Management guidelines and outcome measures in polymyalgia rheumatica (PMR)

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ABSTRACT

Polymyalgia rheumatica (PMR) is a common inflammatory rheumatic disease of the elderly that is subject to wide variations in clinical practice and is managed both in the primary and secondary care settings by general practitioners, rheumatologists and non-rheumatologists. Considerable uncertainty exists relating to diagnosis, management and outcome in patients with PMR. The guidelines presented here seek to improve outcomes for PMR patients by outlining a process to ensure more accurate diagnosis and timely specialist referral. The guidelines are directed to promote more conservative treatment and to ensure early bone protection in order to reduce the common morbidity of osteoporotic fractures. Furthermore, these guidelines specify the goals of treatment, including clinical and patient-based outcomes, and provide advice concerning monitoring for disease activity and complications.

Introduction

Polymyalgia rheumatica (PMR) is one of the most widespread inflammatory rheumatic disease of the elderly, and represents one of the most common indications for long-term steroid therapy in the community (1, 2). PMR is subject to wide variations in clinical practice, and may be managed in primary or secondary care by general practitioners, rheumatologists and non-rheumatologists (3, 4).

The guidelines proposed in this report are based on the best available clinical evidence and experience, with the purpose of promoting the better management of patients with PMR. We have incorporated evidence from the medical literature and expert opinions solicited primarily through the International PMR Classification Criteria Work Group (see member list) and summary proposals of the British Society for Rheumatology (5). The purposes of the guidelines are to:

- Suggest an approach to ensure the more accurate and specific diagnosis of patients presenting with polymyalgic symptoms.
- Encourage timely specialist referral of appropriate cases.
- Promote more cautious treatment than is currently administered to most patients, usually using lower doses of corticosteroids and gradual corticosteroid taper.
- Ensure early bone protection to reduce the common morbidity of osteoporotic fractures related to corticosteroid use and host variables.

The diagnostic problem

Many features of PMR can lead to diagnostic error (6). The proximal pain and stiffness syndrome – the main symptoms of PMR – can be seen in many other illnesses (7). A third of PMR patients have systemic symptoms such as fever, anorexia and weight loss. A considerable number of patients may have additional musculoskeletal manifestations such as peripheral arthritis, distal swelling with pitting edema, and carpal tunnel syndrome (8). PMR is also associated with giant cell arteritis (GCA) in 10–20% of cases, and up to 50% of GCA cases may have PMR at presentation (9). An elevated acute phase reactant – an important diagnostic aid – can occur in many settings, including other rheumatological conditions, neoplasia, and infection (10).

Many clinicians, as well as two sets of diagnostic criteria (Healy; Jones and Hazleman) have regarded a response to corticosteroids (CS) as the primary defining feature of PMR (11-13). However, this criterion may introduce diagnostic error, since CS are potent anti-inflammatory agents that can mask symptoms from a host of serious conditions including osteoarthritis, rotator cuff disease, rheumatoid arthritis,

cancer, and infection, especially if used in high doses and for protracted lengths of time. The initial diagnosis is not sustained in some patients, and requires knowledgeable reassessment and revision (10).

What are the objectives of this guideline?

1. To outline a safe and specific diagnostic process for PMR
2. To specify a minimum data set that should be recorded for the diagnosis of PMR
3. To outline a diagnostic algorithm and clues in the presentation that will help to differentiate PMR from other mimicking conditions
4. To specify referral guidelines for the general practitioner
5. To provide advice on the management of PMR
6. To specify the goals of treatment, including clinical and patient-based outcomes
7. To provide advice on monitoring for disease activity and complications of both disease and treatment

What is the evidence to support these guidelines?

The evidence in support of these guidelines has been reviewed in the proposals of the British Society for Rheumatology PMR guidelines (5).

Key recommendations:

- Use core inclusion criteria as the first step in a staged process to diagnose PMR
- Initiation of low-dose CS with gradual steroid taper
- Early referral to a specialist for atypical cases and treatment dilemmas
- Vigilant monitoring of proximal pain, morning stiffness, disability, osteoporotic risk factors, and for any other symptoms that may suggest an alternative diagnosis
- Prevention of osteoporotic complications

A summary of the recommendations is contained in Figure 1.

QUICK REFERENCE GUIDE

1. **Establish diagnosis of PMR in a step-wise manner**
   ***Include*:** Patients presenting *age* >50 years, *duration* >2 weeks, *bilateral* shoulder and/or pelvic girdle aching, *morning stiffness* duration of >45 minutes, raised erythrocyte sedimentation rate, C-reactive protein e.g. evidence of an acute phase response.
   ***Exclude*:** active cancer, infection, RA and other inflammatory diseases, thyroid, local shoulder and hip conditions, statins
2. **Investigate:** Full blood count, urea and electrolytes, liver function tests, C reactive protein, erythrocyte sedimentation rate, rheumatoid factor (RF), creatinine kinase, thyroid stimulating hormone, protein electrophoresis and urinalysis. May need CXR, ANA
3. **Commence low dose steroids:** 15 mg prednisolone daily or I.M. depomedrone <120 mg
4. **Evaluate steroid response**
   ≥70% patient global response in 1 week: likely to be PMR
   50- 70% response: consider increased dose up to 20 mg
   < 50% response: reconsider diagnosis
5. **Follow up evaluation** – to ensure steroid response is complete and sustained with no other features of alternative diagnosis
6. **Early referral** to a specialist for patients with atypical features or features that increase likelihood of a non-PMR diagnosis or treatment dilemmas
7. **Prevention of osteoporotic complications:**
   Co-prescribe calcium and vitamin D supplements
8. **On-going monitoring of:**

Symptoms	Lab monitoring	Bone density
• Proximal pain	• Full blood count	• BMD every one to two years
• Morning stiffness	• ESR/CRP	
• Disability related to the PMR	• Urea and electrolytes	
• Adverse events	• Glucose	
• Osteoporotic risk factors		
• Other symptoms that may suggest an alternative diagnosis		

9. **Relapses**
   - Increase steroids to previous higher dosage (1st and 2nd relapse)
   - Consider additional immunosuppression, e.g., methotrexate, at 3rd relapse
   - GCA relapse: treat with high dose steroids 40-60 mg prednisolone
   - Consider alternative diagnosis with steroid non- or partial-response

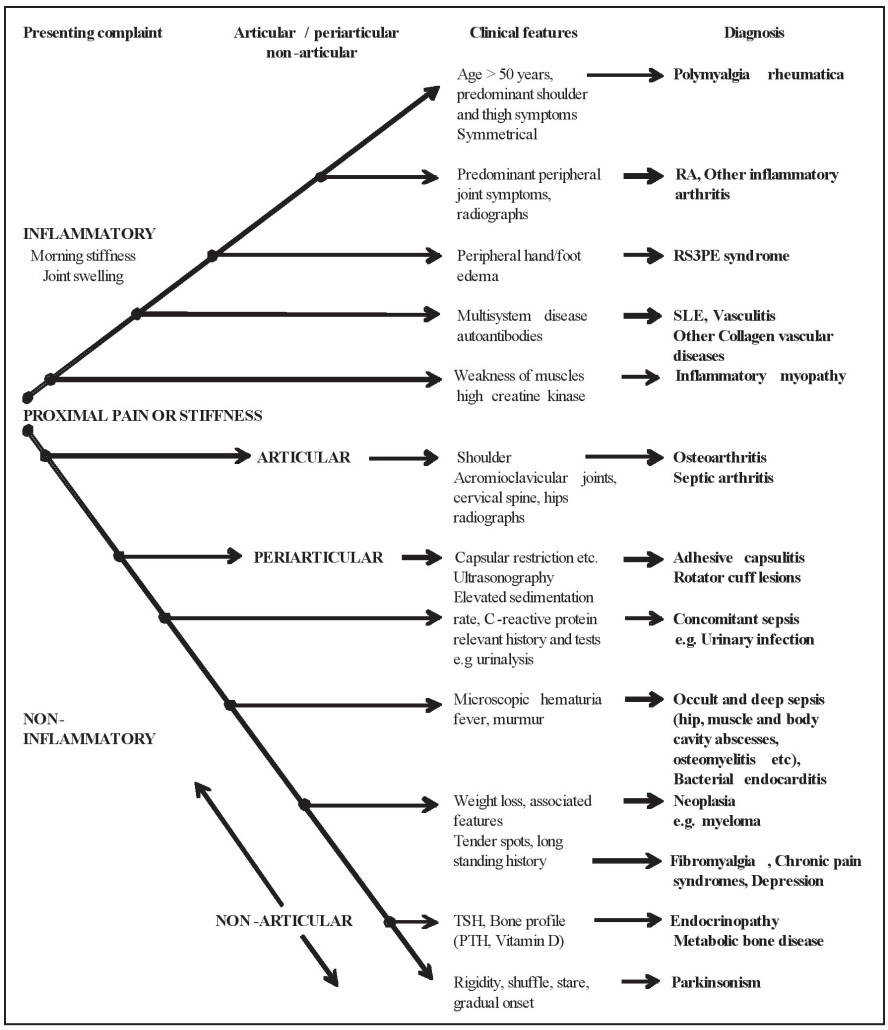
Fig. 1. Quick Reference Guide.

A. Diagnosis of PMR

The International PMR Classification Criteria Work Group, endorsed by the ACR and EULAR, has agreed on an approach (supported by a Delphi survey) for the polymyalgic syndrome that views the diagnosis of PMR as a stepped process (14). A work group of 27 physicians from around the world with an interest in PMR (rheumatologists, non-rheumatologists, statisticians and methodologists) met at the Third International Conference on GCA & PMR in July 2005 in Cambridge (UK), and at subsequent ACR and EULAR meetings to discuss a consensus-based process for the development of classification criteria in PMR.

The work group developed draft 'candidate criteria' through an extensive literature review and comprehensive assessment of the value of laboratory and imaging tests (14). A Delphi survey containing the 43 draft criteria items was sent to 190 rheumatologists and 85 generalists/internists in North America and Europe. Responses were received from 111 practicing rheumatologists from a mix of academic and private practice settings (49 USA, and 62 from 15 countries in Northern/Western Europe and Canada) and 53 generalists/internists (29 USA, 24 UK). More than 70% of the Delphi survey respondents agreed with the experts on 7 of 10 core candidate criteria.

The following draft criteria items have been proposed. A prospective international study recruiting patients with a new presentation of bilateral shoulder pain, to compare cases of new PMR and controls (inflammatory and non-inflammatory) with similar polymyalgic presentation, is currently underway to assess and attempt to validate these criteria (14).



Follow Up as part of the Diagnostic Evaluation: response to steroids or inability to reduce the dose: Carefully review and revise diagnosis if necessary

Fig. 2. How should proximal pain and stiffness be evaluated?

1. Evaluate for inclusion criteria:

Core (essential) criteria: age >50 years, duration >2 weeks, bilateral shoulder and/or pelvic girdle aching, morning stiffness duration >45 minutes, raised erythrocyte sedimentation rate, C-reactive protein, *e.g.*, evidence of an acute phase response.

PMR has been diagnosed with a normal acute phase response, but the work group agreed that the value of acute phase reactants required further investigation in the prospective study.

2. Evaluate for exclusion criteria

Core criteria: contraindications to CS include active infection and cancer

Others: decreased likelihood of PMR, hence try to exclude the following:

- Rheumatic diseases: rheumatoid arthritis (RA), inflammatory arthropathies, systemic lupus erythematosus, other connective tissue disease, inflammatory myopathies
- Drug-induced myalgia, *e.g.*, statins
- Pain syndromes, *e.g.*, fibromyalgia
- Endocrine disorders, *e.g.*, thyroid disease
- Neurologic disorders, *e.g.*, Parkinson's disease

The assessment should note co-existing conditions (as a cause of persistent pain): osteoarthritis (OA), degenerative or other peri-articular conditions involving the shoulder, neck and hips. PMR can occur in the setting of these and other conditions (including depression and fibromyalgia), which therefore must be taken into consideration in the clinical evaluation, but these co-existing conditions must be evaluated for their impact on the sensitivity and specificity of the classification criteria for PMR.

3. Evaluate a standardized response to corticosteroids

The initial dose of oral prednisolone should be 15 mg daily, a dose agreed upon by >90% of the consensus group. Most reported clinical trials have used initial CS doses of 10-20 mg per day (14-17).

What level of response is required, and how soon?

- The work group established with >75% agreement that a patient global response consists of >70% improvement within one week with normalization of inflammatory markers in 3-4 weeks.
- A lesser response encourages diagnostic error, because CS are potent anti-inflammatory agents that mask symptoms from a host of serious conditions including osteoarthritis, rotator cuff problems, rheumatoid arthritis, cancer and infection.
- Useful as this approach should be, it also highlights important unanswered questions that deserve further research:

  1) Can a patient present with proximal pain and stiffness and respond to CS, even though the treating physician does not think he has PMR?

  2) Can patients have PMR even if they do not respond to steroids at a specified dosage?

4. Confirmation of the diagnosis on follow-up

The diagnosis of PMR is not confirmed or sustained in up to 23% of patients on follow-up (18-20). Follow-up visits should include the search for symptoms, signs (*e.g.*, persistent synovitis) and pertinent laboratory abnormalities (*e.g.*, hemoglobin, acute phase reactants, biochemistry, autoantibodies), as well as investigations (*e.g.*, erosions on radiographs) for conditions that may mimic PMR, such as other rheumatologic diseases (*e.g.*, RA) (14).

B. What key diagnostic features of PMR should be routinely documented in the patient's medical record?

Clinical features. Whether the patient meets the core inclusion and exclusion criteria should be documented in his records. Clinical measures of disease activity, including the patient's global assessment (usually using a visual analog scale), and other measures of response which are clinically useful, including the modified Multi-dimensional Health Assessment Questionnaire (MDHAQ) should also be administered to improve the assessment of disease activity and response to therapy.

Laboratory investigations. A minimum dataset required prior to the start of steroid therapy should be recorded.
- Full blood count
- Erythrocyte sedimentation rate or C-reactive protein/plasma viscosity
- Urea and electrolytes
- Liver function tests (ALT and/or AST)
- Bone profile: calcium, alkaline phosphatase
- Protein electrophoresis/Bence Jones protein (if required)
- Creatine kinase
- Rheumatoid factor (antinuclear antibody may also be considered)
- Chest radiograph (in some cases, *e.g.*, prominent systemic symptoms)
- Urinalysis

Imaging. The results of a Delphi exercise did not support the inclusion of PET or MRI scans as required investigations for polymyalgic syndrome (14) on the grounds of lack of availability, cost, and still outstanding issues regarding the interpretation of results. Musculoskeletal ultrasonography bears promise because of its availability, feasibility and good research evidence, and should be studied further (14).

Follow-up as part of the diagnostic evaluation. A poor CS response as defined above, or inability to reduce the dose should prompt careful review and revision of the diagnosis if necessary.

C. When should a primary care provider refer someone with PMR?
A visit to the rheumatologist to confirm the diagnosis of PMR is encouraged in all patients. In addition, early referral to a specialist is recommended for patients with atypical features or features that increase the likelihood of a non-PMR diagnosis such as:

- Younger age (< 60 years)
- Protracted (chronic) onset
- Lack of shoulder involvement
- Lack of inflammatory stiffness
- Prominent systemic features or other 'red flag' features such as high fever, rashes, lymphadenopathy
- Peripheral arthritis or other features of rheumatic disease
- Normal acute phase reactants (APR) or markedly elevated APR

Early referral to a specialist is also recommended for treatment dilemmas such as:
- Incomplete or no response to CS
- Ill-sustained response to CS
- Refractory to reduction of CS
- Contraindications to CS therapy

Patients with typical features, and no atypical features, who show a complete sustained response to low-dose CS and no adverse events can be managed by the primary care provider.

D. How should treatment for a patient with PMR be initiated?
Management principles
- In the absence of features of GCA, there is little indication for urgent steroid prescription before the clinical evaluation is completed.
- Introduce low-dose steroids with gradual steroid tapering (14-17).
- The initial daily prednisolone dose should be 15 mg for 3 weeks, tapering to 12.5 mg for 3 weeks, 10 mg for 4-6 weeks, followed by a reduction by 1 mg (4-8 weeks) or else alternate day reductions (*e.g.*, 10/7.5 mg alternate days and so on). It is important to realize that PMR, while occasionally self-limiting, can be a chronic disease with a protracted clinical course lasting years, with substantial disease and treatment-related morbidity.
- The dose may require adjustment (either higher or lower) depending on the disease severity assessment and co-morbid conditions (*e.g.*, diabetes, cardiac, respiratory, renal diseases, fracture risk), patient compliance, and adverse events.
- Intramuscular methylprednisolone (I.M. depomedrone) is occasionally used in milder cases and may reduce the risk of steroid-related complications (21). The initial dose is 120 mg I.M. repeated at 3 to 4-weekly intervals. The dose is then reduced by 20 mg every 2-3 months and given monthly.
- NSAIDs are not an effective therapy for PMR and should be used with caution, especially in the very elderly and in cases of renal impairment.

Patient education
Patients should be provided with disease education, including educational materials prepared by reputable physicians, institutions, and organizations such as the Arthritis Foundation and the Arthritis Research Campaign.

E. What steps should be taken to prevent the complications of osteoporosis in a patient being treated with corticosteroids for PMR?
Early bone protection is essential. Coprescribe calcium and vitamin D supplementation with steroids; bisphosphonates should be used early if other risk factors are present or if there is a risk of a higher cumulative CS dose due to higher dosages or a longer duration of treatment. Please see the guidelines on glucocorticoid-induced osteoporosis for further details (22). It is important to minimize the osteoporotic risk by using the minimum effective dose of CS.

F. How should the disease course be followed?
Vigilant ongoing monitoring is the key to successful management and the reduction of comorbidity risks:

- Tailor CS treatment in accordance with the degree of inflammatory symptoms (try to distinguish these from symptoms due to coexisting de-

generative conditions, although this may require a specialist rheumatology opinion); the presence of co-morbidities (such as diabetes mellitus, vascular disease and osteoporosis); and the patient's comfort and preferences.
– Relevant symptoms helpful in the follow-up evaluation include proximal pain, stiffness, and disability (for example, using the modified Health Assessment Questionnaire, or morning stiffness).
– Complications of the disease: Ask about headaches jaw claudication
– Inquire about CS-related adverse events: weight, diabetes, osteoporosis, blood pressure, lipid profile. Many studies have shown high rates of CS-related complications in treated PMR patients (23-25). Most studies agree that PMR requires up to 2-3 years of steroid treatment, but sometimes 9 or 10 years of treatment may be needed (26-30). Hence the minimum effective dose should be administered and alternative causes of persistent pain should be sought. High initial dosing and rapid tapering of CS has been shown to be associated with a longer duration of therapy (31).
– Patients with "atypical" or severe symptoms or a poor CS response should be considered for early re-evaluation and rheumatology referral.

Symptoms to monitor
– Proximal pain
– Morning stiffness
– Disability related to the PMR
– Adverse events
– Osteoporotic risk factors
– Other symptoms that may suggest an alternative diagnosis

Lab monitoring
Complete blood count, ESR/CRP, urea and electrolytes, glucose

Bone density
BMD every two years

Frequency of follow-up
Weeks 0, 1, 3, and 6; then months 3, 6, 9, and 12, with extra visits for relapses or adverse events.

G. How should a relapse be managed?
Relapse
A relapse should be evaluated with regard to symptoms and signs, as well as assessment for related conditions, most particularly GCA (*e.g.*, headaches, jaw claudication, visual symptoms), and not solely on the basis of a raised ESR/CRP in an otherwise asymptomatic patient.

Treatment of relapse
In cases of:
– *Clinical features of GCA relapse:* Treat as GCA (usually with oral prednisolone 40-60 mg daily).
– *Clinical features of PMR relapse (first and second relapses):* Increase prednisolone to the previous higher dose and monitor for response. A single I.M. injection of depot methylprednisolone <120 mg can also b e given, as in the treatment of RA flare.
– *Further relapses:* There is insufficient evidence regarding the efficacy of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate. One study concluded that it was effective (32), but others have shown inconsistent results, and one randomised controlled trial showed no effect (32-35).

H. Measures of the process and adherence to guidelines
The following constitutes the minimum dataset that should be recorded prior to CS therapy:
– Clinical features (*e.g.*, symmetrical proximal pain and stiffness); important exclusions
– Investigations, as specified in the guidelines
– Initial steroid dose and tapering
– Monitoring frequency
– Bone protection prescribed
  • Co-prescription of calcium and vitamin D
  • Bisphosphonates in cases of additional risk factors
  • Bone mineral density measurements

Summary
These guidelines for the evaluation and management of patients with PMR are based upon the best available evidence. PMR can be a complicated and protracted disease, with considerable disease- and treatment-related morbidity. Following these guidelines constitutes a minimum best practice. Future studies will be required to evaluate their utility as new disease markers and treatments are developed for better disease control.

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