

# Myeloma

*Synonyms: multiple myeloma, plasma cell neoplasm, myelomatosis*

## What is myeloma?

In myeloma there is malignant proliferation of plasma cells. This produces diffuse bone marrow infiltration causing bone destruction and bone marrow failure. There is also overproduction of a monoclonal antibody (immunoglobulin or 'paraprotein') by the malignant plasma cells, detectable in serum and/or urine. It is also characterised by osteolytic bone lesions, renal disease and immunodeficiency.

Myelomas are subclassified by the type of antibody they produce. Immunoglobulin G (IgG) myeloma is the most common type.

Almost all patients with myeloma evolve from an asymptomatic pre-malignant stage, which is called monoclonal gammopathy of undetermined significance (MGUS). MGUS progresses to myeloma at a rate of 1% per year.

In some patients there is an intermediate asymptomatic but more advanced pre-malignant stage. This is called smouldering (or indolent) myeloma. Smouldering myeloma progresses to myeloma at a rate of 10% per year over the first five years following diagnosis, 3% per year over the following five years, and then at a rate of 1.5% per year. <sup>[1]</sup>

## Causes of myeloma (aetiology) <sup>[2]</sup>

- Neoplastic plasma cells accumulate in the bone marrow and produce a monoclonal protein that causes organ or tissue impairment. It appears to be preceded by [monoclonal gammopathy of undetermined significance \(MGUS\)](#).

- Myeloma arises because of genetic changes that occur during the terminal differentiation of B lymphocytes into plasma cells. In around half of cases, a chromosomal translocation occurs, which places an oncogene into the immunoglobulin heavy chain gene on chromosome 14. The remaining cases are characterised by trisomies of several chromosomes (hyperdiploidy).
- As myeloma develops, further genetic events, such as mutations of the RAS genes, occur. The main RAS genes are KRAS, HRAS and NRAS. They encode proteins that have a role in cell signalling. Mutations of RAS genes cause cells to grow uncontrollably and make cells resistant to some available cancer therapies.
- Imbalanced bone remodelling (increased osteoclast and reduced osteoblast function) causes unopposed osteolysis and hypercalcaemia.
- Plasma cells produce varying amounts of monoclonal free light chains. Light chains in the urine (Bence Jones' proteins) are filtered in the glomeruli and reabsorbed in the proximal tubules. When the light-chain load exceeds the re-absorptive capacity, light chains precipitate out as casts in the distal tubule, causing tubular obstruction and tubulo-interstitial inflammation and acute kidney injury.
- Other causes of renal impairment in patients with myeloma include amyloid deposition, dehydration, hypercalcaemia, hyperviscosity and nephrotoxic drugs.

## How common is myeloma? (Epidemiology) <sup>[3]</sup>

- Multiple myeloma is the second most common haematological cancer. It is responsible for about 2% of all deaths from cancer.
- The incidence in Europe is 4.5–6.0/100,000/year with a mortality rate of 4.1/100,000/year.
- It generally affects older people: median age at presentation is 72 years.
- Myeloma is more common in Afro-Caribbeans than Caucasians, and more common in men.

## Symptoms of myeloma (presentation) [3]

Multiple myeloma can present with a wide variety of symptoms including hypercalcaemia, anaemia, renal impairment and bone pain. Presenting features include:

- Bone pain, particularly backache.
- Pathological fractures.
- Spinal cord/nerve root compression.
- Lethargy (due to anaemia).
- Anorexia.
- Dehydration (due to proximal tubule dysfunction from light-chain precipitation).
- Recurrent bacterial infection.
- Bleeding and/or bruising.
- Features suggesting amyloidosis (eg, cardiac failure, nephrotic syndrome).
- Signs and symptoms of hypercalcaemia (eg, thirst, constipation, nausea, confusion).
- Dizziness, confusion, blurred vision, headaches, epistaxis, cerebrovascular event – due to hyperviscosity.
- Weight loss.

Blood testing may be carried out for other reasons and show:

- Impaired renal function.
- Anaemia: normochromic, normocytic.
- Leukopenia.
- Thrombocytopenia.
- Hypercalcaemia.

- Persistently raised plasma viscosity or erythrocyte sedimentation rate (ESR).

### Important information

If there are signs of spinal cord compression, acute kidney injury or hypercalcaemia, the patient should be admitted to hospital immediately. If a paraprotein is found on routine testing, the patient should be referred to a haematologist or an oncologist. Multidisciplinary care should follow.

## Initial tests for myeloma<sup>[3]</sup>

If symptoms or the results of routine investigations suggest that a patient may have myeloma, then the following investigations should be performed:

- FBC; ESR or plasma viscosity.
- U&Es and creatinine.
- Calcium, albumin, uric acid.
- Serum protein electrophoresis: shows the type of paraprotein.
- Serum free light chain assay.
- Urine protein electrophoresis: looks for the presence of Bence Jones' protein.
- Quantitative immunoglobulin levels (eg, IgG, IgA, IgM levels): non-myelomatous immunoglobulin can be suppressed. The level of the myeloma paraprotein can also be used to assess response to treatment.
- Plain X-ray of symptomatic areas.

It is important to be aware that serum/urine electrophoresis may be negative in up to 5% of people with myeloma, who have the non-secretory form of the disease - if there is a strong clinical suspicion then consider referring even if initial investigations are normal.

The National Institute for Health and Care Excellence (NICE) recommends for people with suspected myeloma:<sup>[4]</sup>

- Use serum protein electrophoresis and serum-free light-chain assay to confirm the presence of a paraprotein indicating possible myeloma or monoclonal gammopathy of undetermined significance (MGUS).
- If serum protein electrophoresis is abnormal, use serum immunofixation to confirm the presence of a paraprotein indicating possible myeloma or MGUS.
- Do not use serum protein electrophoresis, serum immunofixation, serum-free light-chain assay or urine electrophoresis (urine Bence-Jones protein assessment) alone to exclude a diagnosis of myeloma.

#### Editor's note

[Dr Krishna Vakharia](#), 16th October 2023

#### **Suspected cancer: recognition and referral** [5]

NICE has recommended that a person should receive a diagnosis or ruling out of cancer within 28 days of being referred urgently by their GP for suspected cancer.

## Diagnostic tests for myeloma [4]

Further tests in secondary care are then needed to confirm the diagnosis:

- Bone marrow aspirate and trephine biopsy, with plasma cell phenotyping. NICE recommends:
  - When performing a bone marrow aspirate and trephine biopsy to confirm a diagnosis of myeloma, use morphology to determine plasma cell percentage and flow cytometry to determine plasma cell phenotype.
- Immunofixation of serum and urine to confirm and show the subtype of the paraprotein.
- A skeletal survey: NICE recommends imaging to all people with a plasma cell disorder suspected to be myeloma. Whole-body MRI is recommended as first-line imaging. Whole-body low-dose CT can be used as first-line imaging if whole-body MRI is unsuitable.

Tests to estimate tumour burden and prognosis (to be performed by a haematologist):

- Fluorescence in situ hybridisation (FISH) analysis of bone marrow aspirate and trephine biopsy .
- Serum beta-2 microglobulin concentration.
- Serum albumin concentration.
- Quantification of monoclonal proteins in serum and urine.

## Diagnostic criteria

- Because there is a high prevalence of MGUS and because serum protein electrophoresis is frequently carried out, most people who have serum monoclonal proteins detected will not have myeloma but will have MGUS.
- Diagnostic criteria have been set to distinguish MGUS from myeloma.
- The criteria also separate asymptomatic and symptomatic myeloma.
- Asymptomatic myeloma is basically myeloma with no signs of organ or tissue impairment. It was previously referred to as indolent or smouldering myeloma.
- Patients with MGUS and asymptomatic myeloma require monitoring but no immediate treatment. This monitoring should be done in secondary care, unless there is a mutually agreed and resourced enhanced service which allows for it to be done in primary care.
- Patients with symptomatic myeloma need immediate treatment because there is organ impairment.

### International Myeloma Working Group diagnostic criteria

#### Symptomatic myeloma<sup>[1]</sup>

All three criteria needed for diagnosis:

- Monoclonal plasma cells in marrow  $\geq 10\%$ .

- One or more of the following biomarkers of malignancy:
  - $\geq 60\%$  clonal bone marrow plasma cells
  - Involved/uninvolved serum free light chain ratio  $\geq 100$
  - $\geq 1$  focal lesion which is  $\geq 5\text{m}$  in size on MRI studies
- Evidence of myeloma-related organ or tissue impairment:
  - Hypercalcaemia ( $>0.25\text{ mmol/L}$  or  $1\text{ mg/dL}$  higher than the upper limit of normal).
  - Renal insufficiency (creatinine clearance  $< 40\text{ml per min}$  or serum creatinine  $> 177\text{ }\mu\text{mol/L}$  or  $2\text{ mg/dL}$ ).
  - Anaemia: haemoglobin  $<100\text{ g/L}$  or  $20\text{ g}$  below normal range.
  - Lytic bone lesions, osteoporosis, or pathological fractures.

### Smouldering myeloma<sup>[1]</sup>

Both criteria must be met for diagnosis:

- Serum M protein (IgG or IgA)  $\geq 30\text{ g/L}$  or urinary M protein  $\geq 500\text{ mg}$  per 24 hours and/or clonal bone marrow plasma cells 10–60%.
- Absence of myeloma-defining organ or tissue impairment or amyloidosis.

### MGUS<sup>[6]</sup>

All three criteria needed for diagnosis:

- Monoclonal protein  $<30\text{ g/L}$ .
- Monoclonal plasma cells in bone marrow  $<10\%$ .
- Absence of myeloma-related organ or tissue impairment.

## Other investigations

- CT scanning: can be used to detect small lytic lesions that may not be visible on plain X-ray. Consider if bony symptoms are present but plain X-rays are negative. It can show soft tissue disease and can be used to guide biopsy and plan radiotherapy or surgery.

- MRI scanning: can be used to assess soft tissue disease. It is the investigation of choice if spinal cord compression is suspected. It can also show pattern of bone marrow involvement.
- Chromosome analysis: this can be carried out using karyotyping and fluorescence in-situ hybridisation (FISH). This can detect chromosome abnormalities that have been associated with a poorer prognosis. However, how much this information can be used to direct patient management is unclear.
- Beta-2 microglobulin levels: used for staging and to predict prognosis (see below).
- Serum viscosity: should be assessed if there is epistaxis, and when there are neurological symptoms or very high paraprotein levels.

## Differential diagnosis

A monoclonal protein can also be present in:

- MGUS: a paraprotein is found in the blood but there are no other symptoms or signs of myeloma.
- [Amyloid light-chain \(AL\) amyloidosis](#).
- Solitary plasmacytoma.
- [B-cell non-Hodgkin's lymphoma](#) (including [Waldenström's macroglobulinaemia](#)).
- [Chronic lymphocytic leukaemia](#).

## Management of myeloma <sup>[4]</sup>

Myeloma is an incurable disease that is chronic, relapsing and remitting. Treatment is aimed at controlling the disease, prolonging survival and maximising quality of life. Emotional and psychological support for patients, carers and relatives should not be forgotten.

Immediate treatment is currently not recommended for patients with smouldering myeloma. NICE recommends monitoring people with smouldering myeloma every three months for the first five years, and then deciding the frequency of further monitoring based on the long-term stability of the disease.



## Induction for symptomatic myeloma

Management of myeloma is always done in secondary care and patients should never be discharged. If the patient is fit enough, treatment will involve initial induction therapy followed by an autologous stem cell transplant.

Initial options include the following:

- Bortezomib, in combination with dexamethasone +/- thalidomide, for those who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
- Thalidomide, in combination with an alkylating agent and a corticosteroid if high-dose chemotherapy with stem cell transplantation is considered inappropriate. The thalidomide in this regime can be replaced with bortezomib if the patient cannot tolerate thalidomide, or has contraindications to it.
- Lenalidomide plus dexamethasone can also be used in those not eligible for a stem cell transplant if thalidomide is contraindicated or not tolerated. [7]
- Daratumumab plus bortezomib, thalidomide and dexamethasone. This was recommended by NICE in a 2022 technology assessment for patients in whom an autologous stem cell transplant is suitable. [8]

Allogeneic stem cell transplantation should only be carried out in the context of a clinical trial.

## Maintenance

Systematic maintenance therapy is currently not recommended for elderly patients. However, lenalidomide has been approved as monotherapy for the maintenance treatment of younger adult patients with newly diagnosed myeloma who have undergone autologous stem cell transplantation. [9]

## Monitoring

Monitor people who have completed myeloma treatment and recovered – at least every three months. Take into account any risk factors for progression, such as: high-risk fluorescence in-situ hybridisation (FISH), impaired renal function and disease presentation. Monitoring for myeloma and smouldering myeloma should include:

- Assessment of symptoms related to myeloma and myeloma treatment.
- Laboratory tests: FBC, renal function, bone profile, serum immunoglobulins and serum protein electrophoresis. Also, serum-free light-chain assay, if appropriate.
- Do not offer people with myeloma or smouldering myeloma routine skeletal surveys for disease monitoring. Consider symptom-directed imaging for people with myeloma or smouldering myeloma if any new bone symptoms develop.
- For people with myeloma and serological relapse or disease progression, consider whole-body MRI, spinal MRI or fluorodeoxyglucose positron emission tomography CT (FDG PET-CT).
- For people with smouldering myeloma and disease progression, consider whole-body MRI, whole-body low-dose CT, whole-body CT, spinal MRI or FDG PET-CT.

### **Treatment of relapsed and refractory disease**

The choice of therapy depends on several parameters - eg, age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options and the interval since the last therapy.

- Approved options include lenalidomide in combination with dexamethasone, and bortezomib either alone or in combination with pegylated doxorubicin. However, bortezomib is mostly used in combination with dexamethasone in the relapse setting.
- In young patients, a second ASCT may be considered, provided the patient responded well to the previous ASCT.
- Daratumumab monotherapy is an option for treating relapsed and refractory multiple myeloma in adults who have had a proteasome inhibitor and an immunomodulator and whose disease progressed on the last treatment. <sup>[10]</sup>
- Lenalidomide in combination with dexamethasone is recommended by NICE as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies.

- Bortezomib monotherapy is recommended by NICE as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, but only if the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (reduction in serum M protein of 50% or more).
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- Ixazomib with lenalidomide and dexamethasone is recommended in adults who have had two or three lines of therapy so far. [10]

#### Editor's note

Dr Krishna Vakharia 27th June 2023

#### **Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma** [11]

NICE have recommended the above treatment combination to be used second line for treating multiple myeloma. It can only be used if the first treatment included lenalidomide or if lenalidomide is not suitable as second line treatment.

Clinical trials have shown that this combination decreases the risk of dying, or the myeloma becoming worse or returning.

### **Second autologous stem cell transplantation**

NICE recommends a second autologous stem cell transplant for:

- Relapsed myeloma who are suitable and who have completed re-induction therapy without disease progression and had a response duration of more than 24 months after their first autologous stem cell transplant.
- Relapsed myeloma who are suitable and who have completed re-induction therapy without disease progression and had a response duration of between 12 and 24 months after their first autologous stem cell transplant.

People with relapsed myeloma are more likely to be suitable for a second autologous stem cell transplant if they have had a good response to the first autologous stem cell transplant, a lower International Staging System (ISS) stage, not had many prior treatments, good overall fitness, based on resilience, frailty and performance status, and no adverse FISH results.

## **Pain control**

- Analgesics: a variety of drugs may be used for pain relief, ranging from simple analgesics such as paracetamol to potent opioids. Use the analgesic ladder. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided where possible (renal effects and gastric irritation).
- Adjuvant drugs: amitriptyline, carbamazepine or gabapentin can help in neuropathic pain.
- Corticosteroids: these can help to relieve bone pain in late stages.
- Alternative techniques: for example, relaxation, aromatherapy and hypnotherapy may be helpful.
- Radiotherapy: this can be used in bone and soft tissue disease.
- Chemotherapy: if the underlying disease is treated, this should help pain as treatment response occurs.
- Surgery: for example, stabilisation of fractures, treatment of vertebral collapse.

## **Complications**

These include:

- [Hypercalcaemia.](#)
- Renal impairment.
- Anaemia.
- Infection.
- [Spinal cord compression.](#)
- Pathological fractures.
- [Hyperviscosity.](#)

- Peripheral neuropathy.
- Bleeding.
- [AL amyloidosis](#).

More than 80% of myeloma patients suffer from destructive bony lesions, leading to pain, fractures, reduced mobility and neurological deficits.<sup>[12]</sup>

## Management of complications<sup>[4]</sup>

The following recommendations are based on the NICE guidance:

### Preventing bone disease

- To prevent bone disease, use zoledronic acid. Disodium pamidronate can be used if zoledronic acid is contra-indicated or not tolerated. Sodium clodronate can be used if zoledronic acid and disodium pamidronate are contra-indicated, not tolerated or not suitable.
- Consider immediate referral for dental assessment and treatment before starting or as soon as possible after starting zoledronic acid or disodium pamidronate.

### Managing non-spinal bone disease

- If not already on bisphosphonates: zoledronic acid, disodium pamidronate or sodium clodronate as outlined above.
- Assess the risk of fracture.
- Consider surgical stabilisation followed by radiotherapy for non-spinal bones that have fractured or are at high risk of fractures. Consider radiotherapy for non-spinal bones that have fractured or are at high risk of fracture if surgical intervention is unsuitable or not immediately needed.
- Consider radiotherapy for people with myeloma and non-spinal bone disease who need additional pain relief if:
  - Chemotherapy and initial pain management have not led to prompt improvement in pain control.
  - Chemotherapy is unsuitable and current pain medication is not working.

- Consider re-treatment with radiotherapy if pain recurs or if there is regrowth of a previously treated lesion.
  - Consider seeking advice from or referral to specialists in palliative care or pain medicine for people with complex non-spinal bone disease.
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## Managing spinal bone disease

See also the separate [Spinal Cord Compression](#) article.

- Offer people with myeloma and non-spinal bone disease who have not already started bisphosphonates: zoledronic acid, disodium pamidronate or sodium clodronate as outlined above.
- Consider the following as adjuncts to other treatments for all people with myeloma and spinal bone disease: interventional pain management or bracing.
- In people with radiological evidence of myeloma-related spinal instability, consider immediate intervention with spinal surgery/radiotherapy/cement augmentation.
- In people with radiological evidence of myeloma-related spinal bone disease without instability, consider cement augmentation, with or without radiotherapy, or radiotherapy alone.

## Preventing infection

- Offer people with myeloma the seasonal influenza vaccination and consider pneumococcal vaccination for people with myeloma who are under 65.
- Consider intravenous immunoglobulin replacement therapy for people who have hypogammaglobulinaemia and recurrent infections.
- Consider continuing aciclovir or equivalent antiviral prophylaxis after treatment with bortezomib or with other proteasome inhibitors ends.
- Consider aciclovir or equivalent antiviral prophylaxis for people who are taking both immunomodulatory drugs and high-dose steroids.
- Consider testing for hepatitis B, hepatitis C and HIV before starting myeloma treatment.

## Managing peripheral neuropathy

See also the separate [Neuropathic Pain and its Management](#) article.

- If people who are receiving bortezomib develop neuropathic symptoms, consider immediately switching to subcutaneous injections and/or reducing to weekly doses and/or reducing the dose. Consider reducing the dose if people are taking a drug other than bortezomib and develop neuropathic symptoms.
- Temporarily stopping neuropathy-inducing myeloma treatments may need to be considered. If neuropathy does not improve despite stopping myeloma treatment and further treatment is needed, consider switching to myeloma treatments less likely to induce neuropathy.

## Preventing thrombosis

For people with myeloma who are starting immunomodulatory drugs, offer thromboprophylaxis with either low molecular weight heparin (LMWH) at a prophylactic dose, or vitamin K antagonists at a therapeutic dose, to maintain an international normalised ratio (INR) of 2–3. If LMWH or vitamin K antagonists are unsuitable, consider low-dose aspirin.

## Managing fatigue

If other treatable causes of anaemia have been excluded, consider erythropoietin analogues to improve fatigue in people with myeloma who have symptomatic anaemia.

## Prognosis<sup>[2]</sup> <sup>[13]</sup>

- With the onset of new potential therapies, the prognosis for myeloma is improving and survival times have quadrupled in the UK in the last 50 years.
- The prognosis remains variable. Some patients will live for more than eight years after diagnosis, whereas high-risk disease usually causes death within 24 months.
- Cancer Research UK statistics for England state that 29.1% survive for ten years or more, an increase from 10% in the 1970s.

- Survival is the same in males and females but does vary by deprivation, with five-year survival being 50% in the most deprived group and 57% in the least deprived group.
- The international staging system defines three risk categories based on serum concentrations of beta-2 microglobulin and albumin:
  - Stage I: serum beta-2 microglobulin <3.5 mg/L and albumin ≥35 g/L.
  - Stage II: does not fit criteria for stage I or III.
  - Stage III: serum beta-2 microglobulin ≥5.5 mg/L (regardless of albumin level).
- Specific genetic lesions or gene signatures are associated with worse outcomes. IgH translocations involving chromosomes 4 and 16 are considered high-risk and are associated with a worse prognosis.
- Deletion of the short arm of chromosome 17 is also associated with a worse outcome.
- Age and response to treatment are independent prognostic factors. Younger patients who are fit enough for high-dose chemotherapy now have a projected median survival of around seven years.
- Patients who present as an emergency route have a worse prognosis.

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## Further reading

- [Dhakal B, Girnius S, Hari P](#); Recent advances in understanding multiple myeloma. *F1000Res*. 2016 Aug 23;5. doi: 10.12688/f1000research.8777.1. eCollection 2016.
- [Mahajan S, Tandon N, Kumar S](#); The evolution of stem-cell transplantation in multiple myeloma. *Ther Adv Hematol*. 2018 May;9(5):123-133. doi: 10.1177/2040620718761776. Epub 2018 Mar 5.

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