Polymyalgia rheumatica
Tanaz A Kermani, Kenneth J Warrington

Polymyalgia rheumatica is a chronic, inflammatory disorder of unknown cause that affects people over age 50 years. Classic symptoms include pain and long-term morning stiffness of the neck, shoulders, hips, upper arms, and thighs. Although markers of inflammation are often raised, no specific laboratory test exists for the disorder and the diagnosis is based on clinical assessment. Provisional classification criteria were published in April, 2012, by a collaborative initiative of the European League Against Rheumatism and the American College of Rheumatology. Several other disorders can mimic polymyalgia rheumatica. In particular, clinical manifestations can be difficult to differentiate from other forms of inflammatory arthritis such as spondylarthritides and rheumatoid arthritis. Imaging studies such as ultrasonography and MRI typically show a predominantly periarticular inflammatory process. A subset of patients has an associated inflammatory vasculopathy affecting large arteries (giant cell arteritis). The standard treatment is low-dose glucocorticoids, which provide symptomatic relief for most patients. However, disease relapses are common, and treatment with glucocorticoids is associated with substantial morbidity. Improved understanding of disease pathogenesis might allow for more targeted immunotherapy.

Introduction
Polymyalgia rheumatica is a chronic, inflammatory disorder of unknown cause. It is not typically seen in people under age 50 years. Clinically, the disorder is characterised by pain and long-term morning stiffness affecting the neck, shoulders, hips, upper arms, and thighs. There are no specific diagnostic tests; diagnosis is typically based on clinical presentation and evidence of systemic inflammation. Ultrasonography of the shoulders and hips is a useful imaging modality in the initial assessment and often shows findings of bursitis, tenosynovitis, or synovitis. The differential diagnosis is broad and clinicians need to consider several disorders that can mimic the disease. In particular, late-onset spondyloarthritis and rheumatoid arthritis can present with polymyalgic symptoms. A well known association exists between polymyalgia rheumatica and giant cell arteritis, a systemic, granulomatous vasculitis that affects the aorta and its branches.

Epidemiology
711 000 people aged 50 years or older in the USA have polymyalgia rheumatica, according to one estimate. From population-based incidence studies in Olmsted County, MN, USA, the lifetime risk of developing the disease has been estimated at 2·43% for women and 1·66% for men. Polymyalgia rheumatica occurs almost exclusively in people older than age 50 years, and the mean age of onset is about 73 years. In general, its incidence increases with advancing age, and varies by geographical region. Although polymyalgia rheumatica occurs worldwide, the highest incidence is seen in Scandinavian countries and in people of northern European descent. For example, in the county of Aust-Agder, Norway, the annual incidence is 112·6 per 100 000 people aged 50 years and older. In the UK, Denmark, and Sweden, incidence ranges from 41·3 to 84 per 100 000 people in this age group. In Olmsted County, the annual incidence is estimated at 58·7 per 100 000 people in the same age group. The disorder is less common in southern Europe. In Italy and Spain, incidence ranges from 12·7 to 18·7 per 100 000 people aged 50 years and older. In Turkey, the incidence seems to be even lower at 3·15 per 100 000 people in this age group. The incidence has been stable over the past 30 years, based on data from Olmsted County.

Aetiology and pathogenesis
The cause of polymyalgia rheumatica is unknown. Epidemiological studies suggest that both genetic and environmental factors might be important in disease pathogenesis. Although familial aggregation is rare, it has been described. Several studies have reported an association between the disorder and specific polymorphisms in genes related to immune regulation. Genetic polymorphisms associated with disease risk or severity include intercellular adhesion molecule 1, interleukin 1 receptor antagonist, and interleukin 6. A reported association between HLA-DRB1 genotypes and susceptibility to polymyalgia rheumatica remains
Seminar

and fluorodeoxyglucose PET often show inflammation. Articular inflammatory process. Ultrasonography, MRI, and magnetic resonance imaging studies have shown that polymyalgia rheumatica is characterised mainly by a periarticular and extra-articular synovial structures with findings of bursitis affecting the shoulders, hips, and cervical spine. Synovitis of the shoulder and hip joints has also been reported. Histological examination of synovial biopsy specimens shows mild synovitis characterised by a predominance of macrophages and CD4 T cells. Although myalgias are prominent symptoms in patients with polymyalgia rheumatica, muscle inflammation is not typically seen. In a study from 2010, however, increased proinflammatory cytokines were detected in the interstitium of proximal limb muscles (trapezius and vastus lateralis) of patients with the disorder. Cytokine values normalised after 2 weeks of glucocorticoid therapy, in parallel with resolution of symptoms, suggesting that local cytokine production might play a part in disease pathogenesis.

Another intriguing hypothesis is that patients with polymyalgia rheumatica have disturbances of the hypothalamic–pituitary–gonadal axis with some adrenal insufficiency, which has led to the suggestion that so-called endocrinosenesence—age-related decline of dehydroepiandrosterone or androstenedione—might be important in the pathogenesis of the disease. In healthy individuals, administration of interleukin 6 subcutaneously leads to increased adrenocorticotropic hormone and cortisol secretion. In individuals with chronic inflammatory diseases, the ratio of cortisol or adrenocorticotropic hormone in relation to interleukin 6 is reduced, indicating inadequate cortisol secretion in response to the inflammatory status. Several studies have shown reduced cortisol, adrenocorticotropic hormone, androstenedione, dehydroepiandrosterone, and 17-hydroxyprogesterone relative to interleukin 6 in individuals with the disorder. However, whether this hormonal deficiency is implicated in pathogenesis or merely represents an endocrinological response to chronic inflammatory disease remains to be elucidated.

**Polymyalgia rheumatica and giant cell arteritis**

Polymyalgia rheumatica and giant cell arteritis share many similarities, including age at onset, female predominance, and similar geographical distribution, suggesting that they might represent different types of the same disease. Clinically, 40–60% of patients with giant cell arteritis have polymyalgia rheumatica symptoms at diagnosis. Additionally, 16–21% of patients with polymyalgia rheumatica have giant cell arteritis. Both diseases are characterised by a chronic inflammatory state, immune activation, and raised circulating interleukin 6. Furthermore, temporal artery biopsy specimens from patients with polymyalgia rheumatica without clinical features of giant cell arteritis show evidence of subclinical inflammation (detection of messenger RNA transcripts for interleukin 2, interleukin 1, and interleukin 6) even in the absence of histopathological findings of vasculitis. However, by contrast with giant cell arteritis, temporal artery specimens from individuals with isolated polymyalgia rheumatica show that interferon-γ producing T cells are not recruited into vascular tissue. Although temporal artery biopsy is not indicated in routine assessment of patients with polymyalgia rheumatica, it should be pursued in those with symptoms or clinical findings that are suggestive of giant cell arteritis.

**Clinical features**

Patients present with characteristic pain and stiffness affecting the shoulder girdle, hip girdle, and neck muscles. The pain can radiate to the elbows or knees. Patients often report morning stiffness lasting 30 min or longer and worsening stiffness after periods of rest. Symptoms are usually bilateral. Constitutional symptoms, including fatigue, malaise, anorexia, weight loss, and fever (usually low-grade), can occur in 40–50% of patients. In view of the association between polymyalgia rheumatica and giant cell arteritis, identification of symptoms such as headache, jaw claudication, scalp tenderness, visual disorders, carotidynia, and limb claudication is important. If these symptoms are present, diagnostic testing for giant cell arteritis should be done. A subset of patients can present with swelling and pitting oedema of the hands and feet due to tenosynovitis (also called remitting seronegative symmetrical synovitis with pitting oedema syndrome). However, although this variant can be present in patients with polymyalgia rheumatica, it can also be a presenting feature of other inflammatory forms of arthritis including spondyloarthitis and rheumatoid arthritis. The presence of predominantly wrist and hand symptoms warrants
consideration of a diagnosis of rheumatoid arthritis, even in the absence of autoantibodies. Indeed, patients with late-onset spondyloarthritis or rheumatoid arthritis can present with polymyalgic symptoms.52,53

A subset of patients with malignant disease can present with polymyalgia rheumatica-like symptoms. However, the clinical features are usually atypical and symptoms often do not respond to low-dose prednisone or prednisolone. In view of the broad differential diagnosis and mimics of polymyalgia rheumatica, all patients being investigated should undergo a comprehensive physical examination with special attention to vascular, neurological, and musculoskeletal components. Evidence of inflammatory or degenerative arthritis, bursitis, or tendonitis should be sought. Physical examination might reveal stiffness and pain with abduction and movement of the shoulders. Mild synovitis can occasionally be present at the wrists and knees. Peripheral arthritis mainly affecting the wrists and knees might be present in up to a third of patients.54–64

Distal musculoskeletal manifestations, such as metacarpophalangeal joint synovitis, might be seen in 25% of patients. However, the arthritis is typically non-erosive and responds promptly to therapy.65 The presence of wrist synovitis together with synovitis of the metacarpophalangeal or proximal interphalangeal joints might be predictive of development of late-onset rheumatoid arthritis.66 In a recent collaborative initiative67–69 to develop classification criteria for polymyalgia rheumatica, presence of peripheral synovitis (distal swelling, tenosynovitis, or arthritis) was a useful discriminating clinical feature between rheumatoid arthritis (present in 84% of patients) and polymyalgia rheumatica (present in 39% of patients). Synovitis of the feet is typically absent in polymyalgia rheumatica.66 True muscle weakness generally does not occur, but can be difficult to assess in patients with subjective weakness related to stiffness and pain. Patients with symptoms of proximal muscle weakness with little or no pain should be investigated for a myopathy such as polymyositis. The presence of temporal artery tenderness or other abnormalities on vascular examination (diminished peripheral pulses, bruits) in patients with polymyalgia rheumatica should prompt investigation for giant cell arteritis.

Diagnosis
Polymyalgia rheumatica is a clinical diagnosis. At initial presentation, to think of it as a polymyalgia syndrome is helpful, and a careful history and physical examination are crucial in distinguishing it from other disorders that mimic it (panel 1).7075 Several sets of diagnostic criteria have been proposed (panel 2).76–78 An age cutoff is used in most of these systems. Other common criteria are the presence of bilateral shoulder girdle and hip girdle aching, morning stiffness, and a raised ESR. Some of the proposed sets of criteria have used rapid response to low doses of prednisone or prednisolone (≤20 mg) as a confirmation of the diagnosis.79,80 However, use of a prompt response to steroids as a criterion for diagnosis has limitations.81–83 In a prospective study of 129 patients with a new diagnosis of polymyalgia rheumatica receiving standard treatment, 26% of patients still reported proximal pain at week 3 and 29% had more than 30 min of morning stiffness at the 3-week assessment.84 Additionally, only 45% of patients met the study definition of a complete response to treatment at 3 weeks.85 In another prospective study of 125 patients, also treated according to a standard protocol, 71% of patients met the definition for a complete response to glucocorticoid therapy at 4 weeks.86–88 Both these studies raise concerns about use of a prompt response to glucocorticoids to confirm a diagnosis of polymyalgia rheumatica.

Since there are no diagnostic tests for the disease and several other disorders can mimic it, many challenges remain. To address some of these issues, an international
Panel 2: Proposed diagnostic criteria for polymyalgia rheumatica

Bird and colleagues

Seven most valuable criteria for distinguishing polymyalgia rheumatica from mimics are:
• Age 50 years or older
• Onset of illness of less than 2 weeks
• Bilateral shoulder pain, stiffness, or both
• Bilateral upper arm tenderness
• ESR greater than or equal to 40 mm/h
• Morning stiffness for more than 1 h
• Depression, weight loss, or both

A diagnosis of probable polymyalgia is made if any three or more of these criteria are met (sensitivity 92%, specificity 80%)

Jones and Hazleman

Diagnosis of polymyalgia rheumatica requires presence of all the following:
• Shoulder and pelvic girdle pain, mainly muscular but without muscle weakness
• Duration of symptoms at least 2 months
• Morning stiffness
• ESR >30 mm/h or C-reactive protein >57.14 nmol/L (6 mg/L)
• Absence of rheumatoid factor, inflammatory arthritis, and malignant disease
• Absence of objective signs of muscle disease
• Prompt and pronounced response to glucocorticoids

Chuang and colleagues

Diagnosis of polymyalgia rheumatica requires presence of all the following:
• Age 50 years or older
• Bilateral aching and stiffness persisting for 1 month or more affecting two of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs
• ESR >40 mm/h
• Exclusion of other diagnoses except for giant cell arteritis

Healey

Diagnosis of polymyalgia rheumatica requires age greater than 50 years and presence of any three of the following:
• Pain in the neck, shoulder, or pelvic girdle
• Noticeable morning stiffness lasting more than 1 h
• Raised ESR
• Rapid response to low-dose prednisone or prednisolone (20 mg or less)

Presence of rheumatoid factor or antinuclear antibody excludes diagnosis of polymyalgia rheumatica

collaborative initiative between the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) was undertaken to develop classification criteria. On the basis of their findings, provisional classification criteria were published in April, 2012. In the first phase, potential criteria were identified through review of scientific literature, and these were rated by international experts. Criteria with wide acceptance were then assessed by survey of rheumatologists and non-rheumatologists in North America and western Europe. Consensus was achieved for several criteria that were then assessed in a 6-month prospective cohort of 125 patients with polymyalgia rheumatica and 169 patients with disorders that can mimic the disease, who did not have a diagnosis of polymyalgia rheumatica. Inclusion criteria for the polymyalgia rheumatica cohort were age 50 years or older; new bilateral shoulder pain; raised ESR or C-reactive protein (CRP), or both; and no glucocorticoid treatment in the previous 12 weeks. Inclusion criteria for the non-polymyalgia rheumatica cohort were age 50 years or older, bilateral shoulder pain of new onset, and a diagnosis of an inflammatory or non-inflammatory disorder.

Musculoskeletal ultrasound of the shoulders and hips was done in both groups at baseline and at 26 weeks. Patients with polymyalgia rheumatica were given glucocorticoids according to a standard protocol. Periodic assessments were done in both groups. The investigators then developed a scoring algorithm (table). A score of 4 or greater had a sensitivity of 68% and specificity of 78% for discriminating polymyalgia rheumatica from comparison patients. With a combination of clinical criteria and ultrasound criteria, a score of ≥5 had a sensitivity of 66% and specificity of 81% for discriminating patients with the disorder from comparison patients.

Table: European League Against Rheumatism and American College of Rheumatology provisional criteria for classification of polymyalgia rheumatica

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<th>Clinical criteria for scoring algorithm*</th>
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<tr>
<td>Morning stiffness lasting more than 45 min</td>
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<td>Hip pain or restricted range of motion</td>
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<td>Absence of rheumatoid factor and antibody to cyclic citrullinated peptide</td>
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<td>Absence of other joint involvement</td>
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<th>Ultrasound criteria for scoring algorithm*</th>
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<td>At least one shoulder with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis, and at least one hip with synovitis or trochanteric bursitis</td>
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<tr>
<td>Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis</td>
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Required criteria: age 50 years or older, bilateral shoulder pain, and abnormal ESR, C-reactive protein, or both. *With only clinical criteria, a score of ≥4 had a sensitivity of 68% and specificity of 78% for discriminating polymyalgia rheumatica from comparison patients. With a combination of clinical criteria and ultrasound criteria, a score of ≥5 had a sensitivity of 66% and specificity of 81% for discriminating patients with the disorder from comparison patients.

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reported in 6–20% of patients with the disease.\textsuperscript{26–61} CRP, an acute-phase reactant synthesised by the liver, might be a more sensitive marker of inflammation than is ESR.\textsuperscript{44,63} Autoantibodies, including rheumatoid factor and antibody to cyclic citrullinated peptide, are usually negative, and if positive the clinician should strongly consider a diagnosis of late-onset rheumatoid arthritis.\textsuperscript{50,51,70,71} In addition to complete blood count, markers of inflammation, and blood tests for rheumatoid arthritis, other laboratory tests can be helpful in the assessment of patients with suspected polymyalgia rheumatica. These are thyroid stimulating hormone, calcium, electrolytes and creatinine, serum protein electrophoresis, creatine phosphokinase, transaminases, and urinalysis.\textsuperscript{52,69} These tests are important for exclusion of other disorders that often mimic the disease. Raised creatine phosphokinase or persistent transaminase is a more sensitive marker of inflammation than is ESR.\textsuperscript{44,63,64} 

In recent years, because of the increased use of imaging studies, ultrasonography has been added to the routine clinical assessment of patients with polymyalgia rheumatica. It might be useful in the assessment of patients with newly diagnosed disease has shown cervical interspinous bursitis.\textsuperscript{72} PET has also been assessed as an imaging modality for patients with active disease (figure 3). Enhanced fluorodeoxyglucose uptake was present in the shoulders, hips, and the cervical and lumbar interspinous processes.\textsuperscript{24} Other studies have confirmed that a large proportion of patients have vascular fluorodeoxyglucose uptake even in the absence of clinical signs of giant cell arteritis.\textsuperscript{75} However, patients with avid vascular fluorodeoxyglucose uptake probably have clinically unrecognised giant cell arteritis and have been misclassified as having polymyalgia rheumatica. PET is a costly modality and is rarely necessary in routine clinical assessment of patients with polymyalgia rheumatica. It might be useful in the assessment of patients with active disease (figure 3). Enhanced fluorodeoxyglucose uptake was present in the shoulders, hips, and the cervical and lumbar interspinous processes.\textsuperscript{24} Other studies have confirmed that a large proportion of patients have vascular fluorodeoxyglucose uptake even in the absence of clinical signs of giant cell arteritis.\textsuperscript{75} However, patients with avid vascular fluorodeoxyglucose uptake probably have clinically unrecognised giant cell arteritis and have been misclassified as having polymyalgia rheumatica. PET is a costly modality and is rarely necessary in routine clinical assessment of patients with polymyalgia rheumatica.

Although imaging studies are not routinely needed to establish diagnosis of polymyalgia rheumatica, ultrasound is a recommended modality and can add to the specificity of the diagnosis.\textsuperscript{19–31} Radiographs of the affected joints are often normal. The presence of bony erosions on radiographs is consistent with rheumatoid arthritis.\textsuperscript{19} In recent years, because of the increased use of imaging modalities such as ultrasonography and MRI, abnormalities of the periarticular structures are frequently recorded. Patients often have bicipital tendinopathy or hip joint effusions (figure 1), subacromial bursitis, subdeltoid bursitis, and trochanteric bursitis. Other findings that have been reported are glenohumeral or hip joint effusions (figure 1), or tendinopathy.\textsuperscript{21,22,25,50,70,71} Although these ultrasonographic abnormalities are also seen in other inflammatory forms of arthritis, ultrasonography of the shoulders and hips in patients suspected of having polymyalgia rheumatica is clinically useful. In the EULAR-ACR classification study,\textsuperscript{16,31} addition of ultrasonography to the classification criteria improved the specificity in the discrimination of polymyalgia rheumatica from non-polymyalgia rheumatica patients (81% with ultrasonography vs 78% without). The specificity was higher in discrimination of polymyalgia rheumatica from other shoulder disorders (89%) but lower in discrimination of polymyalgia rheumatica from rheumatoid arthritis (70%). In another study, ultrasonography was especially useful to support a diagnosis of polymyalgia rheumatica in patients with normal markers of inflammation.\textsuperscript{73}

MRI typically shows bilateral subacromial and subdeltoid bursitis and trochanteric bursitis (figure 2).\textsuperscript{20,22,70,71} Again, although these findings are not specific to polymyalgia rheumatica,\textsuperscript{73} a greater proportion of patients with the disorder have oedema in extracapsular soft tissue structures surrounding the shoulders than have patients with rheumatoid arthritis.\textsuperscript{73} MRI of the cervical spine in patients with newly diagnosed disease has shown cervical interspinous bursitis.\textsuperscript{72} PET has also been assessed as an imaging modality for patients with active disease (figure 3). Enhanced fluorodeoxyglucose uptake was present in the shoulders, hips, and the cervical and lumbar interspinous processes.\textsuperscript{24} Thus imaging studies suggest that inflammation of extra synovial and capsular structures is a prominent feature of polymyalgia rheumatica.

A subset of patients might also have subclinical vascular inflammation detected on imaging studies. In PET scans, a third of patients with isolated disease were noted to have vascular fluorodeoxyglucose uptake (predominantly in the subclavian arteries), suggesting low-grade, subclinical vessel inflammation.\textsuperscript{24} Other studies have confirmed that a large proportion of patients have vascular fluorodeoxyglucose uptake even in the absence of clinical signs of giant cell arteritis.\textsuperscript{75} However, patients with avid vascular fluorodeoxyglucose uptake probably have clinically unrecognised giant cell arteritis and have been misclassified as having polymyalgia rheumatica.

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patients with unexplained or refractory symptoms in whom an underlying occult malignant disease or subclinical large-vessel vasculitis is a strong possibility. If large-vessel vasculitis is suspected from history (limb claudication, constitutional symptoms) or examination (absent pulses, bruits, asymmetric blood pressure), vascular imaging studies such as ultrasonography, computed tomography angiography, or magnetic resonance angiography should be considered for diagnosis.76

Temporal artery biopsy is not routinely indicated in the diagnostic assessment of patients unless clinical symptoms or findings suggest giant cell arteritis is present.75

**Figure 2:** MRI in a patient with polymyalgia rheumatica
(A) Coronal fast spin echo images showing changes of bilateral trochanteric bursitis (arrows). Axial images (B) show bilateral shoulder synovitis (arrows) in a patient with symptoms of polymyalgia rheumatica.

**Figure 3:** PET in a patient with giant cell arteritis and polymyalgia rheumatica
Composite images show intense fluorodeoxyglucose uptake in the aorta and its branches (arrows) consistent with giant cell arteritis in a patient with isolated clinical symptoms of polymyalgia rheumatica (A). Several years later the patient had a relapse with symptoms of polymyalgia rheumatica. PET scan done at this time (B) showed mild fluorodeoxyglucose uptake in the vessels but avid uptake in the left shoulder and left hip (arrows) consistent with inflammation.

**Treatment and follow-up**

The standard treatment is low-dose glucocorticoids, which characteristically induce rapid resolution of symptoms. There have been no controlled clinical trials assessing the efficacy of glucocorticoids compared with placebo. A systematic review of studies of treatment has been reported.77 Although the high degree of variation between studies precluded the researchers from calculating pooled estimates, they were able to make several treatment recommendations.77 A set of guidelines for management of polymyalgia rheumatica has also been published jointly by the British Society for Rheumatology and British Health Professionals in Rheumatology.69

A typical starting dose of glucocorticoids is 15–20 mg of prednisone or prednisolone daily. Low to moderate doses of glucocorticoids are usually sufficient to alleviate symptoms and high doses (eg, prednisone 40 mg daily) are rarely needed, unless there is clinical suspicion of giant cell arteritis.69 Non-steroidal anti-inflammatory drugs are generally not recommended.77 Symptoms improve after initiation of glucocorticoid therapy; in many patients this improvement occurs within a few days. The initial dose of glucocorticoids is maintained for about 2–4 weeks, followed by a gradual taper. There are no standard protocols for tapering prednisone or prednisolone. However, recommendations advise that these drugs be reduced by 2.5 mg every 2–4 weeks until the dose is at 10 mg daily.69 77 This dose should be maintained for about 1 month, with further reductions of only 1 mg each subsequent month until discontinuation or flare.69 77 In parallel with the clinical response to glucocorticoids, laboratory markers of inflammation also normalise within a few weeks of initiation of therapy. In cases in whom there is no or only part clinical response to glucocorticoids, or when markers of inflammation remain persistently raised, other diagnoses should be considered.

Patients with polymyalgia rheumatica are often managed by generalists,78–80 who should consider referring patients to rheumatologists if they have atypical clinical features or an inadequate response to therapy. Most patients are on treatment for 1–2 years.80–82 In some cases, long-term low-dose glucocorticoids could be necessary to prevent symptomatic relapses. In milder cases, or in patients with several comorbidities, intramuscular methylprednisolone at an initial dose of 120 mg every 3–4 weeks for 3 months followed by a reduction by 20 mg every 2–3 months can be considered.69 In a double-blind, controlled trial of 60 patients with untreated disease who were randomly assigned to intramuscular methylprednisolone (30 patients) or oral prednisolone (30 patients), although remission rates were similar between the two treatment groups, the group assigned to methylprednisolone received a lower cumulative mean glucocorticoid dose and had fewer glucocorticoid-related complications than those given oral prednisolone.89

Long-term glucocorticoid exposure is associated with substantial morbidity.90 Patients should be started on...
appropriate bone-loss prophylaxis with calcium and vitamin D. Bisphosphonate therapy should be initiated in high-risk individuals.17,45 In view of this morbidity, other immunosuppressive drugs have been studied for their steroid-sparing effects. The efficacy of methotrexate for the initial treatment of polymyalgia rheumatica has been assessed in three randomised clinical trials, with mixed results: two showing efficacy16,17 and one showing no steroid-sparing effect.18 In van der Veen and colleagues’ study,18 40 patients with active polymyalgia rheumatica, giant cell arteritis, or both were randomly assigned to methotrexate (7.5 mg once per week) plus prednisone, or prednisone plus placebo. In this investigation, there were no differences between patients given methotrexate or placebo in the time to achieve remission, duration of remission, number of relapses, or cumulative glucocorticoid doses.

Contradictory results were reported in a subsequent randomised, double-blind, placebo-controlled trial,19 in which 72 patients with newly diagnosed disease were randomly assigned to treatment with methotrexate (10 mg once per week) plus prednisone, or prednisone or placebo. The primary endpoint was the proportion of patients no longer taking prednisone at 76 weeks. 28 of 32 patients in the methotrexate group and 16 of 30 patients in the placebo group met the primary endpoint (risk difference 34%; 95% CI 11–53). Additionally, patients in the methotrexate group had significantly fewer relapses and a lower cumulative dose of glucocorticoids than did those on placebo. However, the same investigators assessed 57 of the patients initially enrolled in a follow-up study19 at 5 years and reported that those given methotrexate had the same frequency of glucocorticoid-related adverse events as those given prednisone alone. In clinical practice, methotrexate is not routinely initiated at diagnosis of polymyalgia rheumatica but can be considered in relapsing disease or in patients who are regarded at high risk for developing adverse events related to long-term glucocorticoid exposure.17,43,45

Azathioprine has also been assessed in a small, randomised, double-blind, placebo-controlled trial of 31 patients with polymyalgia rheumatica, giant cell arteritis, or both.19 The primary endpoint was prednisolone dose at the end of 52 weeks. The investigators reported a significant difference in mean prednisolone dose in patients given azathioprine (1.9 mg) versus placebo (4.2 mg) at the end of 52 weeks. The use of azathioprine was associated with an increased frequency of drug-related adverse events. However, these results need to be interpreted with caution. The trial was small and had a high dropout rate; only 65% of patients completed the study. Additionally, the difference in prednisolone dose between the two groups was significant only at 52 weeks, and the doses were similar at all other analysed timepoints.

With the advent of biological therapies, there has been interest in targeting specific inflammatory mediators such as cytokines in patients with polymyalgia rheumatica. The results of a multicentre, randomised, placebo-controlled trial in 40 patients with newly diagnosed disease given infliximab and prednisone or placebo and prednisone showed similar relapses and recurrences in both groups.20 However, whether treatment with antitumour necrosis factor α agents could be helpful in a subset of patients, particularly those with relapsing disease, needs to be assessed. Other therapies targeting the cytokines interleukin 1, interleukin 6, and interleukin 17 are being actively investigated.43

Prognosis
Response to treatment is assessed on the basis of symptoms and markers of inflammation. Despite therapy, relapses are common and arise in roughly 50% of patients.44,45 Factors that have been associated with relapses or long-term glucocorticoid therapy are a higher initial dose of glucocorticoids,46 rapid glucocorticoid taper,46 and female sex.18,44 Persistently raised CRP and interleukin 6 might also be associated with risk of relapses.44 Several studies have shown increased circulating interleukin 6 in patients with active disease, but this measure is not routinely used in clinical follow-up.43,45,46 Ultrasoundography findings might be more sensitive to change with time compared with standard clinical assessment.47 However, these preliminary findings need to be replicated in other studies, and ultrasound is not currently used in routine follow-up.

Clinical diagnosis is not without uncertainty. At initial presentation, to clinically distinguish polymyalgia rheumatica from late-onset rheumatoid arthritis can be difficult, since a subset of patients with polymyalgia rheumatica could have distal arthritis, and late-onset rheumatoid arthritis can present with polyarticular symptoms. Therefore, longitudinal assessment of patients for alternative diagnoses remains important. Several prospective studies have reassessed the final diagnosis in patients initially diagnosed with polymyalgia rheumatica.43,45,46,47,71 In these studies, between 2% and 30% of patients initially thought to have the disease were later reclassified as having rheumatoid arthritis.

Glucocorticoid-related adverse events are common; 65% of 124 patients had adverse events in a population-based study.48 In another investigation, 81% of 129 patients had at least one adverse event (excluding weight gain) from glucocorticoid use, including fractures in six patients.50 Patients with polymyalgia rheumatica have reduced quality of life at time of diagnosis, which improves with treatment.50 Presence of proximal pain and morning stiffness were associated with physical components of quality-of-life measures, whereas, for unclear reasons, raised inflammatory markers were associated with poor mental quality of life.50 The health assessment questionnaire seems to be a useful instrument for the assessment of functional status and response to therapy.50 In particular, activities
such as dressing, grooming, and rising, that are part of the questionnaire, improved with treatment. A minimum set of outcome measures is recommended for use in clinical practice during follow-up, including the health assessment questionnaire, patient-reported pain, morning stiffness, mental function, and an inflammatory marker.79

Not surprisingly, patients have increased health-care use (outpatient physician visits and laboratory tests) during the first year after diagnosis compared with age-matched and sex-matched controls from the general population.80 A diagnosis of polymyalgia rheumatica is also associated with incremental direct medical costs early in the disease course, but these costs seem to be mainly from increased prevalence of cardiovascular comorbidities, including coronary artery disease, peripheral arterial disease, and cerebrovascular disease.81 After adjustment for these comorbidities, the care of patients with polymyalgia rheumatica was no more costly than the management of controls from the general population. Patients with polymyalgia rheumatica seem to have an increased risk of peripheral arterial disease. In a population-based study from Olmsted County, patients had a 2.5-times increased risk of developing peripheral arterial disease compared with a referent cohort of age-matched and sex-matched controls, even after adjustment for hypertension, dyslipidaemia, and diabetes mellitus.81 The reason for this reported increased risk is not clear, but two possibilities are subclinical vasculitis of the leg arteries, or accelerated atherosclerosis from chronic inflammation. A study assessing cardiovascular and cerebrovascular events in polymyalgia rheumatica did not find any association between glucocorticoid therapy and increased risk of these events.82 Overall survival is similar to, or slightly better than, that of the general population.83,84

**Future perspectives**

Disease-specific biomarkers for polymyalgia rheumatica are currently unavailable. Additionally, heterogeneity exists between patients and some have an underlying inflammatory vasculopathy. Therefore, diagnostic biomarkers that allow prompt and accurate diagnosis are eagerly awaited. Discovery and validation of such markers will require collaborative, prospective studies in which patients are assessed and treated in a standardized way, such as that recently undertaken by the EULAR-ACR initiative. Although glucocorticoid therapy is highly effective at suppressing symptoms associated with the disease, relapses are frequent and treatment is associated with substantial morbidity. Improved understanding of disease pathogenesis might allow for more specific, targeted immunotherapy, with a more favourable safety profile. As we progress towards individualised medicine, therapies tailored according to an individual’s inflammatory burden and risk of disease relapses might become possible.

**Contributors**

Both authors contributed equally to this manuscript.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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