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CLINICAL REVIEW

Polymyalgia rheumatica

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Polymyalgia rheumatica causes pain and stiffness that is worst in the morning and particularly affects the shoulders and hips. It is a treatable cause of profound debility and functional impairment.[1] The condition usually presents to primary care and is the most common inflammatory musculoskeletal disease in older people, with an age adjusted incidence of about one in 1000 person years.[2] The lifetime risk has been estimated at 2.4% for women and 1.7% for men.[3] There is little trial based evidence to guide diagnosis and treatment. This review describes current ideas about best practice in the diagnosis and management of this disease, drawing on recent clinical guidelines[4] and highlighting some research priorities.

What is polymyalgia rheumatica?

The site of pathology is unclear and little is known about the causes and pathogenesis of this disease. The clinical diagnosis can be challenging owing to the lack of a specific diagnostic test. Various diagnostic and classification criteria have been proposed.[5-9] Classification criteria have recently been developed by the European League against Rheumatic Diseases and the American College of Rheumatology on the basis of a large prospective, international multicentre study and data driven consensus process. These are currently awaiting validation in an independent dataset (table 1⇓).[10] These criteria are not intended for diagnostic use but are a useful starting point for describing core clinical features of the condition, which include bilateral shoulder and hip pain with an abnormal erythrocyte sedimentation rate (ESR) or C reactive protein (CRP).

What are the objective abnormalities in polymyalgia rheumatica?

Ultrasound studies with power Doppler enhancement suggest inflammation of intra-articular and extra-articular structures (synovitis and bursitis). Histological studies show the presence of macrophages and T cells in the synovium. [11] Some magnetic resonance imaging studies suggest greater involvement of extracapsular structures compared with that seen in rheumatoid arthritis.[12] Positron emission tomography/computed tomography and magnetic resonance imaging studies have also shown that some patients have widespread inflammation in areas where the disease is not clinically apparent, such as the aorta and proximal branches,[13] and between the vertebral spinous processes.[14]

About 90% of patients have an increase in inflammatory markers, including ESR.[15] Plasma viscosity gives similar information to ESR but is less strongly influenced by factors such as anaemia, polycythaemia, sex, or age.[16-19] Fibrinogen levels strongly influence ESR and plasma viscosity in polymyalgia rheumatica; fibrinogen may be a more specific marker than ESR for disease activity in treated polymyalgia.[20] However, other factors, including immunoglobulin and lipid levels, also influence ESR and plasma viscosity and may contribute to interindividual variation in these blood test results. CRP may be more sensitive diagnostically than ESR[15]; CRP production is mainly driven by interleukin 6, which is typically raised in polymyalgia rheumatica. A small prospective study suggested that failure of interleukin 6 to fall with glucocorticoid treatment may predict relapses.[21] However, whether or not it is useful to measure interleukin 6 in clinical practice is unclear. It has been proposed that high interleukin 6 levels result in insufficient glucocorticoid production.[22] However, this does not completely explain how polymyalgia rheumatica develops and ultimately resolves.

There is no general agreement on how high inflammatory markers should be for a diagnosis of polymyalgia rheumatica. Cases with "normal" (within laboratory reference ranges for age and sex) inflammatory markers have been described but are particularly difficult to diagnose,[10 15] and British Society for Rheumatology (BSR) guidelines advise specialist evaluation if inflammatory markers are normal.[4]

Can polymyalgia rheumatica "overlap" with other rheumatological disorders?

Longitudinal studies suggest that polymyalgia rheumatica is a heterogeneous disorder, even after differential diagnoses have been excluded.[21] Features of the disease may be present in other inflammatory diseases, including rheumatoid arthritis (seropositive or seronegative), cranial giant cell arteritis, large vessel vasculitis, spondyloarthropathy,[23 24] and crystal arthropathies such as inflammation caused by calcium pyrophosphate crystals (pseudogout).[25] It has been proposed

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Summary points

- Polymyalgic syndrome can be a presenting feature of a wide range of diseases, including giant cell arteritis and rheumatoid arthritis
- Look for other diseases before starting glucocorticoids (≤20 mg prednisolone or equivalent)
- Carefully document the speed, completeness, and nature of the response to initial glucocorticoid treatment
- Atypical features should prompt early specialist evaluation
- Monitor patients carefully for adverse effects of glucocorticoids and taper drugs on an individual basis

Sources and selection criteria

We searched Medline, Embase, Cochrane Collaboration, and ClinicalTrials.gov using the word "polymyalgia". All study types were included owing to the limited amount of literature available.

that ultrasound imaging of the shoulders, hips, and possibly the small joints might help in the diagnosis by identifying specific features of particular inflammatory diseases,[26] but further studies are needed to clarify its relevance to routine clinical practice, especially in primary care.

Association with giant cell arteritis

Giant cell arteritis is a systemic vasculitis that affects large and medium sized arteries. There has been debate about whether polymyalgia rheumatica and giant cell arteritis are distinct diseases.[27] Although the patient population at risk is similar,[2] observational incidence data from a large primary care based study suggest that the two diseases are diagnosed in the same patient 38 times more often than might be expected owing to chance.[2] Unlike polymyalgia rheumatica, which usually responds to an initial dose of 15-20 mg prednisolone, at least 30-40 mg prednisolone is needed initially in giant cell arteritis for effective symptom relief (for example, from temporal headache or jaw pain). These doses are based on clinical experience and expert consensus.[28] Data from the pre-steroid era suggest that untreated giant cell arteritis commonly results in blindness, so formal dose ranging studies have not been done. High doses of glucocorticoids (≥30 mg prednisolone) have additional ("non-genomic") cellular mechanisms of action compared with low and medium doses (≤15 mg),[29] so the fact that both polymyalgia rheumatica and giant cell arteritis respond to glucocorticoids is not necessarily evidence of a shared disease pathway. Case series show that a subset of patients with polymyalgic syndrome have occult giant cell arteritis on biopsy or imaging,[30 31] but these findings are not universal.

Overlap with rheumatoid arthritis

Rheumatoid arthritis may present with a polymyalgic syndrome before synovitis is clinically detectable.[32] Consequently, some polymyalgia rheumatica cohorts contain a subset of patients who are later diagnosed as having rheumatoid arthritis.[10 33] The addition of anti-cyclic citrullinated peptide antibodies to the classification of rheumatoid arthritis might help to reduce this overlap[34]—these antibodies are rarely present in polymyalgia rheumatica.[35] In observational studies, patients with polymyalgia rheumatica seem to have a greater clinical and laboratory response to glucocorticoids than those with polymyalgic onset rheumatoid arthritis.[36]

Genetic heterogeneity

In contrast to the known association of giant cell arteritis with *HLA-DRB1**04,[37] and of rheumatoid arthritis with subtypes of *HLA-DRB1**01, *HLA-DRB1**04, and *HLA-DRB1**10 alleles,[38] polymyalgia rheumatica has no well replicated *HLA-DRB1* association.[37] It is unclear whether a reported association of *HLA-DRB1**04 with risk of relapse[39] is due to an overlap of polymyalgia rheumatica with subclinical giant cell arteritis or rheumatoid arthritis.[33 40] Rheumatoid arthritis associated *HLA-DRB1* alleles were also associated with relapse in polymyalgia rheumatica.[41]

How is polymyalgia rheumatica diagnosed?

Once the diagnosis is suspected, BSR guidelines recommend a three step procedure (fig 1⇓).[4] Each step is intended to increase the probability that the diagnosis is correct. In the presence of clinical features, supportive investigation results, and a rapid complete response to glucocorticoids, it is thought that a diagnosis of polymyalgia rheumatica can be confidently made in primary care.[4] However, this approach is based on expert consensus and has not been formally evaluated. Arguably, the most challenging step is the first one, which depends on clinical experience and expertise. Where all three features (classic clinical features, supportive investigation results, rapid complete response to glucocorticoids) are not unequivocally present, there are arguments for referring the patient for a specialist opinion.[4]

How can the classic clinical features of polymyalgia rheumatica be identified?

Classic features of polymyalgia are bilateral pain and stiffness in the shoulders and hips in older patients, most commonly those in their 70s and rarely below age 50.[2] Patients may not be able to "turn over in bed or get up from the toilet in the mornings." There is pronounced diurnal variation, with symptoms being worst on waking. Morning stiffness usually lasts for at least an hour.[5] Symptoms may begin suddenly, sometimes accompanied by "flu-like" features, although onset can be more insidious. Generalised restriction of movement results in profound functional impairment. Gait may be affected, although isometric muscle power is relatively intact. Inflammatory markers are typically raised, sometimes with an accompanying normocytic "anaemia of inflammation."[42]

However, other haematological abnormalities (including lymphopenia) should prompt suspicion of other diseases. Look for evidence of giant cell arteritis, such as headache, scalp tenderness, jaw claudication, visual disturbance, or abnormal temporal arteries; if present, urgent specialist referral is needed. Recent limb claudication may signal large vessel giant cell arteritis. Educate patients with suspected polymyalgia rheumatica about the symptoms of giant cell arteritis and warn then to consult urgently if they develop.

There should be no lymphadenopathy or involvement of other organs including the nervous system, skin, hair, lung,

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gastrointestinal tract, or kidney. Consider alternative diagnoses if such clinical features are present. It is important to check for other causes of myopathy, including statin treatment or hypothyroidism (both of which are usually associated with raised creatine kinase).

Musculoskeletal ultrasound often identifies inflammation of structures around the shoulders and hips (subacromial bursitis, glenohumeral synovitis, trochanteric bursitis, hip synovitis).[43] However, these findings are not unique to polymyalgia rheumatica and quoted sensitivity and specificity estimates may be unreliable because of the case-control design of existing diagnostic accuracy studies. The usefulness of ultrasound has yet to be evaluated outside specialist settings. Ultrasound can be useful when diagnosis is uncertain or when overlap conditions (such as rheumatoid arthritis) are suspected. Table 2⇓ provides details of selected differential diagnoses.

What further investigations are recommended before starting glucocorticoids?

There is currently no single diagnostic test for polymyalgia and investigation is largely aimed at excluding other explanations for the symptoms (table 2). BSR guidelines recommend measuring ESR, CRP, full blood count, liver and renal function tests, protein electrophoresis, rheumatoid factor (and anti-citrullinated peptide antibody if available), calcium, alkaline phosphatase, and thyroid function.[4] All of these tests, except for ESR and CRP, are done to exclude other conditions.

Actively look for clues about cancer or infection, especially if there are clinical risk factors (including personal or family history of cancer). Weight loss, fever, or very high inflammatory markers (ESR >100 is atypical for polymyalgia rheumatica) should prompt considerations of cancer, including myeloma and renal cell carcinoma, or occult infection, including endocarditis, osteomyelitis, and paraspinal infection. Microscopic haematuria is not a feature of polymyalgia rheumatica and may be a clue to other conditions.

When should glucocorticoids be started?

It is not known whether glucocorticoids modify the disease process itself or merely alleviate the symptoms of polymyalgia rheumatica. High quality randomised controlled trials of glucocorticoids versus other treatments have not been performed. Before starting glucocorticoids, screen for risk factors for glucocorticoid related adverse effects (such as diabetes, hypertension, peptic ulcer, osteoporosis, psychiatric comorbidity) and treat these appropriately.[4] These factors, together with the patient's weight,[44] may affect the initial choice of dose for a trial of glucocorticoids. In addition, counsel patients about potential adverse effects, which include the above risk factors as well as bruising, skin fragility, myopathy, and weight gain.

Symptoms of many non-polymyalgic disorders, including cancer, may initially respond to glucocorticoids, but lack of response can be a clue to other conditions such as solid tumours or osteoarthritis.[45] The diagnostic value of response to glucocorticoids becomes less specific as the dose increases. A typical starting dose is 15 mg prednisolone (or glucocorticoid equivalent), but some patients respond well to lower doses.[46] These recommendations are based on expert consensus because the studies informing them were largely observational, had various inclusion criteria, and were usually hospital based rather than community based. BSR guidelines recommend specialist evaluation in patients with an incomplete response to 20 mg prednisolone (defined as <70% self reported improvement in symptoms).[4] This is based on a pragmatic trade-off between the sensitivity and specificity of the diagnostic value of various doses of prednisolone, with a conservative approach being recommended as safest in primary care.

Where there is doubt, with the patient's agreement, some specialist practitioners use a "steroid sandwich" (alternating a week of vitamin C (or other placebo) with a week of prednisolone and evaluating the time course of symptomatic response).[47] In classic polymyalgia rheumatica, symptoms resolve within about three days and do not reappear unless the glucocorticoid dose is reduced or stopped. Inflammatory markers should normalise within two to four weeks and remain normal until the dose is reduced. These features would support a diagnosis of classic polymyalgia rheumatica.

When and how should the glucocorticoid dose be tapered?

The dose is gradually tapered over months to years. In most case series the median time to stopping glucocorticoids is about two years,[48] but individuals vary greatly and few studies have been performed in primary care. No head to head trials have looked at the optimum rate of glucocorticoid tapering. Indeed rigid adherence to a tapering protocol may be unhelpful as many patients need to spend some time at a particular dose rather than aiming for a constant rate of reduction. Frequent, rapid changes in glucocorticoid dose are to be avoided where possible. The risks associated with glucocorticoids must be balanced against the risks of relapse, taking into account comorbidities (such as diabetes and hypertension) and the patient's priorities. Observational studies suggest that those with higher inflammatory markers before treatment are at higher risk of relapse[21 49-53] and need a longer duration of treatment.[48 54] Such studies also suggest that patients who need an initial dose of more than 20 mg prednisolone have a higher risk of relapse,[21] and that atypical features may be a predictor of prolonged glucocorticoid requirements (fig 2⇓). In a retrospective study of 135 patients, 26% of patients initially thought to have polymyalgia rheumatica later received a different diagnosis (seronegative rheumatoid arthritis in half of them). These patients were younger, more often male, needed higher initial glucocorticoid doses, and were less able to reduce and stop glucocorticoids during follow-up.[55] In another observational study, patients who needed higher initial glucocorticoid doses were likely to need glucocorticoids for longer, and were also more likely to develop giant cell arteritis at a later date.[48]

There is no evidence that aggressively trying to reduce inflammatory markers improves prognosis in asymptomatic patients and it could mask a second disease. A composite score for monitoring disease activity—the "polymyalgia rheumatica activity score"—incorporates doctor and patient reported elements, as well as CRP concentrations,[56] but this score requires further validation and is seldom used outside research settings.

A degree of trial and error is involved in the tapering of glucocorticoids. Initially, the daily dose is usually reduced by 2.5 mg every two to four weeks, but, after reaching 10 mg daily, it is usually slowed to a mean 0.5-1.0 mg daily dose reduction per month. However, patients vary greatly, and alternate day dosing may be useful in those who cannot tolerate a full reduction in dose. Warn patients to expect a temporary increase in symptoms for about a week after each dose reduction. Prednisolone may need to be reduced very gradually once the dose gets down to 2.5-7.5 mg per day. This could be achieved

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by taking the reduced dose on certain days of the week only; giving an intramuscular glucocorticoid injection followed by a reduction of 2.5-5 mg daily two days later; and giving local glucocorticoid injection(s) to the most symptomatic area(s). These strategies are based on expert consensus (formal comparative studies have not been performed) and shared decision making is important.

What if patients cannot tolerate glucocorticoid withdrawal even years later?

Some patients, often those with atypical polymyalgia or other rheumatological disorders, will require prolonged (>2 years) glucocorticoid treatment (fig 2). When referring for specialist advice, the records from the original presentation of polymyalgia rheumatica are helpful. Re-evaluation after temporarily forcing the dose of glucocorticoids down (with reminders about warning symptoms of giant cell arteritis) can also help diagnostically, because glucocorticoids can mask clinical and imaging features of other inflammatory diseases.

The pattern of disease activity is the first thing to consider in patients who require prolonged treatment with glucocorticoids. Are the symptoms truly inflammatory in nature, and what dose of glucocorticoids is needed for symptom relief? Case series suggest that it is unusual for polymyalgia rheumatica to require more than 10 mg prednisolone daily for more than a year. Other, non-inflammatory causes of musculoskeletal pain are common and could be exacerbated by glucocorticoid related weight gain or by physical deconditioning. Osteoarthritis of the spine, hip, or knee is often identified at this stage. If clinical features suggest subacromial or trochanteric bursitis, then local glucocorticoid injections can help. Even if the symptoms are truly inflammatory and responsive to glucocorticoids, a careful search for another inflammatory disease should be made.

Patients with ongoing or relapsing symptoms, a long duration of morning stiffness, raised inflammatory markers, and no other cause of inflammation may benefit from immunosuppressive treatments under specialist supervision. Although underpowered, randomised controlled trials of methotrexate found no convincing benefit in polymyalgia rheumatica, with confidence intervals of effect sizes close to the null.[57] Small trials of tumour necrosis factor antagonists also failed to show convincing benefit,[58 59] although again they were underpowered to detect small effect sizes or large effect sizes in small subgroups. Leflunomide and tocilizumab have been used in observational case reports and case series,[60 61] but randomised controlled trials have not been performed. Caution is needed when interpreting efficacy outcomes that depend on inflammatory markers, because some drugs (such as tocilizumab) may suppress CRP but have unknown effects on the underlying polymyalgic disease process.

What are the risks of long term glucocorticoids and how can they be reduced?

Patients with polymyalgia rheumatica are committed to months or years of glucocorticoid treatment, with a substantial risk of adverse effects.[62-64] Patients require regular monitoring for potential complications including diabetes and hypertension. Prophylaxis against other glucocorticoid related adverse effects (including gastrointestinal side effects and osteoporosis) should be considered.[64] Adequate calcium and vitamin D intake should be maintained and supplemented if appropriate. If assessment shows a high risk of osteoporotic fracture, a bisphosphonate is the usual first line of treatment.[65] Gastroprotection should be considered, particularly in older patients. Advice on physical activity—especially weight bearing activity—is important, and physiotherapy may be useful if there is deconditioning. A "steroid card" can be useful for patients on long term glucocorticoids.

In patients with mild or localised symptoms, or a high risk of adverse effects from glucocorticoids, intramuscular or periarticular injections of glucocorticoid may be tried, as suggested by a single small trial.[66] Non-steroidal anti-inflammatory drugs have been used,[64] although anecdotal evidence suggests these drugs have a lesser effect than glucocorticoids and a greater risk of gastrointestinal side effects, especially in older people.

What is the prognosis in polymyalgia rheumatica?

Information on prognosis is limited, especially in community settings. Men have a better prognosis than women. Case series and small secondary care based prospective cohorts show wide variations in the duration of glucocorticoid treatment.[21] In some patients, glucocorticoids can be reduced easily and stopped within a year, with no recurrence in symptoms. Others tend to relapse on dose reduction, until the disease seems to "burn itself out" after a few years. A few patients need to be treated for many years, for reasons that are not well understood. Higher inflammatory markers are associated with longer duration of treatment and more relapses. However, it is unclear how much this results from the underlying disease and how much from an over-reliance on blood tests for monitoring disease activity. Tailored treatment and a consistent approach from one well informed doctor can promote shared decision making and reduce the anxiety experienced by many patients with this disease. Patient support groups can play a vital role

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Ongoing research

Keele PMR study (www.keele.ac.uk/pmr): an observational cohort study of patients with newly diagnosed polymyalgia rheumatica in primary care

ADDRESS-PMR: diagnostic accuracy study of ultrasound in patients with suspected polymyalgia rheumatica

Study of tocilizumab to treat polymyalgia rheumatica: NCT01396317

TENOR: Tocilizumab Effect iN pOlymyalgia Rheumatica: NCT01713842

Study on the efficacy and safety of Lodotra (delayed release prednisolone) compared with immediate release prednisone in patients with polymyalgia rheumatica: NCT01821040

Questions for future research

What is the anatomical basis of polymyalgia rheumatica and what causes it?

Can we identify better biomarkers (including imaging tests) for diagnosing and monitoring the disease?

Can we define a core set of robust outcome measures for future research studies in polymyalgia rheumatica, including assessment of the life impact and healthcare costs of the disease and its treatment?

What are the optimum starting doses of glucocorticoids, best delivery methods, and optimum dose reduction strategies for different patients?

What is the role of immunosuppressants such as methotrexate in this disease?

Tips for non-specialists

Do not start glucocorticoids until all relevant investigations have been completed

Have a low threshold for specialist referral of patients without classic symptoms Document findings carefully, including atypical features; these notes may be invaluable later if the patient is unable to stop glucocorticoids

Give the patient written information including symptoms of giant cell arteritis, such as headache, scalp tenderness, jaw claudication, visual disturbance, or abnormal temporal arteries

Once the diagnosis is made, treat the patient not the blood test results

Try to avoid frequent large changes in glucocorticoid dose

Remember that older patients may develop a second disease

Evaluate for comorbidities early on and prescribe bone prophylaxis early

Additional educational resources

Resources for healthcare professionals

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Resources for patients

Polymyalgia rheumatica and giant cell arteritis UK (www.pmrgcauk.com/)—Provides information on polymyalgia rheumatica and giant cell arteritis, peer support from patients, and a telephone helpline

Arthritis Research UK (www.arthritisresearchuk.org/arthritis-information/conditions/polymyalgia-rheumatica.aspx)—Provides written information on the diagnosis and treatment of polymyalgia rheumatica

Patient.co.uk (www.patient.co.uk/health/polymyalgia-rheumatica)—Useful information on the diagnosis and treatment (and treatment side effects) of polymyalgia rheumatica

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Tables

Table 1| Scoring algorithm for provisional European League against Rheumatic Diseases and American College of Rheumatology classification criteria for polymyalgia rheumatica

Required criteria*	Points without ultrasound†	Points with ultrasound‡
Morning stiffness (duration >45 minutes)	2	2
Hip pain or limited range of motion	1	1
Absence of rheumatoid factor or anti-cyclic citrullinated peptide antibodies	2	2
Absence of other joint pain	1	1
Ultrasound: at least 1 abnormal§ shoulder and at least 1 abnormal¶ hip	–	1
Ultrasound: both shoulders abnormal§	–	1

*Age ≥50 years, bilateral shoulder aching, and abnormal C reactive protein or erythrocyte sedimentation rate (or both).

†If total score ≥4, patient is categorised as having polymyalgia rheumatica.

‡If total score ≥5, patient is categorised as having polymyalgia rheumatica.

§Ultrasound evidence of glenohumeral synovitis or subacromial-subdeltoid bursitis.

¶Ultrasound evidence of coxofemoral synovitis or trochanteric bursitis.

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Table 2| Selected differential diagnoses to consider in patients with polymyalgic symptoms*

Category	Example	Possible clues
Inflammatory rheumatological disorders	Rheumatoid arthritis (seropositive or seronegative) and other inflammatory arthritides eg spondyloarthropathy	Peripheral synovitis or sacroiliitis; insidious onset
	Calcium pyrophosphate deposition disease, atypical gout, single or multi-joint sepsis	Swollen joints; consider aspiration
	Giant cell arteritis, other vasculitis	Direct questioning, systems review
	Myositis, other myopathy (for example, statin related)	Creatine kinase
Non-inflammatory rheumatological disorders	Multiple mechanical joint pains (such as lower limb osteoarthritis plus subacromial impingement)	Examination; lack of improvement of symptoms over the day
Rare and important	Infections such as endocarditis, osteomyelitis, paraspinal infection, tuberculosis	Fevers, sweats, microscopic haematuria
	Cancer—for example, myeloma, lymphoma, renal cell carcinoma, carcinoma of prostate, others	Weight loss, monoclonal band (haematological), microscopic haematuria (renal cell carcinoma)
Endocrine	Hypothyroid myopathy	Creatine kinase
	Hyperparathyroidism	Calcium and phosphate concentrations
Neurological	Motor neurone disease	Wasting
	Parkinsonism	Physical signs
Occult fracture	Vertebral, sacral, or pelvic fracture (if present consider osteomalacia or other causes)	Pain on weight bearing

*This is not an exhaustive list of the differential diagnoses of polymyalgic symptoms.

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Figures

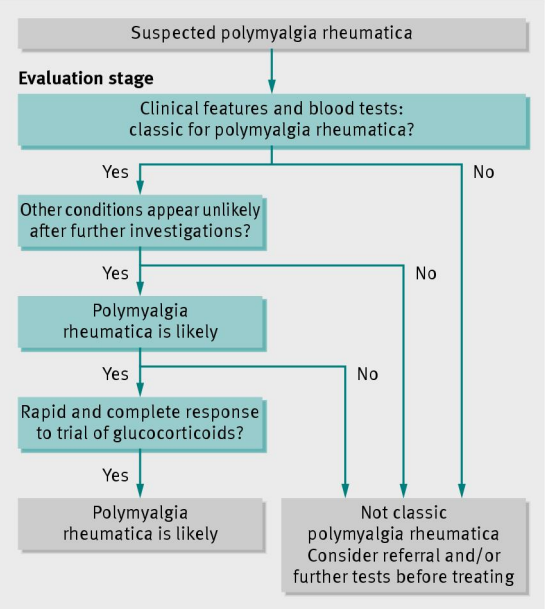

Fig 1 Summary of a three step procedure for evaluating suspected polymyalgia rheumatica; see British Society for Rheumatology guidelines for more detail[4]

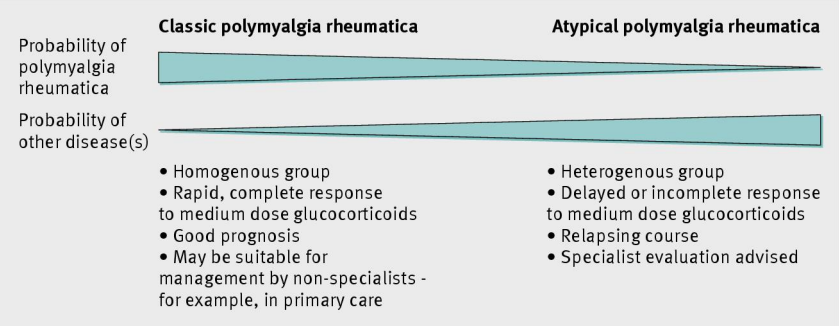

Fig 2 The clinical spectrum of polymyalgia from a diagnostic perspective. The triangles signify “greater” or “lesser” probability and are drawn on an arbitrary scale. There is no general agreement on what “atypical polymyalgia rheumatica” means, or at what point it becomes so atypical that it is no longer safe to make a diagnosis of polymyalgia rheumatica. These patients should probably be managed with input from a specialist

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