for severe cases of Raynaud's, when symptoms are severe and to treat complications

Anti oxidants

These drugs are used to prevent damage to blood vessels

- Vitamin E 100iu-400iu daily (iu = international units, which are used as a measurement in a similar way to mg)
- Vitamin C 500mg-1000mg daily

Best to take both for maximum antioxidant effect

Increase prostacyclin by:

Using evening primrose oil or fish oils (note any make will do). You need to look at the gamolenic acid (GLA) content on the bottle of these capsules. A dose of 320mg per day is recommended. Most capsules of evening primrose oil etc., only contain approximately 40mg. Therefore one would need to take 4 capsules twice a day. Generic GLA (320mg per day) or another alternative is OMACOR (2000-4000mg per day) can be prescribed.

Another option (which may be more costly) is:

- Maxepa (concentrated fish oils) – dose is 5 capsules twice a day

In addition you can now obtain high strength capsules in some supermarkets and health food stores.

Intravenous Treatments

- Iloprost (a nebulised version is also available)

This is a very potent vasodilator and only given on an in-patient or day patient basis usually over 5 days.

SCLERODERMA – SYSTEMIC SCLEROSIS (SSc)

Scleroderma, although uncommon, is the most deadly of the connective tissue diseases. It is often a disabling and disfiguring condition. Management can be maximised and prognosis improved by early diagnosis and referral to a specialist centre. Although there is still no cure for SSc, there are treatments available that aim to arrest the disease process, both in the skin and internal organs.

Between 18 and 20 new cases per million of the population are diagnosed each year. There are an estimated 5-8,000 sufferers in the UK although the precise number is difficult to assess.

Scleroderma is now much better understood. The most important distinction is between localised and systemic forms of the disease. Both types are heterogeneous, and systemic forms in particular require expert assessment to determine the subset, stage and pattern of complications, together with the presence of features of any other autoimmune rheumatic disease (overlap syndrome).

Children may also develop the disease and this requires special attention. Early referral is critical because childhood localised SSc can be associated with growth defects.

What happens after referral?

- The diagnosis and subset are confirmed
- The disease is staged
- Organ involvement is investigated
- Secondary complications are assessed
- A treatment plan is designed

Scleroderma can be classified into localised scleroderma - sometimes called morphea or linear scleroderma. This is particularly common in children and is largely a disease of the skin and underlying connective tissue (muscle and bone). Childhood scleroderma is a very uncommon condition and the Raynaud's & Scleroderma Association is very keen to help patients and their families and to put children in touch with each other if they so wish.

Scleroderma in childhood is often localised and very rarely life threatening; yet because it is often a chronic illness its morbidity problems may pose additional psychological stresses which both patient and family members find difficult to handle. They may feel isolated and come to resent the disease. Adolescence is a particularly difficult time with substantial emotional stress and mood fluctuations that make a chronic disease especially challenging.

Any awareness of these psychological aspects must be taken into account whenever one is dealing with the individual patient, as well as a careful explanation of the disease process, its course, treatment and prognosis.

SYSTEMIC SCLEROSIS - SUBSETS

The major sub-types of Systemic Sclerosis are based on the extent of skin involvement and are called Diffuse Cutaneous SSc (dcSSc) and Limited Cutaneous SSc (lcSSc) - previously called CREST. These two types have different disease progression and organ involvement. Both types of patients need to be under specialist care and should be referred as quickly as possible.

Diffuse Cutaneous SSc (dcSSc)

- Onset of skin changes (puffy or hidebound) within 1 year of onset of Raynaud's
- Presence of tendon friction rubs, arthritis and myalgia
- Early and significant incidence of interstitial lung disease, oliguric renal failure, myocardial involvement and diffuse gastrointestinal disease
- Antitopoisomerase-1 (Scl-70) antibodies (30% of patients)

NB. Risk of renal failure in this group

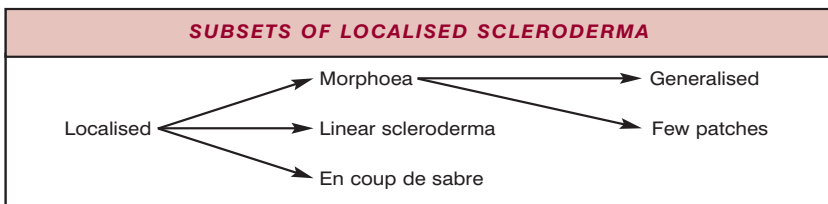
Limited Cutaneous SSc (lcSSc)

- Raynaud's Phenomenon long standing
- Skin involvement limited to hands, face, feet, forearms and lower part of legs
- A significant (10-15 years) late incidence of pulmonary arterial hypertension (PAH), skin calcifications, telangiectasia and gastrointestinal involvement. Some lung fibrosis
- A high incidence of ACA (70-80%)

NB. Though the limited form is generally more benign, PAH is a considerable risk.

In addition, around 20% of cases of SSc have features of another connective tissue disease and these cases are termed overlap syndromes. It is important to recognise these as the other features such as lupus, arthritis or myositis may require treatment and this may have to be modified compared with patients that do not have scleroderma. For example, high dose corticosteroid therapy should be avoided due to an increased risk of scleroderma renal crisis.

NB. If the patient has rapidly changing skin or digital ulcers, refer on an URGENT basis.



TREATMENT

Current approaches to disease modifying therapy include cyclophosphamide, mycophenolate mofetil and methotrexate, as these agents are believed to benefit skin involvement and other aspects of the disease. Such treatments are generally considered for diffuse cutaneous SSc that is active, within the first 3 years from onset. There are ongoing trials of newer drugs that may be more specific for scleroderma and that might offer potential for treating fibrosis. Other priorities include treating inflammation and vascular aspects such as Raynaud's phenomenon and its complications such as digital ulcers. Bosentan may be considered in patients with severe digital ulcer disease and has been shown to reduce new digital ulcer formation. Another major focus of management is on organ based complications such as kidney, lung, gut and heart disease.

It is well established that scleroderma renal crisis must be treated with ACE inhibitor drugs. Patient awareness of the risk of high blood pressure in scleroderma is also critical to help early diagnosis and treatment. Lung complications of scleroderma, including pulmonary hypertension or interstitial fibrosis, are a major cause of mortality and morbidity. Lung fibrosis must be treated when it is severe or progressive and there is now confirmation from clinical trials of the benefit of immunosuppression, although this may not be appropriate in all cases.

Pulmonary hypertension is an important and treatable complication of scleroderma and has benefited from major advances in drug therapy, including the availability of several oral treatments that are of proven benefit. Regular screening with lung function tests and echocardiography is strongly recommended so that treatment can be started as soon as the diagnosis is made. Cardiac involvement in scleroderma remains a major challenge and is the focus of current research to improve detection and treatment.

The gut is the most common organ involved. To improve motility in the oesophagus, domperidone (Motilium) should be tried. To treat acid reflux, ulceration and scarring of the oesophagus, the proton pump inhibitors, omeprazole (Losec) and lansoprazole (Zoton) are good. Additionally, a variety of antacids such as Gaviscon, Magnesium Trisilicate and Aludrox may be tried. These should not be taken at the same time as other drugs as they may impair absorption.

LONG TERM MANAGEMENT - A MAJOR FOCUS

Long-term management of the disease is now a major focus. Treatment by more integrated centres that can provide expert, holistic care, coupled with newer medicines, has led to improvements in quality of life for patients.

Due to a focus on the management and treatment of scleroderma, not just life expectancy, but quality of life has improved for patients. The Raynaud's & Scleroderma Association works tirelessly to help patients live their lives to the fullest extent possible.

As well as focusing on routine screening of established scleroderma cases for complications that may need additional specific therapy, there is also a focus on earlier diagnosis. It is important to detect cases as early as possible and this includes appropriate testing of cases of Raynaud's phenomenon that may be developing early scleroderma or a related connective tissue disease. This is an important area of ongoing research involving collaborations between European and UK scleroderma centres.

This booklet is intended as a guide for health professionals who may come into contact with patients who have Raynaud's and/or scleroderma.



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112 Crewe Road, Alsager, Cheshire ST7 2JA

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Email: info@raynauds.org.uk Website: www.raynauds.org.uk

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