GUIDELINES

Management of rheumatoid arthritis: summary of NICE guidance

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Cite this as: *BMJ* 2009;338:b702
doi:10.1136/bmj.b702

This is one of a series of *BMJ* summaries of new guidelines, which are based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists. The supporting evidence statements and further information about the guidance (including recommendations on biological drugs) are in the full version on bmj.com.

Why read this summary?

Rheumatoid arthritis is a chronic, progressive autoimmune disease associated with inflammation principally in synovial joints and affecting over 400 000 people in the United Kingdom.[1] In recent years it has become clear that pain and disability can be avoided if the disease is recognised early and treated promptly and appropriately. It is therefore crucial that all health professionals have knowledge of the recognition, management, and appropriate referral of patients with rheumatoid arthritis. This article summarises the recommendations in the guideline from the National Institute for Health and Clinical Excellence (NICE) on the management of rheumatoid arthritis, from early identification to managing chronic and severe disease.[2]

Recommendations

NICE recommendations are based on systematic reviews of best available evidence. When minimal evidence is available, recommendations are based on the opinion of the Guideline Development Group (GDG) of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Referral, diagnosis, and investigations

- Refer for specialist opinion anyone with suspected persistent synovitis of undetermined cause. Refer urgently even if blood tests show a normal acute-phase response or negative rheumatoid factor and if:
  -The small joints of the hands or feet are affected
  -More than one joint is affected, or
  -There has been a delay of three months or longer between symptom onset and seeking medical advice.
- Offer to test for rheumatoid factor in people with suspected rheumatoid arthritis who have synovitis.
- Consider measuring anticyclic citrullinated peptide antibodies in people with suspected rheumatoid arthritis if:
  -They are negative for rheumatoid factor, and
  -Combination therapy is being considered (see section on disease modifying antirheumatic drugs).
- X ray the hands and feet early in people with persistent synovitis in these joints.

Communication and education

- Offer verbal and written information to people with rheumatoid arthritis to:
  -Improve their understanding of the condition and its management, and
  -Counter any misconceptions they may have.
- For those wishing to know more, offer participation in existing educational activities, including self management programmes.

The multidisciplinary team

- Ensure ongoing access to a multidisciplinary team with opportunity for periodic assessments and help to manage the condition.
- Ensure people with rheumatoid arthritis have access to a named member of the multidisciplinary team (for example, the specialist nurse), who is responsible for coordinating their care.
- Ensure access, with periodic review, to:
  -Specialist physiotherapy to enhance general fitness, joint flexibility, and muscle strength; to improve function; and to learn about short term pain relief provided by methods such as transcutaneous electrical nerve stimulators (TENS) and wax baths.
  -Specialist occupational therapy if they have problems with everyday activities or hand function.

-A podiatrist if they have foot problems, and make sure functional insoles and therapeutic footwear are available if indicated.
- Offer psychological interventions (for example, relaxation, stress management, and cognitive coping skills) to help adjust to living with the condition.

Management of symptoms: analgesics and NSAIDs

Analgesics

- Offer analgesics (for example, paracetamol, codeine, or compound analgesics) if pain control is inadequate, to potentially reduce their need for long term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 (COX 2) inhibitors.

Non-steroidal anti-inflammatory drugs

- When offering an oral NSAID or COX 2 inhibitor, the first choice should be either a standard NSAID or a COX 2 inhibitor (other than etoricoxib 60 mg) at the lowest effective dose for the shortest possible time. In either case, coprescribe a proton pump inhibitor with the lowest acquisition cost.
- All oral NSAIDs and COX 2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver, and cardiorenal toxicity; therefore, when choosing the agent and dose, consider the individual's risk factors, including age. When prescribing these drugs, consider appropriate assessment and/or monitoring of these risk factors.
- If a person with rheumatoid arthritis needs to take low dose aspirin, consider other analgesics before substituting or adding an NSAID or COX 2 inhibitor (with a proton pump inhibitor) if pain relief is ineffective or insufficient.
- If NSAIDs or COX 2 inhibitors are not providing satisfactory symptom control, review the regimen for disease modifying or biological drugs.

Management of symptoms: disease modifying antirheumatic drugs

For people with newly diagnosed active disease

- Offer a combination of disease modifying antirheumatic drugs as first line treatment as soon as possible, ideally within three months of the onset of persistent symptoms. This should include methotrexate and at least one other, plus short term glucocorticoids.
- If combination therapy with disease modifying drugs is not appropriate (for example, owing to comorbidities or pregnancy), start monotherapy, focusing on fast escalation to a clinically effective dose rather than choice of drug.
- Offer short term oral, intramuscular, or intra-articular glucocorticoids to rapidly improve symptoms (if the individual is not already receiving glucocorticoids as part of the combination therapy).

For people with recent onset disease (within past two years)

- If they have achieved sustained and satisfactory levels of disease control with a combination of disease modifying antirheumatic drugs, cautiously try to reduce doses to levels that still maintain disease control.

For people with established disease (longer than two years)

- If disease is stable, cautiously reduce dosages of disease modifying or biological drugs; return promptly to disease controlling doses at the first sign of a flare-up.
- When introducing new drugs to improve disease control, consider decreasing or stopping an individual's pre-existing rheumatological drugs once the disease is controlled.
- If doses of disease modifying or biological drugs are being decreased, or the drugs are being stopped, arrange for prompt review.

Management of symptoms: glucocorticoids

For people with recent onset or established disease

- Offer short term glucocorticoid treatment for managing flare-ups.

In people with established disease

- Continue long term treatment with glucocorticoids only after fully discussing with the individual the long term complications of the treatment and after offering all other treatment options (including biological drugs).

Monitoring rheumatoid arthritis

- Regularly measure C reactive protein and key components of disease activity (using a composite score such as the DAS28—a disease activity score that includes assessment of 28 joints[3]) to inform decision making about increasing treatment to control disease or cautiously decreasing treatment when disease is controlled. If the disease is of recent onset and active, measure these variables monthly until control reaches a level previously agreed with the individual.
- For people with satisfactorily controlled established disease offer review appointments at a suitable frequency and location, ensuring that they know when and how to get rapid access to specialist care, have access to additional visits for

disease flare-ups, and have ongoing drug monitoring.
- Offer annual review to:

  -Assess disease activity, damage, and overall impact and to measure functional ability (using, for example, the health assessment questionnaire[4])
  -Check for comorbidities such as hypertension, ischaemic heart disease, osteoporosis, and depression
  -Assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung, or eyes
  -Organise appropriate cross referral within the multidisciplinary team
  -Assess the need for referral for surgery.

Timing and referral for surgery

- Offer referral for an early specialist surgical opinion if any of the following do not respond to optimal non-surgical management:

  -Persistent pain as a result of joint damage or other identifiable damage to soft tissue
  -Worsening joint function
  -Progressive deformity
  -Persistent localised synovitis.
- For people with the following complications offer referral for a specialist surgical opinion before damage or deformity becomes irreversible:

  -Imminent or actual tendon rupture
  -Nerve compression (for example, carpal tunnel syndrome)
  -Stress fracture.
- Explain that the main expected benefits of surgery are pain relief, improvement, or prevention of further deterioration (of joint function and deformity). Cosmetic improvements should not be the dominant concern.
- Offer urgent combined medical and surgical management to those with suspected or proved septic arthritis (especially in a prosthetic joint).
- If any symptoms or signs suggesting cervical myelopathy develop (for example, paraesthesiae, weakness, unsteadiness, or extensor plantars) request urgent magnetic resonance imaging, and refer for a specialist surgical opinion.
- Do not let concerns about the long term durability of prosthetic joints influence decisions to offer joint replacements to younger people with rheumatoid arthritis.

Diet and complementary therapies

- Inform people who wish to experiment with their diet that no strong evidence exists that their arthritis will benefit. However, encourage them to follow the principles of a Mediterranean diet (more bread, fruit, vegetables, and fish; less meat; and replace butter and cheese with products based on vegetable and plant oils).

Inform those wishing to try complementary therapies that little or no evidence exists for their long term efficacy and that although some may provide short term symptomatic benefit, complementary therapies should not replace conventional treatment. Advise them that use of such therapies will not preclude the offer of conventional care.

Overcoming barriers

Effective implementation of these recommendations depends on early recognition of persistent synovitis in primary care with rapid referral to specialist care; aggressive use of disease modifying antirheumatic drugs in active disease; close monitoring of disease activity and intervention when control is unsatisfactory; and multidisciplinary care for both recent onset and established rheumatoid arthritis. General practitioners need to be taught how to recognise early synovitis and not to simply treat the symptoms if the synovitis is persistent. Resources are needed for specialist teams to see patients with recent onset rheumatoid arthritis promptly and to follow them up regularly with objective measures. However, this should not be at the expense of treating those with established disease. Annual review and ongoing access to the multidisciplinary team should be available to address the physical and psychosocial impact of rheumatoid arthritis, ensure appropriate medication, and equip the patient with the knowledge, skills, and resources to minimise the effects of the disease.

Contributors: All authors contributed to reviewing the evidence and writing and editing the article.
Funding: The National Collaborating Centre for Chronic Conditions was commissioned and funded by the National Institute for Health and Clinical Excellence to write this summary.
Competing interests: All authors were members of the Guideline Development Group for the NICE guideline (CD the clinical lead, RO'M the lead systematic reviewer, JT the lead health economist, CT the project manager, and MR the chair). CD's department has received grants from Wyeth and Schering-Plough to support research projects, a research nurse, and an audit clerk and from Abbott to purchase an ultrasound machine and training in its use. RO'M, CT and JT had no competing interests.
Provenance and peer review: Commissioned; not externally peer reviewed.

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RATIONAL IMAGING

Incidental thyroid nodule

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Cite this as: *BMJ* 2009;338:b611
doi:10.1136/bmj.b611

Thyroid nodules may be coincidentally detected as a result of neck imaging, and most are benign; the authors discuss how best to decide which nodules are most likely to be malignant and require further evaluation

The patient

A 78 year old man presented with haemoptysis and was found to have a bronchial tumour at bronchoscopy. He was referred for a ^{18}fluorine fluorodeoxyglucose PET-CT scan (which combines positron emission tomography and computed tomography) for accurate staging before surgical treatment; this scan confirmed operable disease. An incidental solitary thyroid nodule was detected, with the scan showing increased uptake of ^{18}fluorine fluorodeoxyglucose within the nodule (fig 1).

What is the next investigation?

Incidental thyroid nodules are usually detected as a consequence of the increasing use and higher resolution of neck imaging with ultrasound, computed tomography, positron emission tomography, and magnetic resonance imaging (MRI). Published data from autopsy series suggest that about 50% of the adult population have thyroid nodules, although data from ultrasound screening studies suggest that the prevalence may be as high as 67%[1]—substantially higher than the 4-8% of cases that are clinically palpable.[2]

The overwhelming majority of thyroid nodules are benign and unlikely to be of any clinical significance. A much smaller percentage will represent thyroid carcinoma of which the commonest type (papillary carcinoma) has an excellent prognosis with a 30 year survival rate of 95%.[3] The incidence of malignant disease in non-palpable nodules—that is, those likely to be detected on cross sectional imaging—is controversial. Although studies suggest similar rates of malignant thyroid disease for non-palpable and palpable nodules,[4] the clinical significance of detecting early microcarcinomas that have an indolent course and excellent prognosis remains debatable.

No evidence based consensus has been reached on how best to manage incidental non-palpable thyroid nodules. No single imaging modality can differentiate benign and malignant disease accurately, and pathological evaluation of all nodules would not be cost effective and could cause unnecessary distress to most patients. Therefore a rational approach about who to investigate further is crucial for identifying the small number of patients with thyroid malignancy without overinvestigating the much larger number with benign disease.

Clinical assessment, on the basis of history and/or clinical examination, is an important first step to identifying which patients might be at a higher risk of malignancy and therefore require imaging (box). The relative strengths and weaknesses of each imaging technique are summarised in the table.

Thyroid function tests

Thyroid stimulating hormone can be used as a screening test in patients with a solitary thyroid nodule for detecting hyperfunctioning adenomas that cause a suppressed thyroid simulating hormone level. Hyperfunctioning nodules account for about 10% of solitary thyroid nodules and are almost always benign.[3] Nearly all patients with thyroid cancer are euthyroid. If any clinical risk factors are present and the level of thyroid simulating hormone is normal, further imaging evaluation may be advisable.

Ultrasound

High resolution ultrasonography is highly sensitive for detecting thyroid nodules. Although ultrasonography cannot definitely distinguish between benign and malignant nodules because of an overlap in ultrasound characteristics, certain features favour benign or malignant aetiology. These features may be used to triage patients into those who require no further investigation and can be reassured and those who should undergo tissue sampling for further evaluation.

Clinical features suggestive of thyroid malignancy[1]:

- Age (<20 years or >60 years)
- Symptoms of dysphagia or dysphonia (local invasion)
- Previous history of neck irradiation
- Prior or family history of thyroid carcinoma
- Firm, hard, or immobile nodules
- Presence of cervical lymphadenopathy
- Rapidly growing nodules

This series provides an update on the best use of different imaging methods for common or important clinical presentations. The series advisers are Fergus Gleeson, consultant radiologist, Churchill Hospital, Oxford, and Kamini Patel, consultant radiologist, Homerton University Hospital, London.

Features such as solid composition, microcalcification, irregular margins, and marked hypoechogenicity are more predictive of malignancy than size criteria alone.[4] The presence of at least one malignant feature has an overall sensitivity of 83% and specificity of 74%.[5] However, features such as a predominantly cystic mass with well defined margins and no calcification are much more typical of benign disease.[1]

Fine needle aspiration cytology

Fine needle aspiration cytology is a highly accurate and cost effective method of evaluating thyroid nodules that show suspicious features on an ultrasound scan. Cytology has a high negative predictive value (95-98%), but up to 15% of specimens may be indeterminate depending on local expertise and other factors.[6] Using fine needle aspiration cytology selectively when investigating thyroid nodules with suspicious ultrasound features can reduce the requirement for excision by at least 25% and doubles the yield of malignancy in those excised.[7]

Although fine needle aspiration cytology is safe and easily performed without major complication, potential minor risks include local haemorrhage and inadvertent tracheal puncture, although these are rare. The procedure is contraindicated in patients who have a bleeding diathesis or who are unable to tolerate the procedure. Local expertise and availability of cytologists vary widely, and core biopsy for histological evaluation may be required at some institutions. Pathological examination must be used selectively, and published guidelines advise that fine needle aspiration cytology should be reserved for thyroid nodules over 1 cm in size and with suspicious ultrasound features as no direct evidence exists that early diagnosis of microcarcinomas (<1 cm) improves life expectancy.[1 6]

Radionuclide scintigraphy

Thyroid scintigraphy allows the functional status of a thyroid nodule to be assessed. It is useful in patients with a suppressed thyroid stimulating hormone level for confirming the presence of a hyperfunctioning nodule, in which malignancy is extremely rare. In contrast, solitary hypofunctioning nodules have a 10-15% incidence of malignancy.[3] Scintigraphy is generally not helpful for determining which nodules are more likely to be malignant in euthyroid patients. Functional imaging may be useful in patients with indeterminate cytology as the demonstration of tracer uptake in a thyroid nodule virtually excludes malignancy.

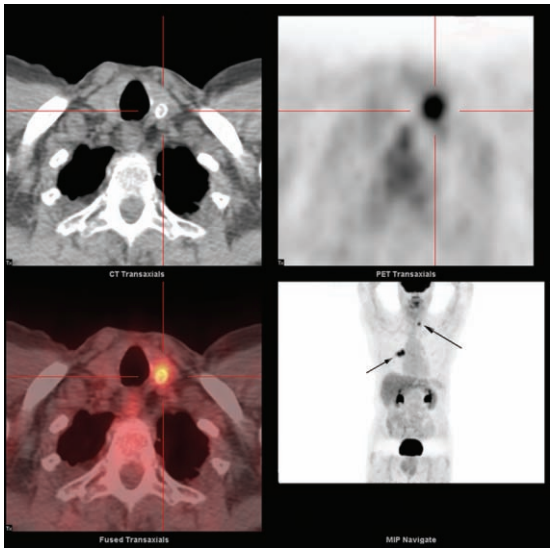

Fig 1 | Half body PET-CT scan. The axial CT scan (top left), PET scan (top right), and fused PET-CT scan (bottom left) show abnormal focal uptake of ^{18}fluorine fluorodeoxyglucose in the left lobe of the thyroid gland (indicated by red "crosshairs"). The maximum intensity projection of the PET scan (bottom right) shows abnormal focal uptake of ^{18}fluorine fluorodeoxyglucose in the thyroid gland (long arrow) and two adjacent foci of abnormal ^{18}fluorine fluorodeoxyglucose activity in the right lung in keeping with the primary lung carcinoma and an adjacent right hilar node (short arrow)

Positron emission tomography-computed tomography

PET-CT is a new hybrid imaging technique that combines functional (positron emission tomography) and anatomical (computed tomography) images to localise sites of increased metabolic activity more accurately in patients with malignancy. The most commonly used radiotracer, ^{18}fluorine fluorodeoxyglucose (a glucose analogue), is a sensitive marker of increased glucose metabolism, which occurs in a variety of malignant tumours. PET-CT scanning is commonly used in patients with potentially operable lung and oesophageal cancer and in the evaluation of patients with lymphoma.

Focal ^{18}fluorine fluorodeoxyglucose uptake in a thyroid nodule is seen as a coincidental finding in some patients, and, although not specific, it is associated with an increased risk of thyroid malignancy

Comparison of imaging modalities for evaluating thyroid nodules

	Strengths	Weaknesses
Ultrasonography	High sensitivity; useful for guiding fine needle aspiration cytology; no radiation exposure; widespread availability and low cost	Low specificity
Computed tomography	Evaluation of substernal disease; staging of metastatic disease; widespread availability	Moderate radiation exposure; limited sensitivity for intrathyroidal lesions
Magnetic resonance imaging	Local staging of malignancy; no radiation exposure	Limited sensitivity; less availability and relatively higher cost
Radionuclide scintigraphy	Cheap; useful for confirming benign disease if thyroid stimulating hormone level is suppressed	Poor sensitivity; low radiation exposure; may be unhelpful if thyroid stimulating hormone level is normal
PET-CT	High sensitivity; high negative predictive value may help reduce unnecessary surgery	Low specificity; high cost and limited availability; high radiation exposure

PET-CT= fused positron emission tomography and computed tomography.

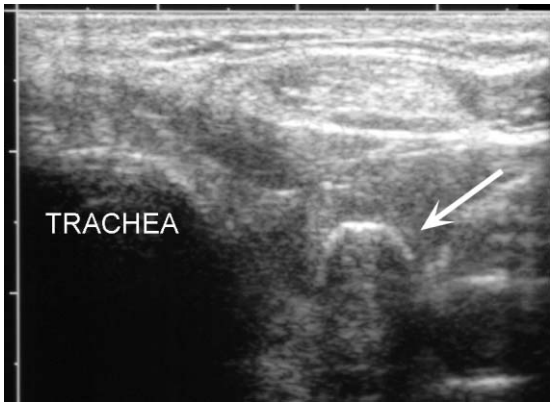

Fig 2 | Axial image from a high resolution ultrasound scan of the thyroid showing the thyroid nodule with peripheral calcification and posterior acoustic shadowing (arrow). This is an unusual appearance of thyroid malignancy and is more usually seen in benign nodules. Microcalcification in a nodule (not seen in this case) would be much more suspicious

(up to 35% of solitary thyroid nodules showing uptake are malignant), and further evaluation with ultrasonography and fine needle aspiration cytology is essential.[8] Although the positive predictive value is relatively low, PET-CT scanning has a reported negative predictive value of 100%.[9] This could potentially help to reduce, by up to two thirds, the number of unnecessary thyroidectomies performed for benign disease in patients with indeterminate cytology.[9]

In the UK the use of PET-CT scanning is limited by availability and strict referral criteria, but the cost savings from reducing unnecessary surgery would offset the high cost of the investigation. Once the technique becomes more widely available, this may be a valuable future use.

LEARNING POINTS

Thyroid nodules are very common, and the overwhelming majority are benign

Thyroid nodules may be coincidentally detected as a result of the increasing use of neck imaging

No imaging modality can reliably differentiate between benign and malignant thyroid nodules, but ultrasonography is the best technique for evaluating nodules and triaging those that require histological evaluation

Ultrasound guided fine needle aspiration cytology is accurate, cheap, and safe in most cases, but local resources vary

Metabolically active thyroid nodules detected on fused positron emission tomography and computed tomography (PET-CT) are associated with a 1 in 3 chance of malignancy and should be further evaluated

PET-CT may have a future role in reducing unnecessary surgery in patients with indeterminate cytology because of its high negative predictive value

Computed tomography and magnetic resonance imaging

Cross sectional imaging with CT or MRI is not particular sensitive for detecting intrathyroidal lesions and cannot reliably distinguish between benign and malignant nodules. As a result, each has a limited role in the evaluation of incidentally discovered thyroid nodules but may be valuable in the staging of patients with proved thyroid malignancy. Although cross sectional imaging is not part of routine staging for thyroid cancer, it is useful for assessing substernal thyroid masses and for evaluating local extension, cervical lymphadenopathy, and distant metastatic disease.

Outcome

Before surgery for the patient's lung cancer, ultrasonography confirmed the presence of a solitary thyroid nodule that had irregular margins and peripheral calcification (fig 2). Ultrasound guided fine needle aspiration cytology was performed at the same time, and cytology was suspicious for malignancy. The patient went on to have curative resection of his lung carcinoma and thyroidectomy with radioiodine ablation for follicular thyroid carcinoma. He has remained disease-free to date, with no evidence of recurrence of either tumour.

Contributors: AFS had the original idea. AFS and GG selected the patient. CNP and AFS searched the literature. CNP wrote the paper. AFS and GG reviewed and edited the paper and reassessed the literature. AFS is the guarantor.
Funding: None.
Competing interests: None declared.
Provenance and peer review: Commissioned; externally peer reviewed.
Patient consent not required (patient anonymised, dead, or hypothetical).

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