

# *best tests*

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**Osteoporotic fracture prevention  
a new approach**

**Acute Monoarthritis**

**Monitoring Response to Drug Treatment**

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Professor Murray Tilyard

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**Web**

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**1 Osteoporotic fracture prevention: a new approach**

An introduction to FRAX, a new WHO endorsed approach for the prevention of osteoporotic fractures.

**7 Acute monoarthritis: differentiating between crystals, sepsis and trauma**

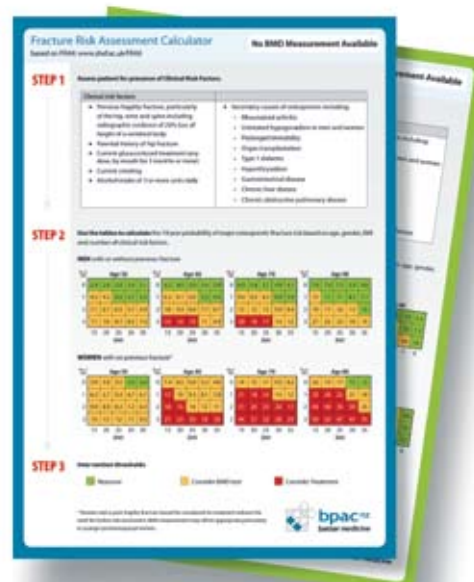
Acute monoarthritis is characterised by pain and swelling of a single joint. There are a number of causes, with crystals, trauma and infection being the most common. This article looks at the laboratory tests required when investigating acute monoarthritis.

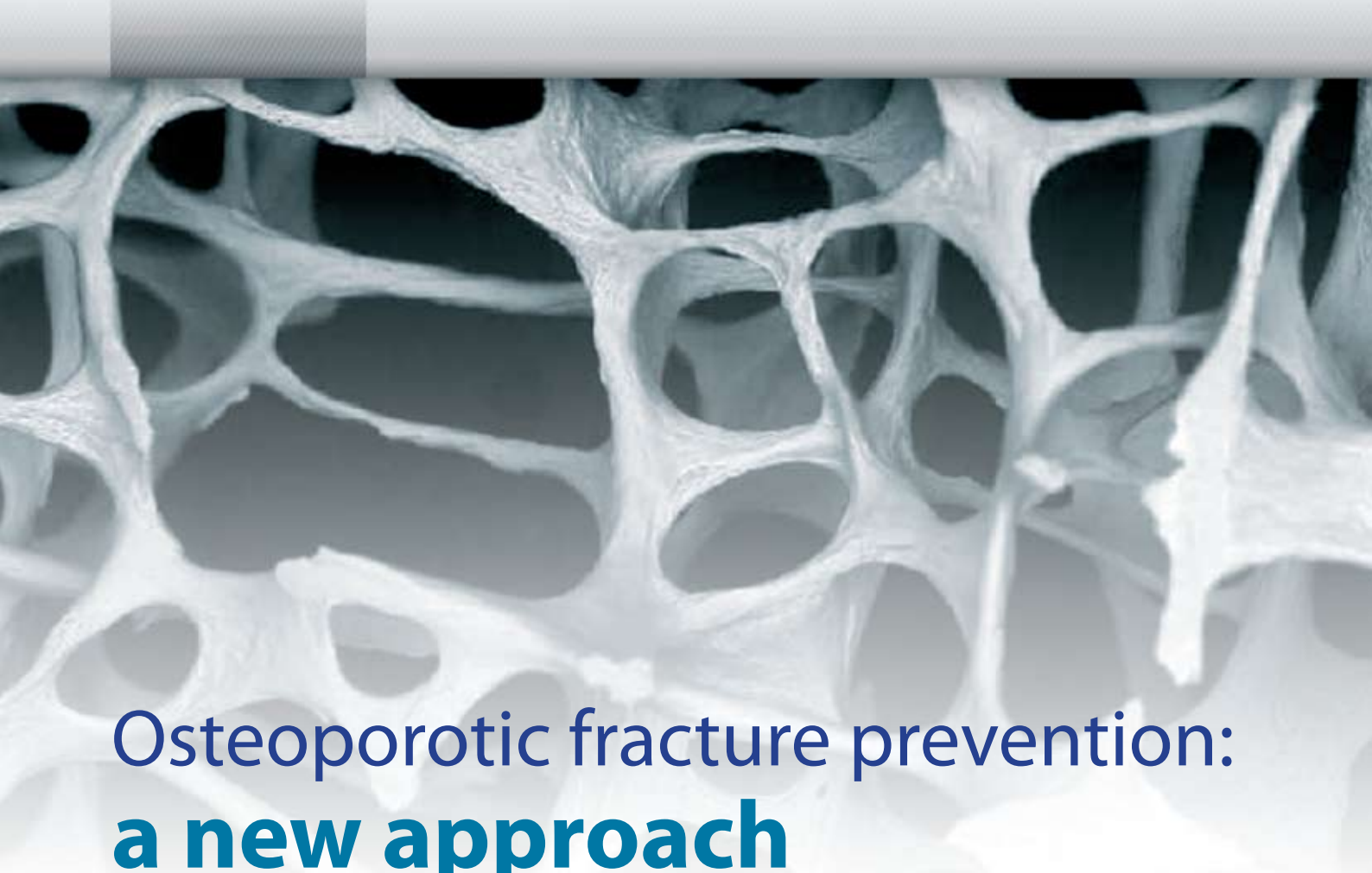
**10 Monitoring Response to Drug Treatment**

Clinicians are frequently asked to monitor the effects of drug treatment with the objective of ensuring safe and effective therapy. In this article we present the first in a series which focus on optimal monitoring of drug treatment.

**Fracture Risk Assessment Calculator**

Pullout reference tool for calculating risk of major osteoporotic fracture.





# Osteoporotic fracture prevention: a new approach

## Background

This article introduces a new approach to the prevention of osteoporotic fractures. Up to now the emphasis has been on trying to detect osteoporosis, at an early phase of the disease, in time to give effective therapy. However, osteoporotic fracture prevention is going through a quiet revolution regarding who to screen, who to test and who to treat. Underlying this change is a paradigm shift away from making a diagnosis of osteoporosis to a multi-factorial assessment of osteoporotic fracture risk. The model used for this is endorsed by WHO and is called FRAX.

This change can be compared to the evolution in the approach to management of cardiovascular disease over the last 30 years. During this period there has been a shift of emphasis from the diagnosis of a disease, such as ischaemic heart disease, to the current approach to prevention which focuses on multi-factorial analysis of cardiovascular risk, with recommendations of lifestyle and therapeutic interventions depending on the severity of risk of an adverse event.

## Relying on bone mineral density is not enough

Screening for and treating osteoporosis has, until recently, been the only way to try and reduce fragility fractures. Diagnosing osteoporosis requires assessment of bone mineral density (BMD) with a DEXA.

There is a strong association between low BMD and fracture risk. However **the majority of fragility fractures (in postmenopausal women) occur in those without osteoporosis** (T-score  $<-2.5$ ). For example the proportion of women aged 50 diagnosed with osteoporosis is about 5%, however approximately 20% will suffer from a fragility fracture in the next 10 years. It is apparent that measurement of BMD alone only captures a minority of the fracture risk.

The cause of fragility fracture is increasingly recognised as multi-factorial, with risk factors that act independently of BMD and loss of bone with age. For example between the ages of 50-90 years the annual incidence of hip fracture would be expected to increase fourfold if based on age-related bone loss alone. But other risk factors make the actual increase closer to 30-fold.

### Improving assessment of fracture risk with FRAX

The WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield has developed the FRAX tool to calculate the probability of an osteoporotic fracture based on a variety of established clinical risk factors, using either a body mass index (BMI) or a BMD T-score. The major advantage of FRAX is that it provides a better predictor of fragility fracture risk than BMD alone and hopefully will lead to significant reduction in osteoporotic fractures.

The FRAX online calculator which is freely available at [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX) (Figure 1) allows the calculation of an individual's probability of a fragility fracture. The same calculator is used if BMD is not available. The BMD box is simply left blank.

Risk tables (similar to cardiovascular risk tables) developed from the FRAX tool, are also available at the same site and have been included with this document as a reference tool.

The online tool provides a more accurate estimate than the paper based tables as it gives weightings to the different clinical risk factors according their predictive strength. In general, smoking and alcohol are weak risk factors, glucocorticoid use and secondary causes of osteoporosis are moderate risk factors, and a prior fracture (in men) and a parental history of hip fracture are strong risk factors. The paper based risk tables don't weight the risk factors instead an average probability is provided.

Figure 1: FRAX online calculator (see [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX))

The screenshot shows the FRAX online calculator interface. At the top, it displays 'Country : UK' and a 'Name / ID' field. A link for 'About the risk factors' is also present. The main section is titled 'Questionnaire:' and contains 12 numbered questions with input fields and radio buttons. The questions are: 1. Age (60), 2. Sex (Male), 3. Weight (85 kg), 4. Height (180 cm), 5. Previous fracture (No), 6. Parent fractured hip (No), 7. Current smoking (No), 8. Glucocorticoids (No), 9. Rheumatoid arthritis (Yes), 10. Secondary osteoporosis (No), 11. Alcohol 3 more units per day (Yes), and 12. Femoral neck BMD (blank). There are 'Clear' and 'Calculate' buttons. A red summary box on the right shows 'BMI 26.2' and 'The ten year probability of fracture (%) without BMD'. It contains a table with two rows: 'Major osteoporotic' with a value of 6.3, and 'Hip fracture' with a value of 1.1. A 'View NOGG Guidance' button is located below the table.

**Country : UK**      **Name / ID :**       [About the risk factors](#) ⓘ

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth  
 Age:       Date of birth: Y:  M:  D:

2. Sex       Male     Female

3. Weight (kg)     

4. Height (cm)     

5. Previous fracture       No     Yes

6. Parent fractured hip       No     Yes

7. Current smoking       No     Yes

8. Glucocorticoids       No     Yes

9. Rheumatoid arthritis       No     Yes

10. Secondary osteoporosis       No     Yes

11. Alcohol 3 more units per day       No     Yes

12. Femoral neck BMD

**BMI 26.2**

**The ten year probability of fracture (%)**

**without BMD**

■ Major osteoporotic	<b>6.3</b>
■ Hip fracture	<b>1.1</b>

# How does FRAX work?

## Assessing an individual patient's risk where there is no BMD measurement

To assess an individual patient's risk, where there is no BMD measurement, the probability of a fragility fracture is calculated according to age, gender, BMI and the number of clinical risk factors present. (Note BMI is used as a surrogate for BMD as while a low BMI is a significant risk factor for hip fracture, its value in predicting other fractures is less than a BMD T-score at the femoral neck.)

The clinical risk factors for assessment of fragility fracture probability using FRAX are shown in Table 1 below.

Some clinical risk factors are so strong that even if the BMD is normal osteoporotic treatment is advised e.g. prior fragility fracture.

**Table 1:** Clinical risk factors for assessment of fragility fracture probability

Clinical risk factors	
<ul style="list-style-type: none"><li>▪ Age</li><li>▪ Sex</li><li>▪ Low body mass index</li><li>▪ Previous fragility fracture, particularly of the hip, wrist and spine including radiographic evidence of 20% loss of height of a vertebral body</li><li>▪ Parental history of hip fracture</li><li>▪ Current glucocorticoid treatment (any dose, by mouth for 3 months or more)</li><li>▪ Current smoking</li><li>▪ Alcohol intake of 3 or more units daily</li></ul>	<ul style="list-style-type: none"><li>▪ Secondary causes of osteoporosis including:<ul style="list-style-type: none"><li>• Rheumatoid arthritis</li><li>• Untreated hypogonadism in men and women</li><li>• Prolonged immobility</li><li>• Organ transplantation</li><li>• Type 1 diabetes</li><li>• Hyperthyroidism</li><li>• Gastrointestinal disease</li><li>• Chronic liver disease</li><li>• Chronic obstructive pulmonary disease</li></ul></li></ul>

### Example 1: Assessing an individual patients risk where there is no BMD measurement

Using risk tables calculated using the FRAX tool, the probabilities of a fragility fracture can be estimated based on gender, age, BMI and the number of additional clinical risk factors. Note: additional clinical risk factors refers to those other than gender, age, and BMI.

For example: a woman aged 60 with a BMI of 20 and two additional clinical risk factors would have a probability of a having major osteoporotic fracture of 15% in the next ten years.

#### FRAX Risk Tables: WOMEN with no previous fracture

No. of CRFs	Age 50					Age 60					Age 70					Age 80				
0	3.9	3.6	3.5	3.0	2.6	7.4	6.5	6.0	5.2	4.6	14	12	11	9.5	8.2	22	19	17	15	12
1	6.3	5.7	5.4	4.7	4.1	12	10	9.3	8.1	7.0	21	18	16	14	12	32	28	25	21	18
2	9.9	8.8	8.2	7.2	6.3	18	15	14	12	11	31	26	23	20	17	44	40	35	30	25
3	15	13	12	11	9.5	27	23	20	18	16	44	37	32	28	24	56	52	47	41	35
	15	20	25	30	35	15	20	25	30	35	15	20	25	30	35	15	20	25	30	35
	BMI					BMI					BMI					BMI				

### Example 2: Assessing an individual patients risk where there is a BMD measurement

To assess an individual patient’s risk where there is a BMD measurement the probability of a fragility fracture is calculated as above except that the BMD T-score at the femoral neck is substituted for BMI.

For example: a woman aged 70 with a BMD of -4 and two additional clinical risk factors would have a probability of a having major osteoporotic fracture of 54% in the next ten years.

#### FRAX Risk Tables: WOMEN with no previous fracture

No. of CRFs	Age 50					Age 60					Age 70					Age 80				
1	26	13	7.6	5.5	4.8	32	18	11	8.0	6.8	41	25	15	11	8.9	45	29	19	13	9.6
2	37	19	11	8.1	7.0	44	25	16	12	9.8	54	34	21	15	12	57	40	26	18	13
3	51	27	16	12	10	58	35	23	16	14	67	45	29	20	16	67	51	35	25	17
	-4	-3	-2	-1	0	-4	-3	-2	-1	0	-4	-3	-2	-1	0	-4	-3	-2	-1	0
	BMD					BMD					BMD					BMD				

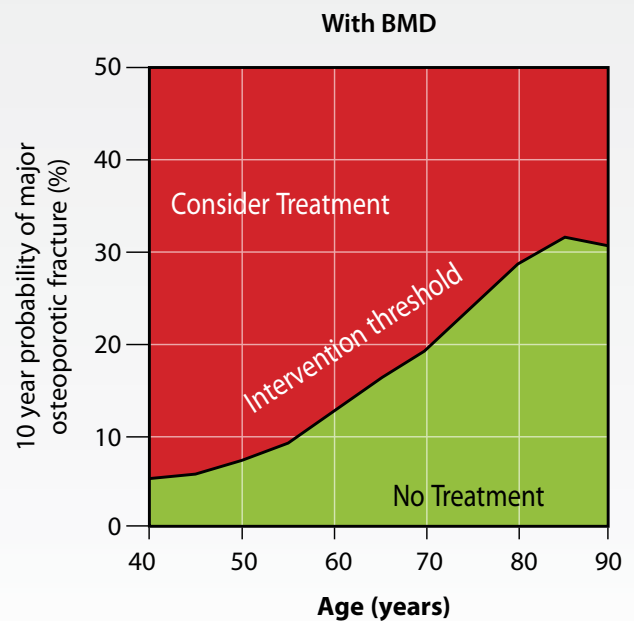
The use of FRAX does not exclude clinical judgement. Some patients at risk of fragility fracture can not be accurately assessed using the FRAX model, for example women with anorexia nervosa, and will need to be identified opportunistically.

# Intervention thresholds

Intervention thresholds have been suggested by the National Osteoporosis Guideline Group (NOGG) for the UK.

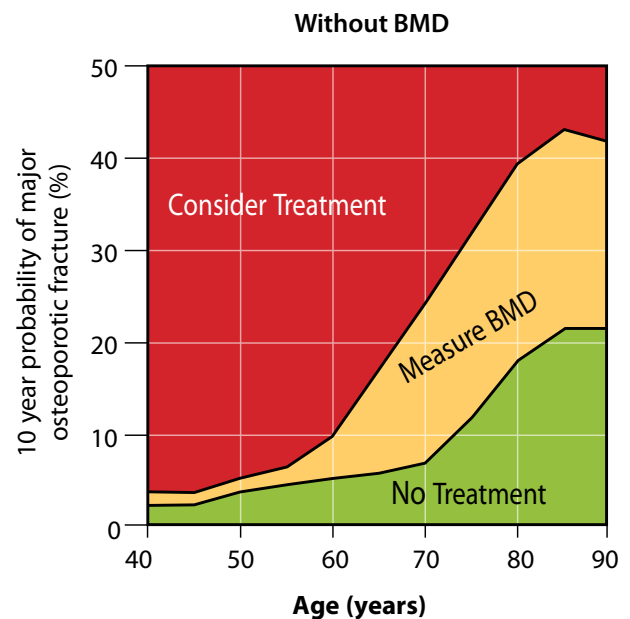
## Assessment with BMD

Where the risk has been estimated using BMD an intervention threshold has been suggested. This threshold is equivalent to that associated with a prior fracture, and therefore rises with age.



## Assessment without BMD

Where the risk has been calculated using BMI an intermediate category (orange) is used indicating that probabilities lie on the border of the intervention threshold. The NOGG recommend that in this instance a BMD T-score is obtained to better characterise the risk.



These intervention thresholds have been incorporated into risk tables in a similar way to the colour coding of the New Zealand cardiovascular risk tables.

- Green denotes that an individual's risk lies below the intervention threshold i.e. treatment is not indicated
- Yellow denotes that probabilities lie between in an intermediate zone between reassurance and treatment and that a BMD should be considered to improve the estimate of fracture risk.
- Red denotes the fracture probability is consistently above the upper assessment threshold, irrespective of the mix of clinical risk factors, so that treatment can generally be strongly recommended.

### FRAX risk tables with intervention thresholds

This is an example. For the full tables see the pull out section.

#### WOMEN with no previous fracture

No. of CRFs	Age 50					No. of CRFs	Age 60					No. of CRFs	Age 70					No. of CRFs	Age 80				
0	3.9	3.6	3.5	3.0	2.6	0	7.4	6.5	6.0	5.2	4.6	0	14	12	11	9.5	8.2	0	22	19	17	15	12
1	6.3	5.7	5.4	4.7	4.1	1	12	10	9.3	8.1	7.0	1	21	18	16	14	12	1	32	28	25	21	18
2	9.9	8.8	8.2	7.2	6.3	2	18	15	14	12	11	2	31	26	23	20	17	2	44	40	35	30	25
3	15	13	12	11	9.5	3	27	23	20	18	16	3	44	37	32	28	24	3	56	52	47	41	35
	15	20	25	30	35		15	20	25	30	35		15	20	25	30	35		15	20	25	30	35
	BMI						BMI						BMI						BMI				

<span style="display: inline-block; width: 15px; height: 15px; background-color: #90EE90; border: 1px solid black; margin-right: 5px;"></span> Reassure	<span style="display: inline-block; width: 15px; height: 15px; background-color: #FFD700; border: 1px solid black; margin-right: 5px;"></span> Consider BMD Test	<span style="display: inline-block; width: 15px; height: 15px; background-color: #FF0000; border: 1px solid black; margin-right: 5px;"></span> Consider Treatment
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### Interventions thresholds in the New Zealand context

The major advantage of FRAX is that it provides a better predictor of fragility fracture risk than BMD alone.

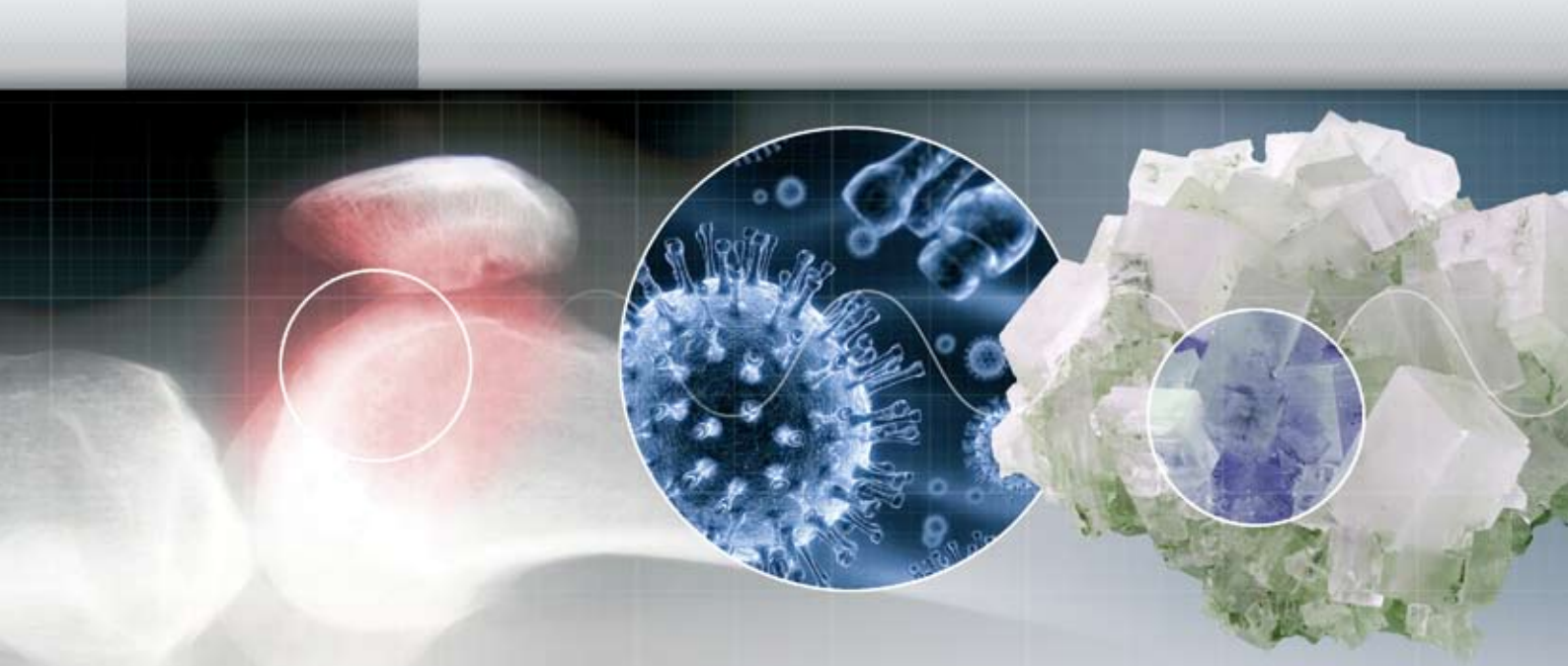
Given the limited access to DEXA in NZ the FRAX tool offers a practical way for GPs to accurately assess a patient's risk of fragility fracture. This provides the opportunity to reassure patients at low risk, and target the use of DEXA to those at high risk.

For more information on the prevention of osteoporotic fracture see BPJ 17. For further information about the FRAX tool, refer to: [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)

#### References

1. Osteoporosis: Clinical guideline for prevention and treatment, Executive Summary. Available from: [http://www.shef.ac.uk/NOGG/NOGG\\_Executive\\_Summary.pdf](http://www.shef.ac.uk/NOGG/NOGG_Executive_Summary.pdf)
2. NOGG. Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Available from: [http://www.shef.ac.uk/NOGG/NOGG\\_Pocket\\_Guide\\_for\\_Healthcare\\_Professionals.pdf](http://www.shef.ac.uk/NOGG/NOGG_Pocket_Guide_for_Healthcare_Professionals.pdf)

SEM pictures of bone are from the Bone Research Society, [www.brsoc.org.uk](http://www.brsoc.org.uk)



# Acute monoarthritis: differentiating between crystals, sepsis and trauma

Acute monoarthritis is characterised by pain and swelling of a single joint. There are a number of causes, with crystals, trauma and infection being the most common. Bursitis and tendinitis can present in a similar manner so it is important to establish that the problem is within the joint.<sup>1</sup>

## Septic arthritis

The most important diagnosis to exclude is septic (infectious) arthritis, which if inadequately treated may cause permanent joint damage, and death in up to 11% of patients.

Septic arthritis usually affects single large joints, most frequently the knee. The patient often presents with systemic symptoms of sepsis (e.g., fever and malaise), as well as the rapid onset of swelling, warmth and local pain in the involved joint. Redness around the joint is an important clue, limiting diagnosis to either infectious or crystal-induced arthritis.

There is increased risk of septic arthritis in those who are older (especially > 80 years), have skin infections, recent joint surgery, a hip or knee prosthesis, rheumatoid arthritis, diabetes mellitus, are immunosuppressed or IV drug users.<sup>2</sup>

*Staphylococcus aureus* causes most septic arthritis in adults. Gonococcal infections are a rare but important cause of septic arthritis in sexually active young adults although there is often less associated morbidity due to less articular damage. Occasionally monoarthritis may be caused by other pathogens.

If the patient has septic arthritis admission is usually required for drainage of the joint, management of sepsis syndrome and IV antibiotics.

## Crystal-induced arthritis

Gout is caused by precipitation of monosodium urate crystals in the synovial fluid. Gout predominantly affects the first metatarsophalangeal joints, midfoot, ankles or knees. For further information see BPJ 8.<sup>3</sup>

Pseudogout is caused by precipitation of calcium pyrophosphate dihydrate crystals and affects mainly the knees and wrists, but can occur in the first metatarsophalangeal and other joints as well. Rarely, calcium oxalate, apatite and lipid crystals may be found.

## Trauma-induced arthritis

A painful swollen joint can be caused by joint trauma. It is often associated with mild-to-moderate joint swelling in the absence of erythema, and the pain is characteristically exacerbated on movement and relieved at rest. The pain of traumatic arthritis is felt within seconds to minutes of the trauma, in contrast to the pain of infectious and crystal-induced arthritis which often develops over hours.

## Joint aspiration

Although most resources suggest joint aspiration (arthrocentesis) is required in most patients with monoarthritis to confirm etiology, it is not always performed. However, if septic arthritis is suspected on clinical grounds, patients are usually referred to secondary care for joint aspiration and empirical IV antibiotics whilst awaiting culture results.

Joint aspiration in primary care depends on the skill and experience of the practitioner and availability of local secondary services. When performing joint aspiration aseptic technique is crucial to avoid introduction of infection.

Generally joint aspiration will not be required if a patient has classic signs and symptoms of gout, in which case the condition can be treated on clinical grounds.

## Laboratory tests

### Analysis of synovial fluid

Synovial fluid analysis includes cell count, WBC differential, Gram stain, culture and crystal examination. Testing synovial fluid for protein, rheumatoid factor and uric acid does not aid diagnosis.<sup>2</sup>

### Blood tests

Blood tests are rarely diagnostic in the acute phase.

### CBC and CRP

An elevated white blood count and increased CRP can occur in septic arthritis, but may also be present in gout and pseudogout. CBC and CRP have low specificity especially in children, the immunosuppressed and elderly people.

### Serum uric acid

Serum uric acid levels are often normal in acute gout and elevated uric acid is a non-specific marker for gout. People with gout can also have septic arthritis. For further guidance on uric acid levels see BPJ 8.<sup>3</sup>

### Blood cultures

Blood cultures should be taken when septic arthritis is suspected. If septic arthritis is suspected, the patient should be referred for orthopaedic opinion. Blood cultures can be collected while patient is with GP or during orthopedic assessment. A summary of tests that may be performed is provided in Table 1.

### Specimen criteria

Criteria for collection tubes vary between laboratories. It is best to check the collection guide of the local laboratory.

## References

1. Palmer T, Toombs J. Managing joint pain in primary care. *J Am Board Fam Pract* 2004;17:S32–42.
2. Siva C, Velazquez C, Mody A et al. Diagnosing Acute Monoarthritis in Adults: A Practical Approach for the Family Physician *Am Fam Physician* 2003;68:83-90
3. BPAC. Best practice Journal. Treatment of Gout: hit the target. *BPJ* 2007, issue 8. Available from [www.bpac.org.nz](http://www.bpac.org.nz) keyword "gout"
4. Cibere J. *Rheumatology*;4. Acute monoarthritis. *CMAJ*;162(11):1577-83.

**Table1:** Summary of tests that may be indicated when investigating acute monoarthritis<sup>4</sup>

Possible diagnosis	Cause	History and physical examination	Synovial fluid analysis	Common pitfalls
<b>Septic arthritis</b>	<p>Bacteria – most often staphylococcal, occasionally gonococcal in young sexually active people</p> <p>Other bacteria</p> <p>Fungi</p> <p>Viruses</p>	<p>Severe joint pain and tenderness</p> <p>Heat, marked swelling</p> <p>Redness</p> <p>Patient unable to move joint; often refuses passive movement</p> <p>Patient often unable to tolerate any pressure on joint</p>	<p>Opaque</p> <p>Leukocyte count elevated</p> <p>Granulocytes &gt; 85%</p> <p>Culture positive</p>	<p>Culture may be negative if patient previously treated with antibiotics</p> <p>CBC - elevated white count is suggestive of infection, but may also be present in gout and pseudogout. It is not always a reliable sign of septic arthritis, particularly in children</p> <p>CRP - is generally higher in septic arthritis than in gout, but is not diagnostic. It is a useful marker of response to treatment. Inflammatory response may be blunted in immunocompromised patient</p> <p>Blood culture – should be taken when septic arthritis is suspected</p>
<b>Crystal-induced arthritis</b>	<p>Monosodium urate crystals (gout)</p> <p>Calcium pyrophosphate crystals (pseudogout)</p> <p>Apatite crystals</p> <p>Calcium oxalate crystals</p>	<p>Severe joint pain and tenderness</p> <p>Heat, marked swelling</p> <p>Redness</p> <p>Patient unable to move joint; often refuses passive movement</p> <p>Patient often unable to tolerate any pressure on joint</p>	<p>Opaque</p> <p>Leukocyte count elevated</p> <p>Granulocytes &gt; 85%</p> <p>Culture positive</p>	<p>Patient may have concomitant infectious arthritis with positive culture</p> <p>Uric acid – is non specific as hyperuricaemia is reasonably common general population. Uric acid levels may be normal during attack, therefore is a nonspecific marker.</p>
<b>Trauma-induced arthritis</b>	<p>Fracture</p> <p>Internal derangement</p> <p>Herarthrosis</p>	<p>Joint tenderness on movement</p> <p>Warmth, mild-to-moderate swelling</p> <p>No redness</p> <p>Pain worse with activity</p> <p>History of trauma; onset of pain within minutes of trauma</p>	<p>Fluid transparent or blood stained</p>	<p>History of trauma may not be elicited with osteoporosis</p>



# Monitoring Response to Drug Treatment

## Introduction

Clinicians are frequently asked to monitor the effects of drug treatment with the objective of ensuring safe and effective therapy. In this issue we present the first in a series of articles which focus on optimal monitoring of drug treatment.

Monitoring takes many forms and there is evidence that in many situations it is done inappropriately (too much or too little or at the wrong time) or not targeted at specific parameters that are clinically useful. A New Zealand study showed that over 50% of serum digoxin concentrations were not taken at the correct time to allow meaningful interpretation of the result, and 5% of the measurements led to inappropriate dose adjustments.<sup>1</sup> Other studies have shown excessive and unnecessary monitoring of antiepileptic drug concentrations and we now know that routine monitoring of CK and liver function tests in people taking statins is unnecessary. On the other hand, failure to check the CBC in a person taking clozapine or not attaining therapeutic drug concentrations in a person taking lithium can have severe consequences. Monitoring is also much more than objective laboratory testing as it often includes the participation of the patient by their informed reporting of signals of clinical response or adverse drug reactions.

Despite comprising at least 30 – 40% of all blood tests in general practice,<sup>2</sup> monitoring is relatively poorly studied and is often associated with non-specific and even vague guidelines. Improvements in monitoring by clinicians and patients are likely to improve benefits, reduce adverse events and reduce costs.

Some examples of monitoring include:

- Monitoring laboratory tests (e.g. LFTs, CBC) to check for early signs of an adverse drug reaction.  
*Objective monitoring for adverse effects.*
- Monitoring drug concentrations (e.g. digoxin, lithium) to attain therapeutic response without dose related toxicity, or to confirm compliance.
- Monitoring for signs or symptoms which may be indicative of a side effect or adverse drug reaction, e.g. delirium or constipation with a tricyclic antidepressant, or muscle pain with a statin.  
*Subjective monitoring for adverse effects*
- Monitoring biochemical markers as a response to treatment and/or toxicity, e.g. lipid profile with statins, INR with warfarin, TSH with thyroxine.
- Monitoring clinical response to treatment, e.g. preventers and relievers in asthma therapy.

## “Know the abnormality that you are going to follow during treatment. Pick something you can measure.”

Meador C. A Little Book of Doctors' Rules.

Lyons: IARC Press, 1999

This article provides a general introduction to some of the principles of monitoring the response to drug therapy in order to ensure optimum response without significant adverse effects. In future issues suggested monitoring strategies will be described for specific drug and therapeutic categories.

### Monitoring Strategies

An overriding principle of monitoring is that there should be justification and some degree of assurance that the practice will actually meet the objectives the test. Furthermore, the test must be correctly performed, e.g. in the right time frame, and be interpreted correctly to be meaningful.

Monitoring Strategy (adapted from Glasziou et al<sup>2</sup>)

- Is the test a good predictor of relevant clinical outcomes or adverse effects?  
*Will routine monitoring of CBC detect drug-induced agranulocytosis? Are clinical symptoms more reliable?*
- Can the test detect changes in risk early?  
*Is the CBC likely to pick-up on a downward trend in the blood count as an early sign of the problems?*
- Is there an optimum interval for monitoring?  
*Is the blood dyscrasia more likely to occur within a certain timeframe that may dictate the duration of monitoring?*
- Is random testing useful or can it be made acceptable by repeated measurements?  
*What is the value of a one-off CBC? Is there any value in monitoring more frequently?*
- Is the test accessible and acceptable to patients and cost effective for health care providers?  
*If checking the CBC is very unlikely to detect an outcome is it worthwhile?*

- Are there any additional risk factors which provide further justification for testing?

*Will a history of blood dyscrasias or concurrent use of a medicine with a similar adverse effect profile provide justification to change the monitoring parameters?*

### Objective monitoring for adverse effects.

Many drugs have laboratory monitoring recommendations mentioned in their data sheets. However, if the above criteria are applied the supporting evidence for many monitoring schedules is relatively weak. In addition, vague statements such as periodic checking of liver function or occasional checking of electrolytes are generally unhelpful as they lack precise guidance.

The antithyroid drug carbimazole can cause agranulocytosis but this is relatively rare and it usually occurs rapidly without an indicative downward trend in the blood count. Therefore a routine CBC every few months or random testing are very unlikely to identify the event. Early signs of infection such as a sore throat or fever are much more reliable predictors of agranulocytosis so the emphasis should be placed on educating the patient on early warning signs rather than blood tests.

In contrast clozapine induced agranulocytosis is much more common, usually occurs early in treatment and can often be detected early by regular blood tests which can show a downward trend in the neutrophil count. More is known about the “natural history” of clozapine induced agranulocytosis which justifies the rigorous and specific monitoring regimen.

If the effect is relatively common, such as hypothyroidism induced by lithium, regular measurement of TSH is justified as the condition can be detected before significant symptoms appear allowing the introduction of thyroid replacement therapy or an alternative drug.

## Monitoring drug concentrations

Therapeutic drug monitoring (TDM) by measuring serum concentrations is useful for a relatively small range of drugs that meet specific criteria. For most drugs, the serum concentration does not correlate well with therapeutic effect and treatment is guided solely by clinical response. For drugs that do have a good correlation between concentration and effect, TDM can assist monitoring and guide dose adjustment in addition to assessing clinical response.

Generally, criteria for TDM are as follows:

- There is a narrow range between a sub-therapeutic serum drug concentration (SDC) and a toxic SDC. This is referred to as the drug's therapeutic range.
- There is a predictable relationship between the SDC and therapeutic or toxic effects.
- The measurement of SDC must be better or enhance other methods of monitoring.
- There is an unpredictable relationship between the dose administered and the SDC.
- There is a suitable assay for the drug.

Lithium is a good example where TDM is useful if not essential for optimal treatment. Serum lithium concentrations are clearly related to clinical effect; if the concentration is too low a clinical response is unlikely but if the concentration is too high the risk of toxicity is increased. The range that includes clinical response without toxicity is the therapeutic concentration range. Unfortunately, due to interindividual variability in drug handling, it is not possible to accurately predict what lithium concentration will be attained from any given dose. Therefore TDM can be used to titrate the initial dose to give a target drug concentration and the dose can be further adjusted according to clinical response or adverse effects. If response is sub-optimal, the SDC may guide the magnitude of a dose increase without significant risk of adverse effects. Subsequently, measurement of SDC can be used to check compliance or assess the impact of drug interactions that may change lithium concentrations. Other drugs which are candidates for TDM include digoxin, some antiepileptic drugs, theophylline and some antibiotics. In future issues specific monitoring strategies will be discussed.

## Subjective monitoring of adverse effects

Patients and carers should be informed about what to look for and report early signs of possible adverse effects. This has to be done in the context of explaining the benefits of treatment.

A person taking a statin should be informed to report myalgia especially if this is of sudden onset, is severe or worsens or appears with an increase in dose. A subsequent check of the CK may indicate the need to reduce the dose or consider alternative treatment. In this case subjective reporting of symptoms may indicate the potential value of an objective laboratory test.

The situation with statins is well known but it should be realised that all drugs have adverse effects that are potentially preventable if the early warning signs are recognised. Many adverse effects are very predictable as they are dose related and an extension of the drug's pharmacological effect.

Advice directly to the patient about what to look for, or a simple note in the patient's records, can be valuable in detecting adverse effects at an early stage and possibly preventing more serious consequences. For example, if a patient in residential care is prescribed haloperidol for psychoses and agitation, a flag can be made in the patient's notes to "monitor" for common adverse effects such as constipation and hypotension. Early identification of these effects can reduce drug related morbidity.

Some examples of subjective monitoring parameters with possible causes and action points are given in Table 1. This will be expanded in future issues.

### References:

1. Sidwell A, Barclay M, Begg E, Moore G. Digoxin therapeutic monitoring; An audit and review. *NZMJ*;2003;116:U704
2. Glasziou P, Irwig L, Mant D. Monitoring in chronic disease: a rational approach. *BMJ* 2005;330:644-648

**Table 1:** Some examples of subjective monitoring parameters with possible causes and action points

Drug or drug class	Monitoring parameter, possible cause and action.
<b>Drugs causing leucopenia</b>	Infection, sore throat, fever <i>Check CBC</i>
<b>Drugs with anticholinergic effects</b>	Constipation, urinary retention, drowsiness <i>Reduce doses or modify drug treatment</i>
<b>Anihypertensives</b>	Postural hypotension, dizziness; especially on diuretics. <i>Modify doses or drugs, check electrolytes</i>
<b>Serotonin Re-uptake Inhibitors</b>	Agitation and restlessness in early treatment. Dose may be too high or drug unsuitable. <i>Reduce dose or change drug. Review diagnosis.</i>
<b>NSAIDs</b>	Darkened stools may indicate GI bleeding. <i>Check for blood in stools. CBC.</i>
<b>Digoxin</b>	Changes in vision, especially colour vision may indicate digoxin toxicity or hypokalaemia <i>Check serum digoxin concentration, renal function and electrolytes</i>
<b>Phenytoin</b>	Ataxia may indicate toxicity due to high blood concentrations. <i>Check serum concentration of phenytoin and compliance</i>
<b>Amiodarone</b>	Intractable cough – may indicate pneumonitis <i>Chest X-ray</i>

