RATIONAL TESTING

Investigating symmetrical polyarthritis of recent origin

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What are the key tests for someone with polyarticular symptoms and at what point do you refer? This article goes through the diagnostic steps

A 32 year old woman presents to her general practitioner with a month’s history of painful wrists and feet and increased tiredness, which she attributes to carrying and looking after her 6 month old son. When asked, she describes early morning stiffness for an hour and finds that over the counter ibuprofen eases the pain. She has no clinically significant history, such as psoriasis, recent infection, or diarrhoea. On examination, she has mildly swollen wrists and tenderness on compression of her metatarsophalangeal joints.

What are the next investigations?

Given the polyarticular joint involvement, morning stiffness, and response to anti-inflammatory agents in our patient, inflammatory arthritis needs to be considered, although the course of early inflammatory arthritis is highly variable. In a prospective population based study in Sweden, 151 new cases of recent onset undifferentiated inflammatory arthritis were identified over a period of one year. When reviewed a year later, 21% of these patients had a diagnosis of rheumatoid arthritis, 36% still had undifferentiated arthritis, 24% reactive arthritis, and 7% psoriatic arthritis.1 In other studies of recent onset undifferentiated arthritis, the arthritis progressed to rheumatoid arthritis at one year in a third of cases and was self limiting in 40-50% of cases. Polyarticular onset and small joint involvement (box) consistently predicted an unfavourable outcome.2-5

Full blood count, erythrocyte sedimentation rate, C reactive protein, and anticyclic citrullinated peptide (anti-CCP) (or rheumatoid factor) help in confirming a diagnosis of rheumatoid arthritis and indicating the likely prognosis. Other antibodies such as antinuclear antibody and extractable nuclear antibodies were not indicated in the initial investigations of our patient as she had no sicca symptoms (dry eyes and mouth), hair loss, malar rash, photosensitivity, or Raynaud’s phenomenon to suggest conditions such as systemic lupus erythematosus and Sjögren’s syndrome. Radiography of hands and feet may aid diagnosis by showing erosion or narrowing of joint spaces but is often normal and should not delay urgent referral of patients to a rheumatologist when inflammatory arthritis is suspected. If radiographic change is already evident at presentation, the prognosis is likely to be poor.

C reactive protein or erythrocyte sedimentation rate

C reactive protein and erythrocyte sedimentation rate can be raised in inflammatory arthritis. The degree of increase is highly variable and can be absent in about 40% of patients with recent onset disease6 and would not exclude the diagnosis of rheumatoid arthritis. Where the erythrocyte sedimentation rate is >100 mm/h or the C reactive protein is >120 mg/l, other diagnoses such as infection, vasculitis, or crystal arthritis need to be considered. In patients with raised acute phase proteins, the full blood count may also show a mild normochromic normocytic anaemia (haemoglobin concentration 90-110 g/l) and increased platelet count.

Rheumatoid factor or anti-CCP

A strongly positive rheumatoid factor increases the likelihood of early rheumatoid arthritis—particularly in patients with a polyarticular onset of arthritis—and
correlates with a less favourable outcome.\(^2\) Rheumatoid factor is absent in 38% of patients with rheumatoid arthritis\(^4\) and can be falsely positive in many other conditions, such as lupus, Sjögren’s syndrome, acute and chronic infections, cryoglobulinaemia, and lymphoproliferative disorders. It is also found in 1-2% of healthy individuals, increasing to 20% over the age of 65. Anti-CCP is an antibody with greater specificity than rheumatoid factor for rheumatoid arthritis, and, if available, should be requested in preference to it. Anti-CCP is particularly useful in patients negative for rheumatoid factor where rheumatoid arthritis is suspected. Anti-CCP has consistently been shown to be the strongest independent predictor of radiographic progression (odds ratio 4.0; 95% confidence interval 1.6 to 10.0) especially at higher titres (>200 U/ml). Rheumatoid factor has also shown a clear correlation with radiological damage (odds ratio 3.1; 1.2 to 7.9).\(^3\)

Outcome

Given the suggestive clinical features in our case scenario, the general practitioner referred the patient urgently to the rheumatology department, despite normal full blood count, erythrocyte sedimentation rate, C reactive protein, rheumatoid factor, and x ray films of hands and feet. The patient had further investigations, which showed strongly positive anti-CCP antibodies (>600 U/ml) and active synovitis without erosion on high resolution ultrasound scanning of her wrists using colour flow Doppler. Magnetic resonance imaging would have been a useful alternative investigation to identify synovitis, soft tissue abnormality, bone oedema, and joint erosion—many months before any changes would have been detected on plain radiographs.\(^7\) The additional tests in our rheumatology department confirmed a diagnosis of rheumatoid arthritis in this patient, and as she was not breastfeeding or considering future pregnancy, treatment with disease modifying antirheumatic drugs was started, in accordance with recommendations for England, Wales, and Northern Ireland from the National Institute for Health and Clinical Excellence (NICE).\(^8\)

Rheumatoid arthritis affects 29 women and 18 men per 100 000 people a year in Sweden\(^1\) and similar numbers of patients in the United Kingdom.\(^2\) The cause of the disease is unknown, but genetic and environmental factors are considered important. Onset is usually gradual but needs to be differentiated from self limiting diseases as early as possible to ensure that patients at high risk of joint damage are seen early, given the growing evidence that early therapeutic intervention improves control and reduces joint damage;\(^10\) it is also important to differentiate rheumatoid arthritis from self limiting arthropathies to avoid unnecessary use of potentially toxic treatments.

The formal diagnostic criteria for rheumatoid arthritis\(^11\) perform very poorly in early disease and cannot be used for therapeutic decision making. However, prospective studies have identified factors associated with an unfavourable outcome (box)\(^11\) that can be used to support the need for urgent referral to a rheumatologist and treatment with disease modifying antirheumatic drugs in accordance with the NICE guidelines\(^12\) and European\(^13\) and US\(^13\) guidelines. The advent of anti-tumour necrosis factor and other biological agents has made it possible to treat rheumatoid arthritis so effectively that remission or low disease activity within three to six months is an achievable goal in many patients with rheumatoid arthritis.\(^14\)

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6 Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1990 and 2004: analyses from Finland and the United States. J Rheumatol 2009;36:1387-90.
GUIDELINES

Management of stable chronic obstructive pulmonary disease in primary and secondary care: summary of updated NICE guidance

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Over three million people in the United Kingdom are estimated to have chronic obstructive pulmonary disease (COPD), of whom more than two million remain undiagnosed, representing the so called “missing millions” alluded to in the draft national strategy for COPD.1 3 This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the management of stable chronic obstructive pulmonary disease in primary and secondary care,4 which update the COPD guidelines first published by NICE in 2004.1 The summary contains the most important recommendations relating to new diagnostic criteria for COPD, changes to the classification of severity of airflow obstruction, the need for multidimensional severity assessment, a new algorithm for inhaled drug treatments (figure), and the value of early pulmonary rehabilitation.

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group’s experience and opinion of what constitutes good practice. Evidence levels for the updated recommendations are in the full version of this article on bmj.com.

Diagnosing COPD

- Consider a diagnosis of COPD in patients aged over 35 years who have a risk factor (generally smoking) and present with exertional breathlessness, chronic cough, regular sputum production, frequent winter “bronchitis” or wheeze.
- Measure post-bronchodilator spirometry to confirm the diagnosis of COPD. (Updated recommendation.)
- Consider alternative diagnoses or investigations in: 
  - Older people without typical symptoms of COPD where the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) is <0.7.
  - Younger people with symptoms of COPD where the FEV1/FVC ratio is ≥0.7. (Updated recommendation.)
- Assess the severity of airflow obstruction according to the reduction in FEV1, as shown in table 1. (Updated recommendation.) This classification of severity of airflow obstruction is now aligned with other international guidelines5 8; it refers only to the severity of airflow obstruction and not the clinical severity of COPD, for which a more comprehensive assessment is necessary.
- Disability related to COPD can be poorly reflected in the FEV1. A more comprehensive assessment of severity includes the degree of airflow obstruction

Abbreviations: SAMA = short acting muscarinic antagonist, LAMA = long acting muscarinic antagonist, LABA = long acting beta agonist, ICS = inhaled corticosteroid

* Short acting beta agonist (as required) may continue at all stages

Offer therapy (strong evidence)  —— Consider therapy (less strong evidence)

Algorithm for use of inhaled therapies

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and disability, the frequency of exacerbations, and the following known prognostic factors: breathlessness (Medical Research Council dyspnoea scale (table 2), health status, body mass index, cor pulmonale, FEV₁, exercise capacity (for example, six minute walking test—usually only available in secondary care), transfer factor for carbon monoxide (usually only available in secondary care), and partial pressure of oxygen in arterial blood (usually only available in secondary care). Calculate the BODE index (body mass index, airflow obstruction (FEV₁ % predicted), dyspnoea, and exercise capacity (six minute walking distance, usually not available in primary care)⁵) to assess prognosis where its component information is currently available. (Updated recommendation.)

Specialist referral
Refer for specialist advice when clinically indicated. This may be appropriate at all stages of the disease and not only in the most severely disabled patients. Indications include diagnostic uncertainty, rapidly changing disease (both on spirometry and in symptoms), and onset of complications such as cor pulmonale (see full guidance for detailed table).

Stopping smoking
• Encourage all patients with COPD who are still smoking to stop, regardless of age; offer help to do so, at every opportunity
• Unless contraindicated, offer nicotine replacement therapy (varenicline or bupropion, as appropriate) to patients with COPD who are planning to stop smoking, together with an appropriate support programme to optimise smoking quit rates. (Updated recommendation, based on two NICE documents.¹⁰ ¹¹)

Promoting effective inhaled therapy
• A new clinical algorithm provides an evidence based rationale for the sequencing of inhaled drugs used singly and in combination according to persistence of symptoms, exacerbations, and severity of airflow obstruction (figure) and clarifies options for escalating inhaled treatment according to whether FEV₁ is above or below 50%. (Updated recommendation.)
• Be aware of the potential risk of developing side effects (including non-fatal pneumonia) in people with COPD treated with inhaled corticosteroids and be prepared to discuss with patients. (Updated recommendation.)

Providing pulmonary rehabilitation
• Make pulmonary rehabilitation available to all appropriate people with COPD (see below), including those who have had a recent hospital admission for an acute exacerbation. (Updated recommendation.)
• Offer pulmonary rehabilitation to all patients who consider themselves functionally disabled by COPD (usually Medical Research Council grade 3 and above (table 2)). Pulmonary rehabilitation is not suitable for patients who are unable to walk, have unstable angina, or had a recent myocardial infarction.

Management of exacerbations and use of non-invasive ventilation
Recommendations on management of exacerbations and use of non-invasive ventilation were not included in the scope of the update and so remain unchanged from the 2004 guideline, except where considered necessary for consistency with other recent specific guidelines (for example, the British Thoracic Society’s guideline for emergency oxygen use in adult patients).¹² ²³

Overcoming barriers
Age related interpretation of spirometry and its relation to clinical severity assessment may be a challenge for some non-specialists; this will require education and training. Measurement of post-bronchodilator spirometry is likely to result in minimal increase in resource use as reversibility testing (which is not recommended in the guideline) is currently undertaken to fulfil Quality Outcome Framework criteria. Realigning severity of airflow obstruction to agree with other international guidelines will lead to some patients having their severity stage reclassified; patients will need reassurance that their clinical condition, need for appropriate treatment, and prognosis all remain unchanged.²⁴ ²⁵ There is a potential economic impact of stronger new recommendations on
inhaled therapies. In people with mild COPD the primary course of action is to encourage smoking cessation. Other treatments, recommended only when symptoms persist and/or when needed to prevent exacerbations, become more cost effective as the severity of disease progresses.

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ANSWERS TO ENDGAMES, p 53. For long answers go to the Education channel on bmj.com

PICTURE QUIZ

A patient with CLL and a dry cough

1  The computed tomography scans of the thorax show multiple, bilateral, well defined pulmonary nodules that have progressed over the six week interval (figs 1 and 2).

2  The most likely diagnosis is acute pulmonary histoplasmosis.

3  Moderately severe and severe acute pulmonary histoplasmosis is treated with liposomal amphotericin B for one to two weeks, followed by itraconazole for a total of 12 weeks, whereas asymptomatic cases do not usually require treatment.

4  CLL is associated with immunodeficiency, and this could cause reactivation of asymptomatic histoplasmosis acquired during travel in an endemic area.

STATISTICAL QUESTION

Factorial trials

Answers a, c, and d are true; b is false.

ON EXAMINATION QUIZ

Answer B is correct. More questions on this topic are available from www.onexamination.com/endgames until midnight on Wednesday.