Raynaud’s phenomenon is caused by episodic vasospasm and ischaemia of the extremities in response to cold or emotional stimuli, which result in a characteristic triphasic colour change in extremities—usually fingers or toes—from white, to blue, to red. Raynaud’s phenomenon may be primary, in direct response to stimuli, or secondary to an underlying condition. In 10-20% of cases it may be the first presentation of, or may precede the onset of, a connective tissue disease (such as scleroderma or mixed connective tissue disease), so that underlying causes must be ruled out.

Raynaud’s phenomenon is triggered by a change in temperature rather than simply exposure to cold. Patients can have attacks throughout the year—for example, if they move from a warm environment to an air conditioned one, stand in a cold wind (even on a relatively warm day), or hold a cold milk bottle.1

A recent consensus statement on terminology produced by the vascular medicine section of the Royal Society of Medicine recommended abandoning the terms Raynaud’s syndrome and Raynaud’s disease because of the lack of consensus on their use (Raynaud’s phenomenon: new insights, new treatments. Conference organised by the Vascular Medicine Section of the Royal Society of Medicine. 2011 May). In this review we refer to primary and secondary Raynaud’s phenomenon. Recent advances in the management and treatment of this phenomenon have followed on from the findings of randomised controlled trials of treatment strategies. We review observational studies, randomised controlled trials, systematic reviews, and guidelines to provide an overview of the clinical presentation of Raynaud’s phenomenon, its risk factors, its diagnosis, and the current and potential treatments.

Who gets Raynaud’s phenomenon?
The prevalence of Raynaud’s phenomenon varies widely across countries and populations. Non-population based studies of prevalence show that 3-12.5% of men and 6-20% of women report symptoms of Raynaud’s phenomenon. The average age of onset is lower in women than in men, and prevalence is higher in colder climates.2 Family history, oestrogen exposure, and emotional stress are commonly associated with the phenomenon in women, whereas smoking and hand arm vibration syndrome (HAVS)3 are more commonly implicated in men.2 Information from the Raynaud’s and Scleroderma Association states that smoking reduces body temperature by 1°C over 20 minutes.4 Many conditions have been associated with secondary Raynaud’s phenomenon (box 1), most notably systemic sclerosis and mixed connective tissue disorders. An observational study of about 1500 people found that 89% of Raynaud’s phenomenon was classified as primary and...
11% as secondary.\(^5\) Around 12.5% of patients with Raynaud’s phenomenon develop scleroderma and 13.6% develop connective tissue diseases.\(^6\)

**What are the symptoms?**

Patients with Raynaud’s phenomenon classically report intermittent triphasic changes in the colour of the extremities (fingers, toes, nose, cheeks, and ears)—usually triggered by cold exposure or emotional stress—from white (owing to vasoconstriction), to blue (tissue hypoxia), to red on rewarming (reperfusion) (figs 1 and 2). Colour changes are associated with tightness in the first two stages and burning pain in the reperfusion stage. Not all of the three phases are needed to make a diagnosis.\(^7\) Colour changes occur intermittently and tend to resolve when the digits are rewarmed. An attack may last for minutes to hours. Patients with secondary Raynaud’s phenomenon are more likely to have severe disease, which, if left untreated, can progress to ulceration or gangrene of extremities.

**What causes Raynaud’s phenomenon?**

The pathophysiology of Raynaud’s phenomenon is poorly understood and is thought to differ between primary and secondary disease. A recent review discussed pathogenesis.\(^8\) Abnormalities of the blood vessel wall are thought to be functional in primary Raynaud’s phenomenon and structural in secondary disease. Abnormalities of neural control mechanisms are considered less likely to be important in the pathogenesis of primary Raynaud’s phenomenon. Intravascular factors—such as platelet activation, defective fibrinolysis, reduced red blood cell deformability, and increased blood viscosity—are associated with secondary Raynaud’s phenomenon, whereas white blood cell activation and oxidative stress have been reported in primary and secondary disease. The key to appropriate treatment lies in understanding the underlying mechanism, but there is still some way to go before a clear understanding is able to inform a gold standard treatment.\(^8\)

**How are patients with Raynaud’s phenomenon assessed?**

Raynaud’s phenomenon is diagnosed clinically.

**History**

Ask patients about the frequency and pattern of colour changes, which stage(s) they experience, which digits are affected, associated features such as pain and changes in sensation, what triggers an attack, and what relieves it. A symptom diary can help to produce a clear picture of attacks. Encourage patients to photograph the affected extremities during an attack.

A full systemic inquiry will detect secondary causes (box 2). Key questions to ask include whether the patient has any evidence of a rash, photosensitivity, migraines, joint pains, ulcers, dysphagia, and xerostomia. Occupations of note are those involving cold exposure and vibrating tools. If employers do not help facilitate reduced exposure to vibrating tools, patients may be entitled to compensation under the Control of Vibration at Work Regulations 2005.\(^9\) Ask about drugs that may predispose patients to the phenomenon or aggravate it: β blockers, vinyl chloride, chemotherapy, ergot derivatives, amphetamines, cocaine, oestrogen (unopposed oestrogen replacement therapy, oral contraceptives), clonidine, and sympathomimetics. Also ask about current smoking because smoking aggravates the condition.

The Raynaud’s condition score (box 3) is an ordinal score from 0–10 that measures the level of difficulty experienced by patients; it may help determine the impact of the condition on the patient’s functioning.

**Examination (look, feel, move)**

Examination may be tailored according to clues from the history.

In the hands look for colour changes, nail bed changes, and skin integrity. Sclerodactyly, flexion deformities, tendon friction rubs, and calcinosis are seen in systemic sclerosis. Digital ulcerations (fig 3) are not normal and always reflect secondary Raynaud’s phenomenon; they should prompt careful examination for other signs of connective tissue disease and referral to a specialist.

Feel for peripheral pulses. Synovitis suggests an inflammatory arthropathy.

Move all joints and assess for pain and contracture. In the face look for a malar rash, non-scarring alopecia, and oral ulcers, which may suggest systemic lupus...
erythematous, and for tightening of the skin, which is indicative of systemic sclerosis.

Identify any dry skin, telangiectasia, and the salt and pepper appearance of hyperpigmentation and hypopigmentation, which are indicative of systemic sclerosis. Also look for livedo reticularis, which suggests systemic lupus erythematosus or antiphospholipid syndrome.

Assess for arrhythmias, especially atrial fibrillation and murmurs, which provide evidence of thromboembolic disease (or rarely Libman-Sacks endocarditis). Pulmonary fibrosis suggests systemic sclerosis.

**Box 2** Distinguishing primary and secondary Raynaud’s phenomenon

**Primary disease**
- Younger age (<30, but can be any age)
- Female
- Genetic component (30% have an affected first degree relative)
- No symptoms/signs of underlying disease
- No tissue necrosis or gangrene
- Normal nail fold capillaries
- Normal erythrocyte sedimentation rate
- Negative antineutrophil antibodies

**Secondary disease**
- Older age (>30, but can be any age)
- Less common (10-20%)
- Symptoms and signs of underlying disease
- Tightness of finger skin; more severe pain
- Digital ischaemia (digital pitting scars, ulceration, or gangrene)
- Abnormal nail fold capillaries
- Raised erythrocyte sedimentation rate
- Positive antineutrophil antibodies or anti-extractable nuclear antigen antibodies

**Box 3** Raynaud’s condition score[*]

The patient is asked about the frequency, duration, and severity of attacks to arrive at a single score expressed on a scale of 0-10 (0=patient not handicapped by attacks; 10=patient extremely handicapped).

**Questions**
- How many attacks have you had today?
- How long did they last?
- How much pain, numbness, or other symptoms have you had today?
- How much has Raynaud’s affected the use of your hands today?

**Box 4** Specialist secondary care investigations

**Infrared thermography**
Detects infrared energy emitted from skin, converts it to temperature, and displays an image of temperature distribution

**Laser Doppler flowmetry**
A non-invasive continuous measure of microcirculatory blood flow that uses monochromatic light emitted from a low power laser

**Portable radiometry**
Measures the temperature at the centre of the whorl of the palmar aspect of each fingertip

**Digital plethymography**
Air pressures that occur in a sensing cuff applied to the finger are amplified and filtered to make it possible to measure arterial blood flow

**Investigations**

Patients with primary Raynaud’s phenomenon do not routinely need blood tests.

Patients with a clinical suspicion of secondary Raynaud’s phenomenon should have a full blood count to look for anaemia and lymphopenia, which suggest an underlying autoimmune disease; immunology tests for antinuclear antibodies (ANA), extractable nuclear antibodies (ENA), anti Scl-70 (topoisomerase I), anti-Ro (SS-A), and anti-La (SS-B); inflammatory markers such as erythrocyte sedimentation rate and plasma viscosity. Negative results cannot exclude a secondary cause.

Patients with unilateral signs should have a chest radiograph to look for a cervical rib compressing the bronchial and cephalic vascular branches. Perform magnetic resonance imaging if thoracic outlet syndrome is suspected.

Specialist investigations performed in secondary care include infrared thermography, laser Doppler flowmetry, portable radiometry, and digital plethymography, all of which highlight a pattern of changes consistent with scleroderma (box 4). The results of these are often analysed together with a cold stimulation test, which measures the response of the digits to cooling and rewarming.Digits usually rewarm in less than 15 minutes, but in Raynaud’s phenomenon this phase is longer than 20 minutes.

Refer patients with suspected secondary disease for capillaroscopy if possible because ophthalmoscopy (20× magnification, dermatoscope 10× magnification) can miss capillary changes. The gold standard method is videocapillaroscopy (200× magnification, or a biomicroscope). A patient with primary Raynaud’s phenomenon will have regular disposition of capillary loops along the nail bed. In contrast, patients with secondary disease will have architectural disorganisation, giant capillaries, haemorrhages, loss of capillaries, and avascular areas (“scleroderma pattern,” seen in 95% cases of systemic sclerosis). Around 80% of patients with Raynaud’s phenomenon, scleroderma antibodies, and a scleroderma pattern on capillaroscopy will develop scleroderma after 15 years, but if capillaroscopy is normal the likelihood of developing scleroderma is almost nil.

Capillaroscopy is now part of the new definition for early systemic sclerosis proposed by the European League Against Rheumatism (EULAR).

**When and who to refer?**
Most patients can be managed in primary care. However, referral (usually to a rheumatologist) should be considered if:
CLINICAL REVIEW

- The diagnosis is in doubt
- A secondary cause is suspected
- The cause is thought to be job related (refer to occupational health services)
- The patient is aged under 12 years
- Digital ulcerations are present
- The symptoms are poorly controlled, despite appropriate conservative management.

How is Raynaud’s phenomenon treated?
The first step in managing Raynaud’s phenomenon in primary care is lifestyle modification. Such advice can be given to patients while awaiting investigations and referral to secondary care if an underlying cause is suspected. Most people with primary Raynaud’s phenomenon respond well to lifestyle measures and need no further treatment. Patients with secondary Raynaud’s phenomenon require treatment of the underlying disorder, which entails referral to secondary care.

Non-drug based treatments
Conservative approaches to treatment aim to reduce exposure to triggers, such as cold and emotional stress.

Advise the patient to try to keep warm, perhaps by using hand and feet warmers, which are commercially available. The frequency and severity of attacks can be reduced by avoiding dramatic changes in environmental temperature and taking steps to reduce occupational cold exposure. Vasodilation can be increased during attacks by rotating the arms in a windmill pattern, placing the hands under warm water or in a warm body fold such as the axilla, and performing the swing-arm manoeuvre (raising both arms above the shoulders and forcefully swinging them across the body to generate a force that promotes blood flow distally to the fingers). Another simple tip is to avoid carrying bags by the handles, which impairs circulation to the fingers. There is little objective evidence to suggest that any nutritional supplement benefits patients with the condition. Minimising stress through general relaxation techniques may be of benefit. Biofeedback has been a popular treatment, but a recent Cochrane review found it to be no more effective than sham biofeedback. Support groups can provide helpful tips and guidance on self-management. A prospective study showed that smoking cessation may help to reduce the severity but not occurrence of the condition.

Ginkgo biloba has been investigated over the past 10 years. A double blind placebo controlled trial found a 56% reduction in the frequency of attacks in established Raynaud’s phenomenon (compared with a 27% reduction in the placebo group). Another randomised multicentre flexible dose open trial found a 31% reduction compared with 50.1% for nifedipine, suggesting that Ginkgo may not be as effective as nifedipine. However, given that Ginkgo had no adverse effects and was well tolerated, further research may be worthwhile.

Drug treatments
Several randomised controlled trials are under way that may lead to an increase in the number of treatments for Raynaud’s phenomenon. However, to date, no guidelines have been published on the medical treatment of Raynaud’s phenomenon. We discuss drugs that are currently used off-label in the treatment of this condition and which the clinician may consider using on a case by case basis, taking care to balance evidence on efficacy versus toxicity. It is also important to review prescription drugs that aggravate symptoms.

Vasodilators
Calcium channel blockers—Non-cardioselective dihydropyridine calcium channel blockers are most widely used in the treatment of Raynaud’s phenomenon. Nifedipine promotes relaxation of vascular smooth muscle cells and leads to vasodilatation. A meta-analysis of randomised controlled trials found that nifedipine (10-20 mg three times daily) reduced the number of attacks by 2.8–5.0 a week and reduced their severity by 33%. However, effects may be short lived, and longer acting calcium channel blockers or amlopidine and diltiazem may be needed. Unfortunately, patients commonly report troubling adverse effects such as hypotension, flushing, headache, and tachycardia, so alternative treatments have been researched.

Topical nitrates—A randomised controlled study of 33 patients found that topical glyceryltrinitrate applied to the dorsum of the finger resulted in digital vasodilatation with fewer systemic side effects than with oral nitrates. Two large recent randomised controlled trials of MQX-503, a new formulation of nitroglycerin, applied to the affected finger found that it reduces the severity of Raynaud’s phenomenon, but not the duration or frequency of attacks. Evidence on topical nitrates is limited, but the results of current trials may provide more robust evidence of efficacy.

Prostaglandins—Prostaglandins have vasodilatory and antiproliferative effects, and they inhibit platelet aggregation. Their side effects are similar to those of calcium channel blockers. The European League Against Rheumatism recommends prostaglandins when calcium channel blockers have failed. Most published studies have focused on the use of intravenous iloprost. A randomised open label single centre study and a 2009 Cochrane review found that iloprost reduces the frequency and severity of attacks. A randomised study found cyclic use to be beneficial in terms of patient adherence and quality of life. However, two randomised controlled trials found that iloprost was

TIPS FOR THE NON-SPECIALIST
Examine patients with troublesome Raynaud’s phenomenon carefully, looking for an underlying condition, although 80–90% will have no identifiable cause
Offer conservative management options to everyone, even those awaiting referral or investigations; these include avoidance of stress and cold, smoking cessation, and ensuring that extremities are kept warm
Nifedipine is the only drug licensed for use; other effective treatments are used off-label and are best prescribed by a specialist
Refer patients with possible underlying disease, those who present with ulceration or signs of ischaemic digits, and those whose symptoms do not improve on treatment with a calcium channel blocker to a specialist
only slightly better than nifedipine, and because ilo-
prost is more expensive, the European League Against
Rheumatism has advised that nifedipine should remain
the first line drug for patients with Raynaud’s phenomenon.
A double blind multicentre placebo controlled study and
randomised double blind study found that orally admin-
istered prostaglandins are less effective than intravenous
ones, although higher doses may confer benefit. Research
is currently ongoing into the use of treprostinil, an oral
prostaglandin analogue.

**Phosphodiesterase type 5 inhibitors (sildenafil, tadala-
fl, and vardenafil)—** Phosphodiesterase type 5 breaks
down cGMP in endothelial cells. Inhibition of this enzyme
increases the amount of cGMP available to promote vascu-
lar smooth muscle relaxation and blood flow. A randomised
double blind placebo controlled fixed dose crossover study
and two case series found a decrease in the frequency and
severity of attacks in patients treated with oral sildenafil but
not tadalafil compared with placebo. These inhibitors also
have a favourable effect on the Raynaud’s condition score
and ulcer healing. The benefits of these orally delivered
and well tolerated drugs suggest that they may be an effec-
tive treatment for patients with severe and disabling Ray-
naud’s phenomenon, although further studies are needed.

**Antioxidants—** N-acetylcysteine acts as a vasodilator via
modulation of the vasodilator adrenomedullin. A recent
observational study found that it decreases the frequency and
severity of attacks. The number of digital ulcers and
ulcer healing also improved. Only slightly better than nifedipine, and because ilo-
prost is more expensive, the European League Against
Rheumatism has advised that nifedipine should remain
the first line drug for patients with Raynaud’s phenomenon.

**Endothelin receptor antagonists (bosentan)—** Endothel-
in is a potent vasoconstrictor of vascular smooth muscle
cells. Among its other actions, bosentan exerts a consistent
effect on vasculature. The Randomized Placebo-controlled
Investigation of Digital Ulcers in Scleroderma (RAPIDS-1
and 2) trials have shown that the number of new digital
ulcers in patients with secondary Raynaud’s phenomenon
decreased significantly when treated with bosentan. The
European League Against Rheumatism recommends its use
when symptoms are refractory to treatment with calcium
channel blockers and prostaglandins.

**Serotonin reuptake inhibitors**—The exact role of sero-
tonin reuptake inhibitors in the treatment of Raynaud’s
phenomenon is not yet clear. These agents block the
uptake of serotonin, which is a vasoconstrictor. A pilot
study of 53 patients showed that fluoxetine reduces the
severity and frequency of attacks compared with nifed-
ipine in primary Raynaud’s phenomenon. Its effect in sec-
ondary Raynaud’s phenomenon was less pronounced. A Cochrane review of a small number of studies con-
cluded that another serotonin reuptake inhibitor, ketan-
serin, was not beneficial in the treatment of Raynaud’s
phenomenon. This agent may have a role in patients
who cannot tolerate other drugs because of hypotension,
but more research is needed.

**Botulinum toxin A**—Botulinum toxin A blocks vaso-
striction and, although there are no blinded placebo trials
to date, preliminary reports have suggested that it can
improve symptoms, decrease frequency of attacks, and
improve healing of digital ulcers.

**Others**

**Statins**—After the observation that statins affect endothel-
ial function, a 2008 randomised trial compared atorvastatin
and placebo in patients with Raynaud’s phenomenon associ-
ated with systemic sclerosis. Treatment with atorvastatin
reduced the number of digital ulcers compared with placebo. Endothelial markers of activation
also improved compared with placebo.

**Aspirin**—Although there is no firm evidence to support
its use in patients with Raynaud’s phenomenon, daily
aspirin is commonly prescribed for patients who have no
contraindications.

**Does surgery have a role in treatment?**
For a small number of patients with severe and disabling
symptoms surgical intervention may be considered. Surgical interventions include arterial reconstruction,
peripheral sympathectomy, embolectomy, and ulcer
debridement, or a combination of techniques.

Cervical sympathectomy is no longer recommended
because observational studies showed that it was not
effective in the long term and that side effects were
intolerable—patients often needed digital amputation.
A therapeutic study with grade III evidence study found
that digital artery (palmar) sympathectomy can lead to
complete healing and a decrease in the number of ulcers,
although it is a highly specialised procedure and this ben-
efit is not seen for chronic digital ischaemia. Decom-
pression arteriolyis and arterial reconstruction can be
performed at the same time.
In chronic ulceration and in critical digital ischaemia, surgical debridement may reduce the need for amputation if osteomyelitis develops.

**Contributors:** All authors contributed equally to the writing of this article. AM and BS are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student) for her contributions to this article. AM and BS are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.

**Funding:** No special funding received.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the Competing interests section if osteomyelitis develops.

**Funding** and BG are guarantors. Thanks to April Lauren Rose Goundry (fourth-year medical student), who helped to edit and proofread this review article.