

# Paraproteins, MGUS and Myeloma

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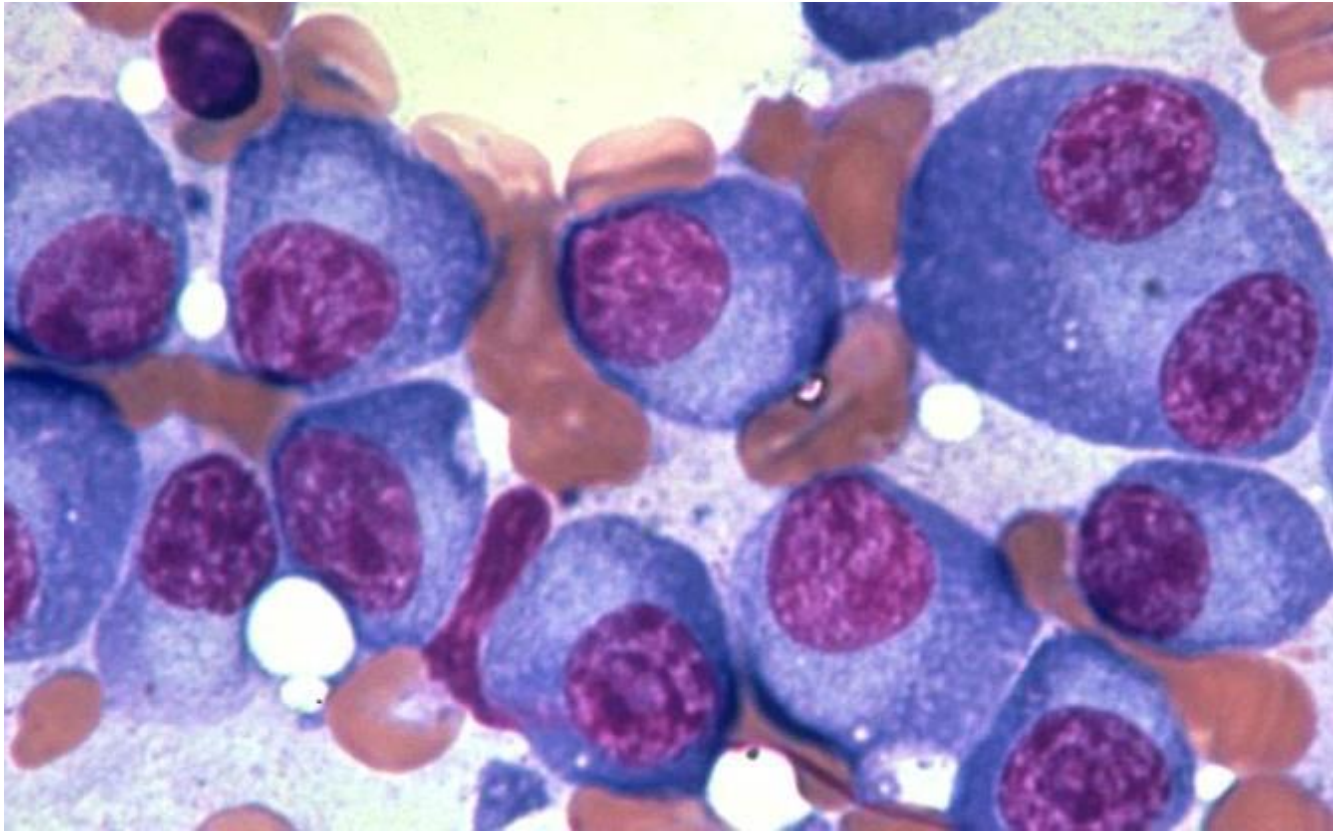
The Royal Marsden

# Talk Outline

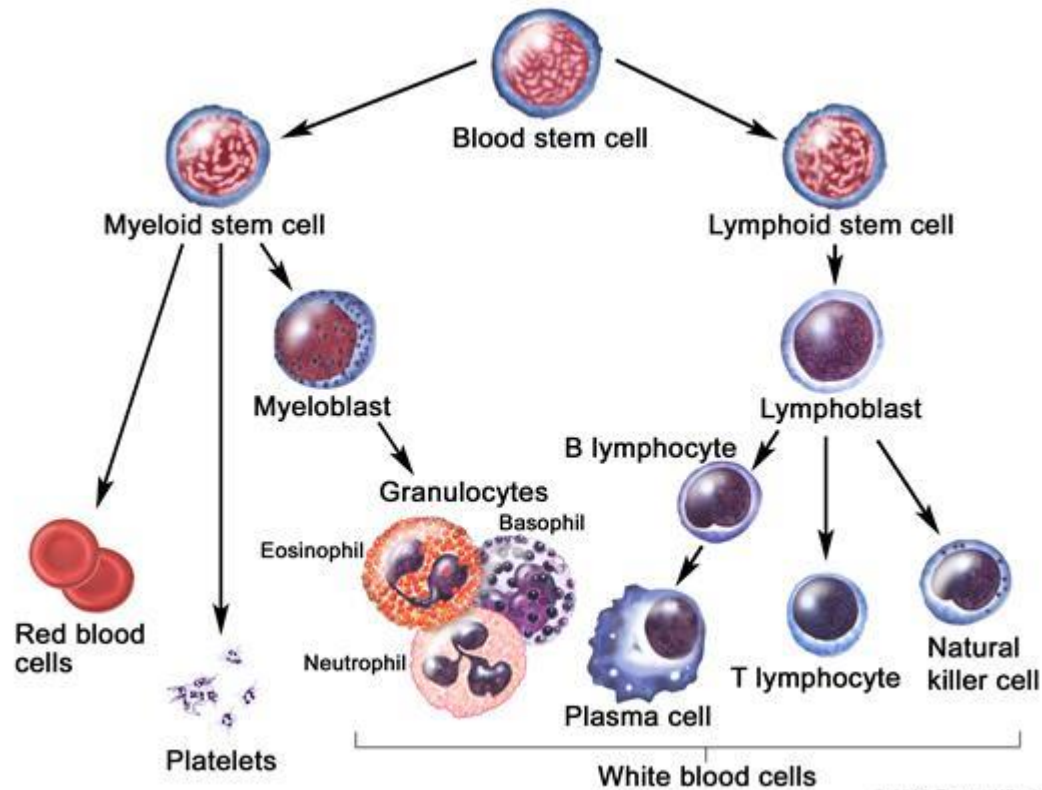
- Biology of plasma cells and paraproteins
- Laboratory Tests and interpretation
- When to request protein electrophoresis
- How to deal with a positive result
- When to refer
- Management of MGUS in the Community
- Myeloma prognosis and treatment: The basics



# Myeloma is a malignancy of plasma cells



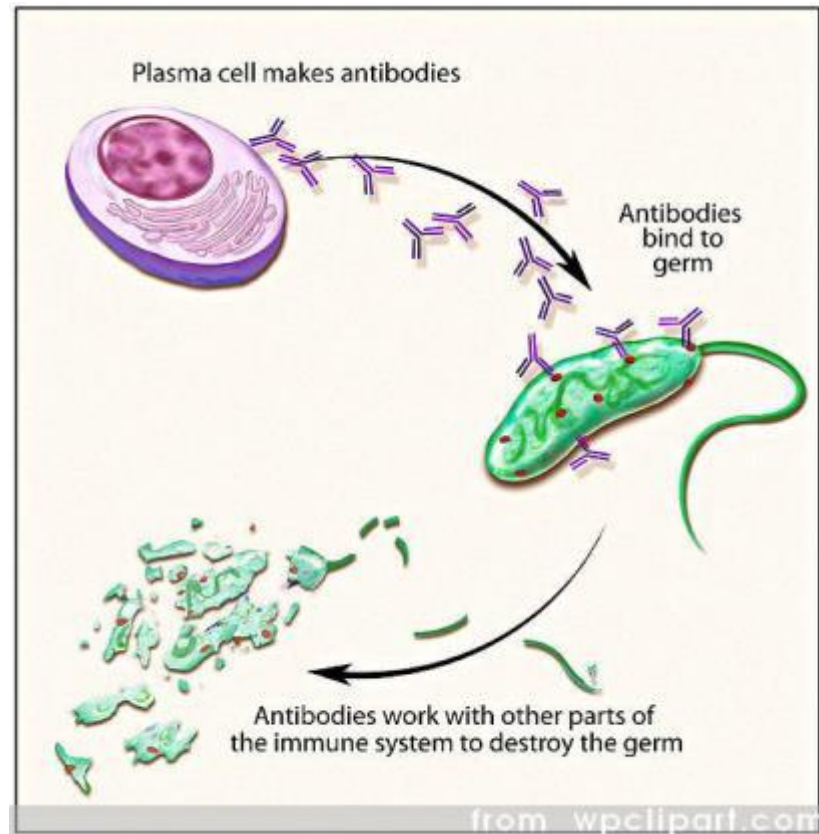
# Plasma cells are terminally differentiated B cells



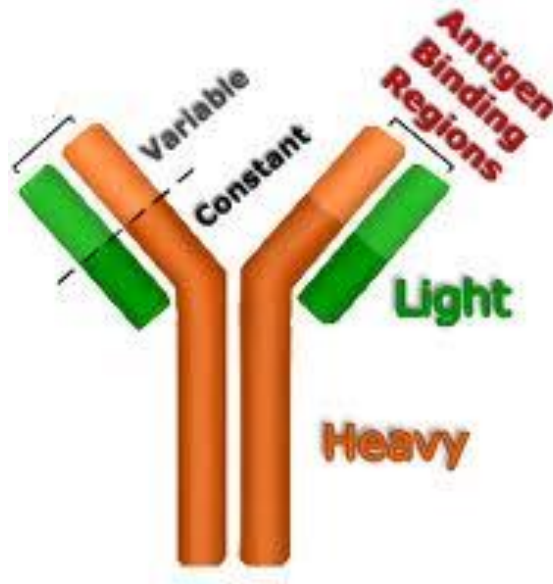
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# Plasma cells produce specific antibodies

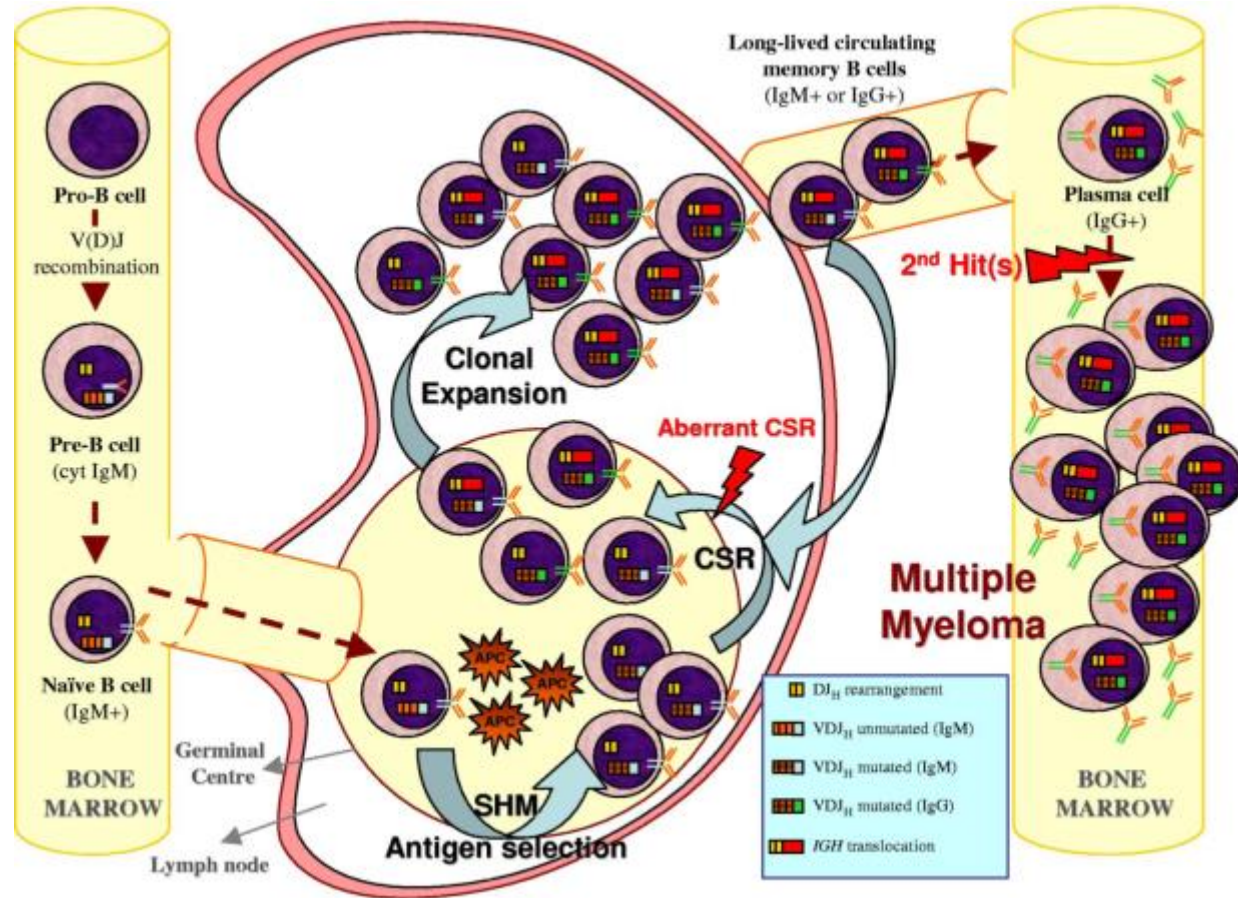


# Antibodies



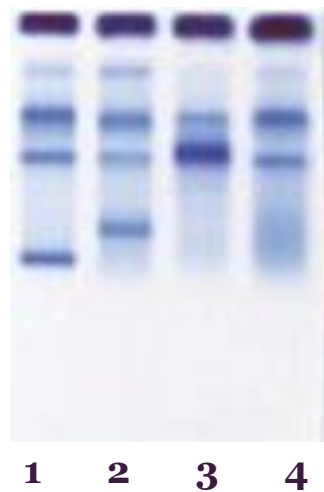


# Plasma cell development



# Laboratory Tests for a Monoclonal Protein:

## 1. Serum Protein Electrophoresis

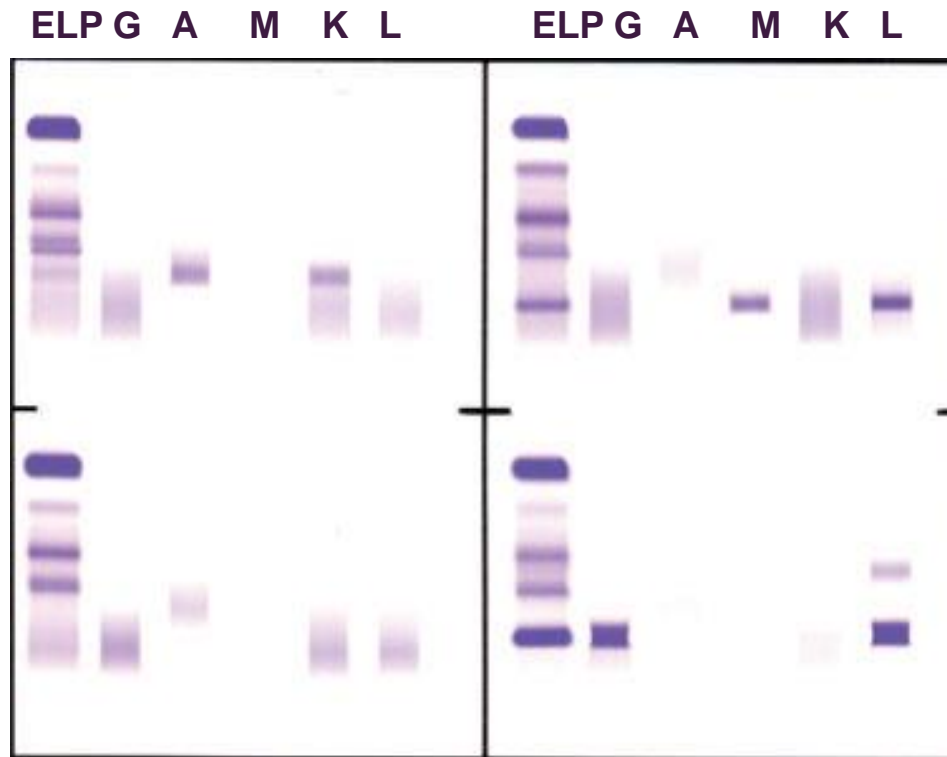


- ← Lane 3 – IgA kappa paraprotein 28 g/L
- ← Lane 2 – IgM kappa paraprotein 8 g/L
- ← Lane 3 – IgG lambda paraprotein 7 g/L

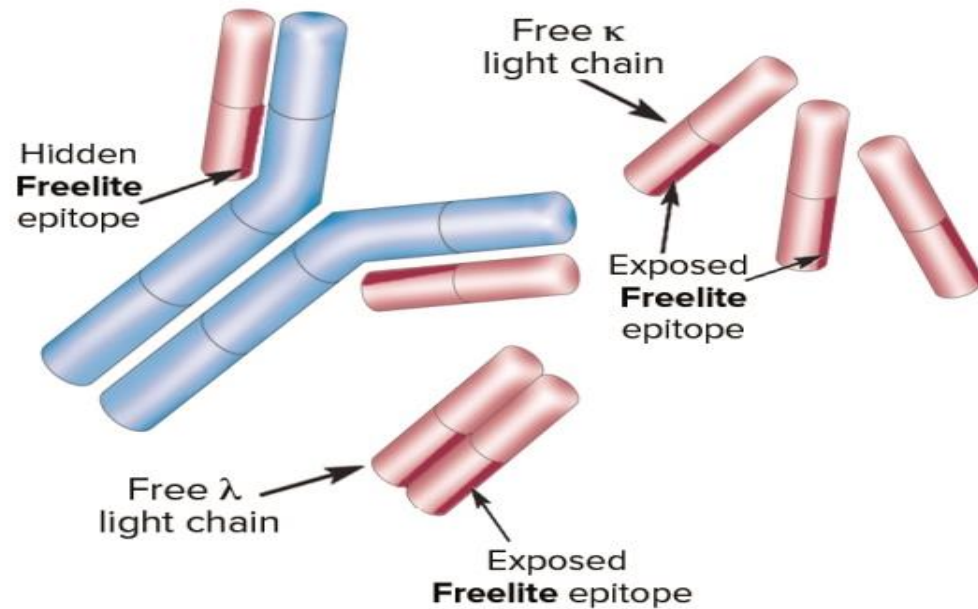




# Laboratory Tests for a Monoclonal Protein: Immunofixation



# Laboratory Tests for a Monoclonal Protein: Serum Free Lightchains (Freelites)



# Laboratory Tests for a Monoclonal Protein: Urine Protein Electrophoresis

- Positive or negative for Bence Jones Protein (BJP) which are just free light chains which have undergone glomerular filtration



# When to Test for a Monoclonal Protein

- Raised ESR or plasma viscosity
- Unexplained anaemia, hypercalcaemia or renal failure
- Raised total protein/globulins
- Reduction of one or more immunoglobulin class levels (IgG, IgA, IgM)



# What to Request

- FBC
- U+E
- Calcium
- Serum protein electrophoresis
- Urine protein electrophoresis or serum freelight chains



# How to interpret a positive result

- Monoclonal proteins can be associated with:
  - MGUS
  - Myeloma
  - Solitary Plasmacytoma
  - AL amyloidosis
  - Waldenstroms Macroglobulinaemia
  - Low grade B-NHL and other B-cell LPDs
  - Rare disorders caused by paraprotein damage (usually neurological)



# How to Investigate a Positive Result: Take a History for Signs/Symptoms of Myeloma, Lymphoma/LPD and Amyloidosis

## – **Myeloma**

- Bone/back pain
- Anaemia
- Renal impairment
- Hypercalcaemia
- Hyperviscosity

## – **Lymphoma/LPD**

- Lymphadenopathy
- Hepatosplenomegaly
- Hyperviscosity
- Anaemia
- B symptoms (sweats, unexplained weight loss)





# How to Investigate a Positive Result: Take a History for Signs/Symptoms of Myeloma, Lymphoma/LPD and Amyloidosis

- **Amyloidosis**
- Macroglossia
- Unexplained cardiac failure
- Nephrotic syndrome
- Peripheral neuropathy
- Carpal tunnel syndrome (often bilateral)



# When to Refer to Haematology

- Signs or symptoms of myeloma, lymphoma or amyloidosis
- Significant BJP ( $>500$  mg/L)
- IgD or IgE M-proteins
- IgG PP  $>15$  g/L
- IgA or IgM PP  $>10$  g/L



# The Majority of Patients will have MGUS

(monoclonal paraprotein of undetermined significance)

- Paraprotein < 30 g/L
- Plasma cells <10% in bone marrow
- No myeloma associated organ damage (bone marrow failure, hypercalcaemia, renal impairment, bone destruction)



# Prognosis of MGUS

- Associated with increased risk of malignant transformation
- Also associated with osteoporosis and DVT
- Risk of malignant transformation can be stratified based on level of PP, isotype of PP and sFLC ratio
- Higher risk of progression associated with non-IgG isotype, PP > 15 g/L and abnormal sFLC ratio



# MGUS - risk of progression

- Mayo risk model
- 1 point for non-IgG isotype, PP > 15 g/L and abnormal sFLC ratio

Number of risk factors	Risk category	20 year progression risk (%)	20 year risk accounting for death as a competing factor (%)
0	Low	5	2
1	Low-intermediate	21	10
2	High-intermediate	37	18
3	High	58	27

# Management of MGUS in the community

- 4 monthly tests for the first year
- Then reduced to 6-12 monthly if stable
- Tests should include:
  - FBC
  - U+E
  - Calcium
  - Serum protein electrophoresis
  - Serum freelight chains



# Myeloma - Epidemiology

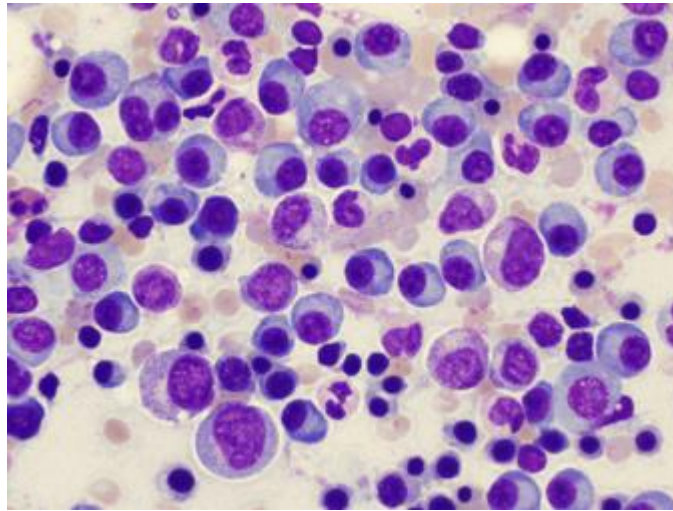
- 5000 new cases in the UK per year
- 10-15% of all haematological malignancies
- Incidence increases with age – average age at diagnosis 70
- 40% of patients present aged <60 years
- 1 – 2% aged <40 years
- More common in men than women (60:40)
- Racial differences in incidence (twice as common in black compared with caucasian, less common if of Asian origin)





# Myeloma: Presentation

## 1. Bone marrow failure



- Anaemia (usually normocytic, sometimes macrocytic)
- Neutropenia and thrombocytopenia are less common)



# Myeloma: Presentation

## 2. Bone pain

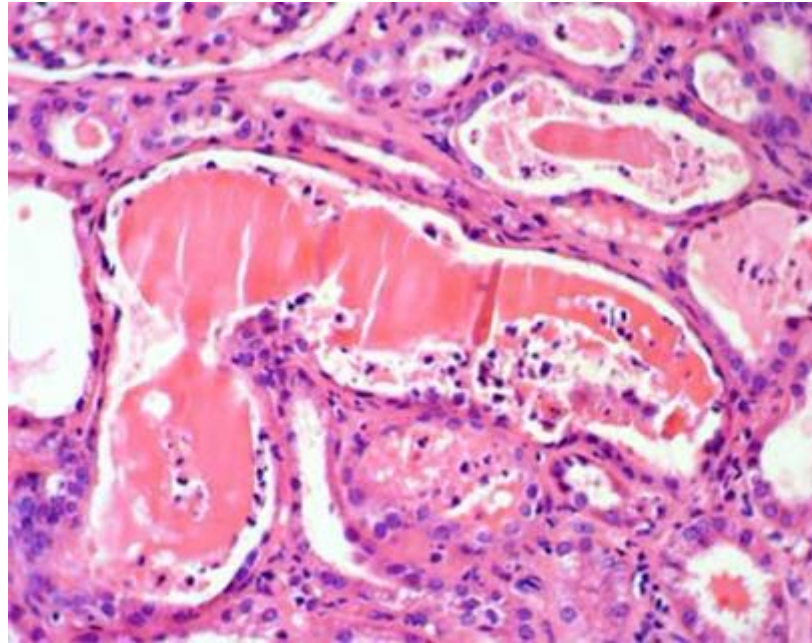


- Back pain is most common
- Any bone in the axial skeleton can be affected – ribs are another common site of pain
- 3% of patients present with spinal cord compression



# Myeloma: Presentation

## 3. Renal Failure



- Usually cast nephropathy due to high light chain load
- Often exacerbated by hypercalcaemia, NSAID use
- Light chain deposition and amyloid deposition are rarer causes



# Myeloma: Presentation

## 4. Infection



- Pneumonia is most common
- Nearly all patients have immune paresis at presentation (suppression of normal immunoglobulins)



# Myeloma: Presentation

## 5. Hypercalcaemia

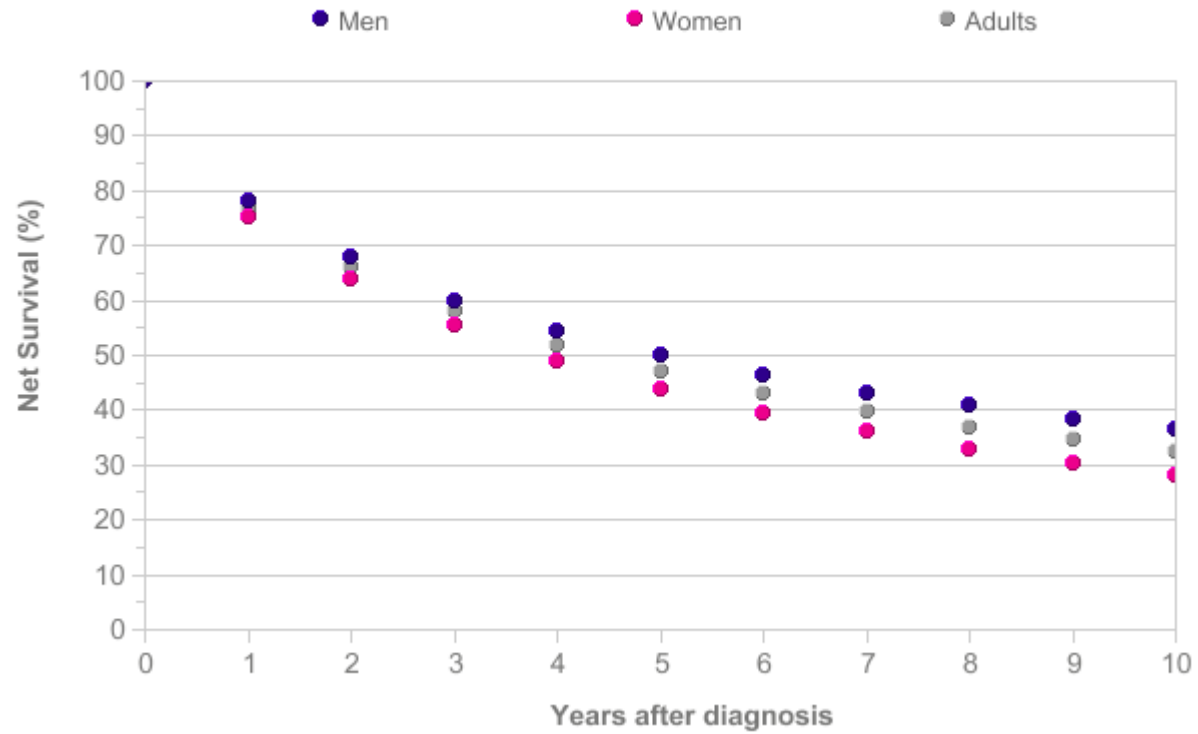


- Due to bone lysis
- Causes renal failure, abdominal pain, constipation and confusion



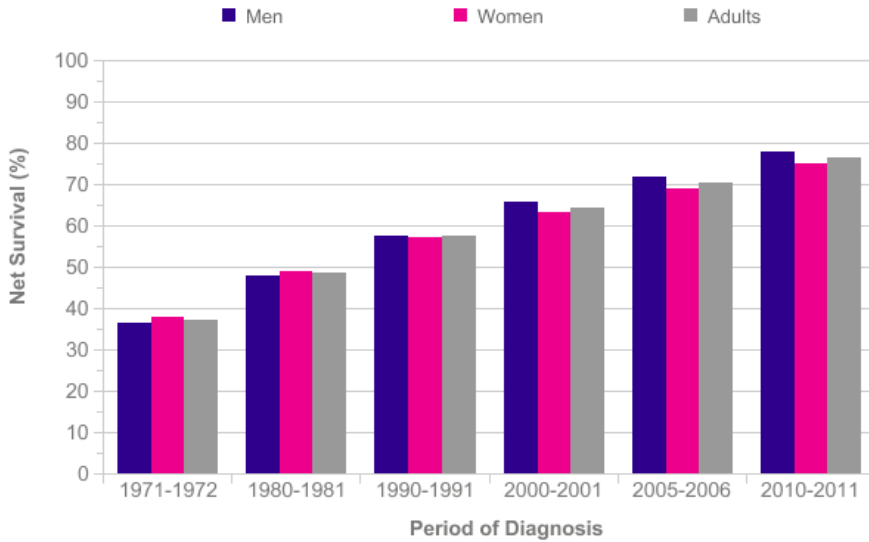
# Myeloma - prognosis

Net Survival – England and Wales 2010-11

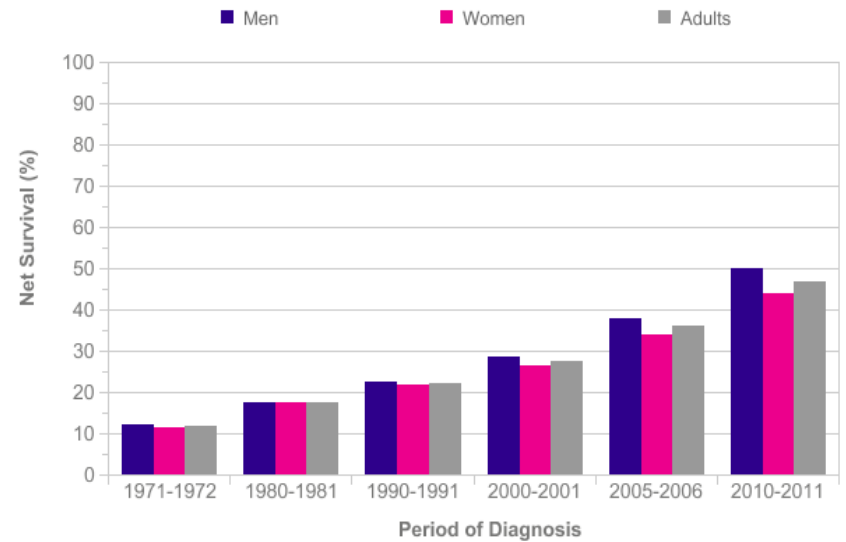


# Myeloma - Prognosis Change over time

## 1 year survival



## 5 year survival





# Myeloma Treatments

- Drugs
- Radiotherapy (to pathological fractures, spinal cord compression and for palliation of pain for focal lesions)
- Bisphosphonates (zoledronic acid) – for fracture prevention, prevention of hypercalcaemia
- Aggressive treatment of infections, especially in the first 6 months



# Myeloma Treatment: Chemotherapies

- Alkylating Agents
  - Melphalan
  - Cyclophosphamide
- Corticosteroids
  - Dexamethasone
  - Prednisolone
- Immunomodulatory Drugs
  - Thalidomide
  - Lenalidomide (Revlimid)
  - Pomalidomide
- Proteasome inhibitors
  - Bortezomib (Velcade)
  - Carfilzomib



# Myeloma Treatment: Chemotherapies

- Histone deacetylase inhibitors
  - Panobinostat
- Monoclonal antibodies
  - Daratumumab



# Myeloma Chemotherapy: General Concepts

- Usually combine agents with triplet therapy (e.g. VTD (velcade, thalidomide and dexamethasone))
- Treat until maximum response (based on biochemical marker)
- Younger, fitter patients will receive an autologous stem cell transplant
- Usually stop treatment once maximum response is reached
- Increasing evidence for ongoing therapy (maintenance)



# Myeloma Therapy: Future Directions

- Immunotherapies
  - checkpoint inhibitors
  - CAR-T therapy



# Scenario

- 79 year old man
- No concerning symptoms
- Routine blood tests
  - Hb 129 g/L
  - MCV 99
  - WBC, Plt normal
  - U+E, calcium normal
  - IgG kappa paraprotein of 9 g/L
  - sFCL: kappa 79 mg/L, lambda 10 mg/L, ratio 7.9

