Elevated Immunoglobulins and Paraproteins

NWL Pathology GP Study Afternoon
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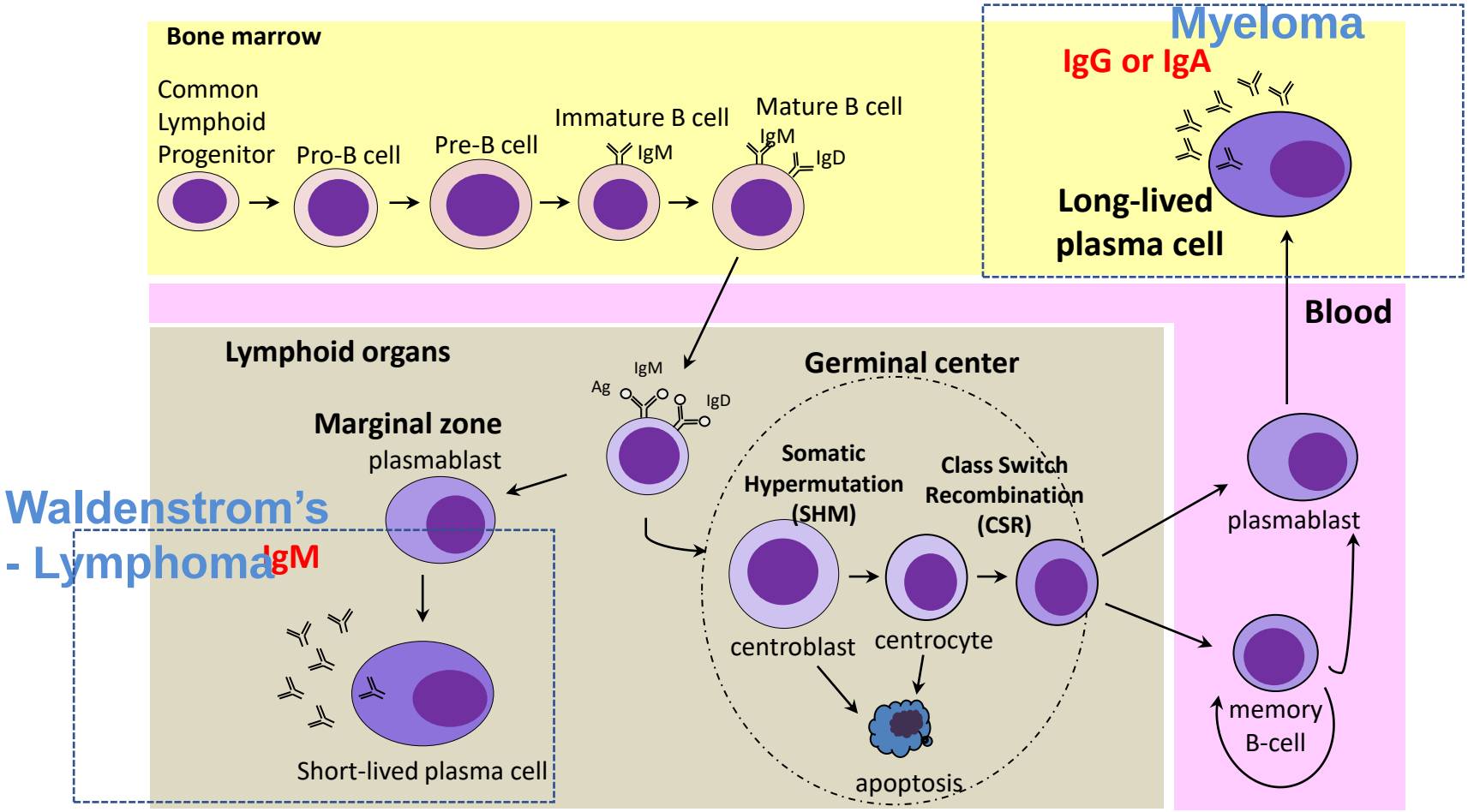
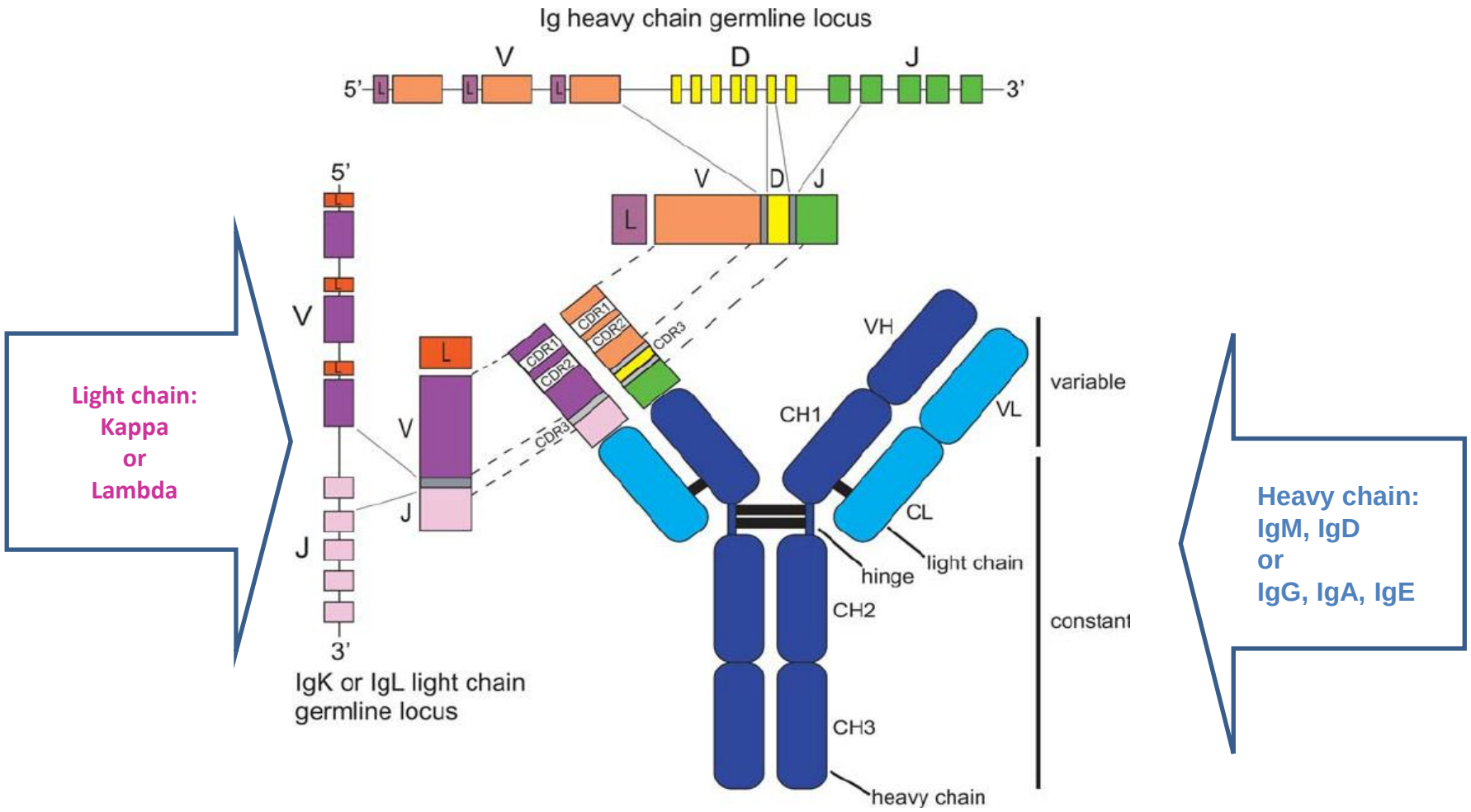
Learning objectives

- Recognise the main abnormalities of serum immunoglobulins
- Differentiate neoplastic from non-neoplastic immunoglobulin disorders
- Use a practical diagnostic algorithm to diagnose the underlying disorder
- Understand the diagnostic and prognostic value of paraprotein
- How to use paraproteins for monitoring and clinical management

B cell development and disease



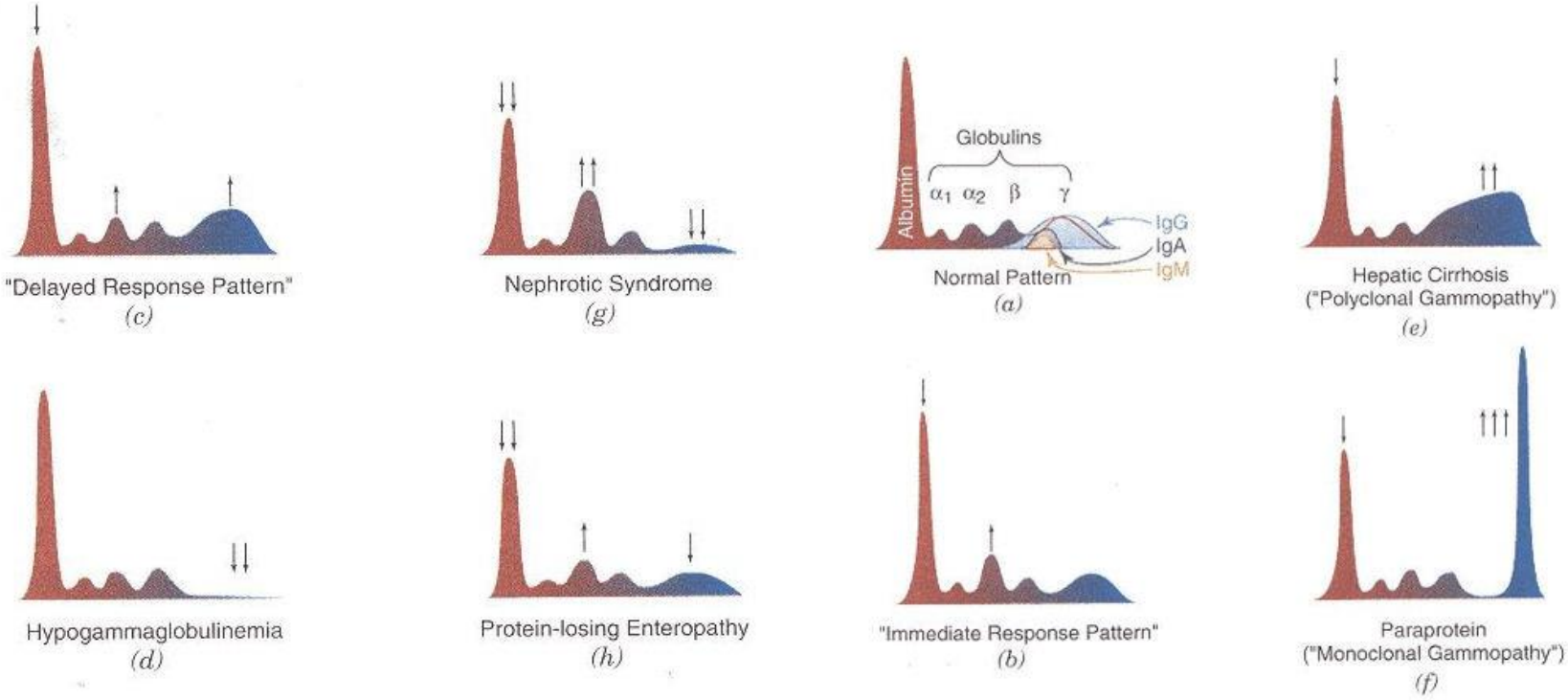
Immunoglobulin structure



Boyd &Joshi, Microbiology Spectrum 2014

Laboratory methods to detect abnormal immunoglobulins

- **Serum protein electrophoresis**

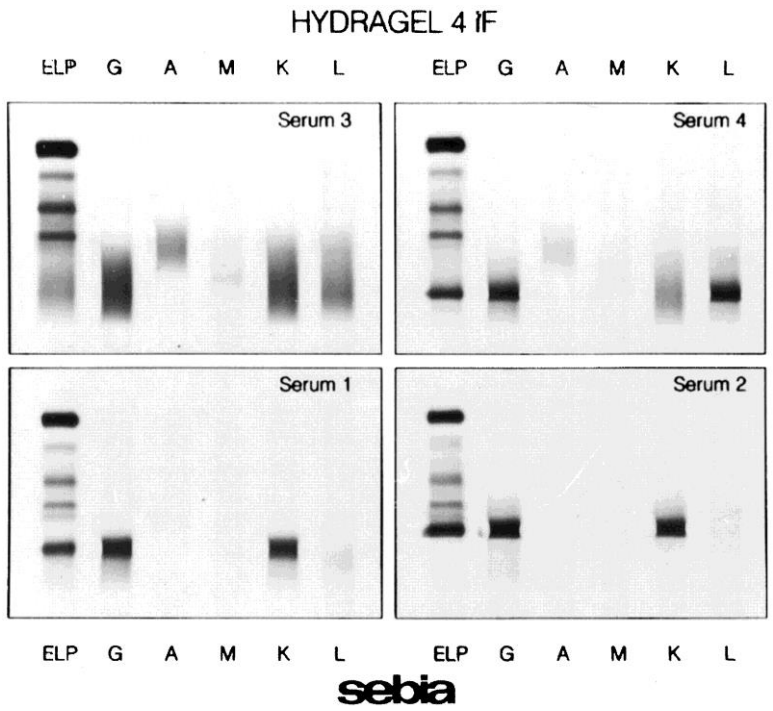


Laboratory methods to detect abnormal immunoglobulins

Immunofixation

normal

IgGkappa PP

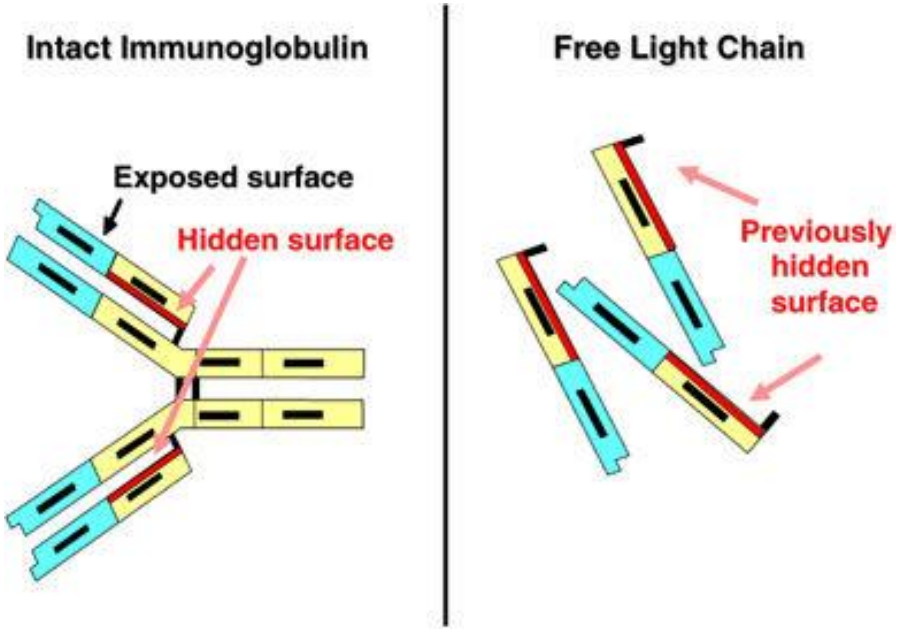


IgGlambda PP

IgGkappa PP

Laboratory methods to detect abnormal immunoglobulins

Serum free light chains



Abnormal immunoglobulins

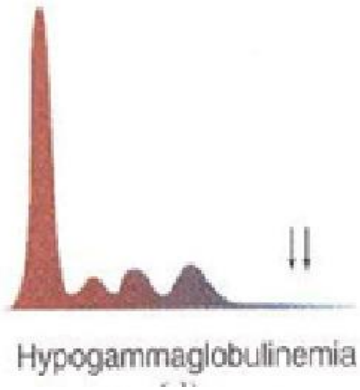
- **Elevated polyclonal immunoglobulins**
- **Monoclonal immunoglobulin (paraprotein)**
- **Hypoglobulinaemia**

A practical approach to abnormal immunoglobulins

1. Are immunoglobulin levels decreased?

Hypoglobulinaemia (low immunoglobulin levels)

- Hereditary conditions
  - family history, recurrent infections, IgA deficiency
- Acquired
  - Nephrotic syndrome
  - immunosuppressive therapies
  - chronic lymphocytic leukaemia (CLL)
  - **light chain or non-secretory myeloma**: **check serum free light chains**

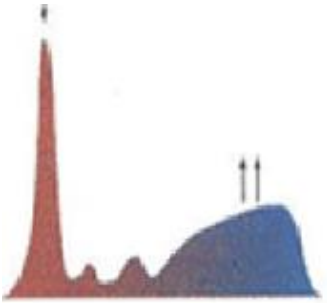


A practical approach to abnormal immunoglobulins

2. Are elevated immunoglobulin levels polyclonal or monoclonal?

Polyclonal immunoglobulins*

- Chronic infection (osteomyelitis, endocarditis, HIV, EBV)
- Inflammation, IgG4 related disease
- Autoimmune (RA, SLE, Sjogren)
- Neoplasm (lung, liver, gastric, rare T cell lymphomas)
- Liver disease (cirrhosis, chronic hepatitis)



* May include several tiny monoclonal bands

A practical approach to abnormal immunoglobulins

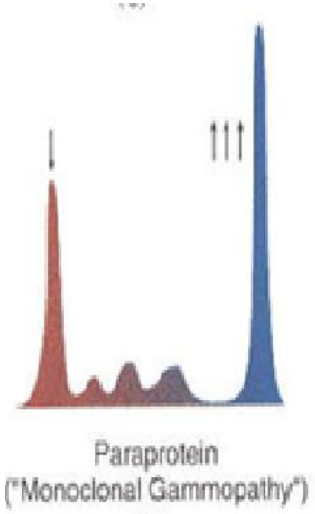
3. Presence of monoclonal immunoglobulin: IgM or non-IgM

IgM paraproteinaemia

- IgM MGUS
- Waldenstrom's macroglobulinaemia / lymphoplasmacytic lymphoma
- Marginal zone lymphoma
- Other non-Hodgkin lymphoma

IgG or IgA paraproteinaemia

- MGUS
- Myeloma (smouldering and symptomatic)
- Plasmacytoma
- Amyloidosis
- POEMS



IgM paraproteins*

Clinical evaluation for Waldenstrom's other B cell NHL

- Anaemia
- Lymphadenopathy
- Splenomegaly
- Hyperviscosity (more common than in other PP)
- B symptoms
- Neuropathy, even in otherwise asymptomatic patients
- Proteinuria
- **NO** bone lesions

Infiltration of the bone marrow by lymphoplasmacytic lymphoma sets the diagnosis of Waldenstrom's macroglobulinaemia

- IgM MGUS has higher risk for progression than IgG MGUS

*It is not synonymous to M-spike

IgM paraproteins

When to refer to haematology

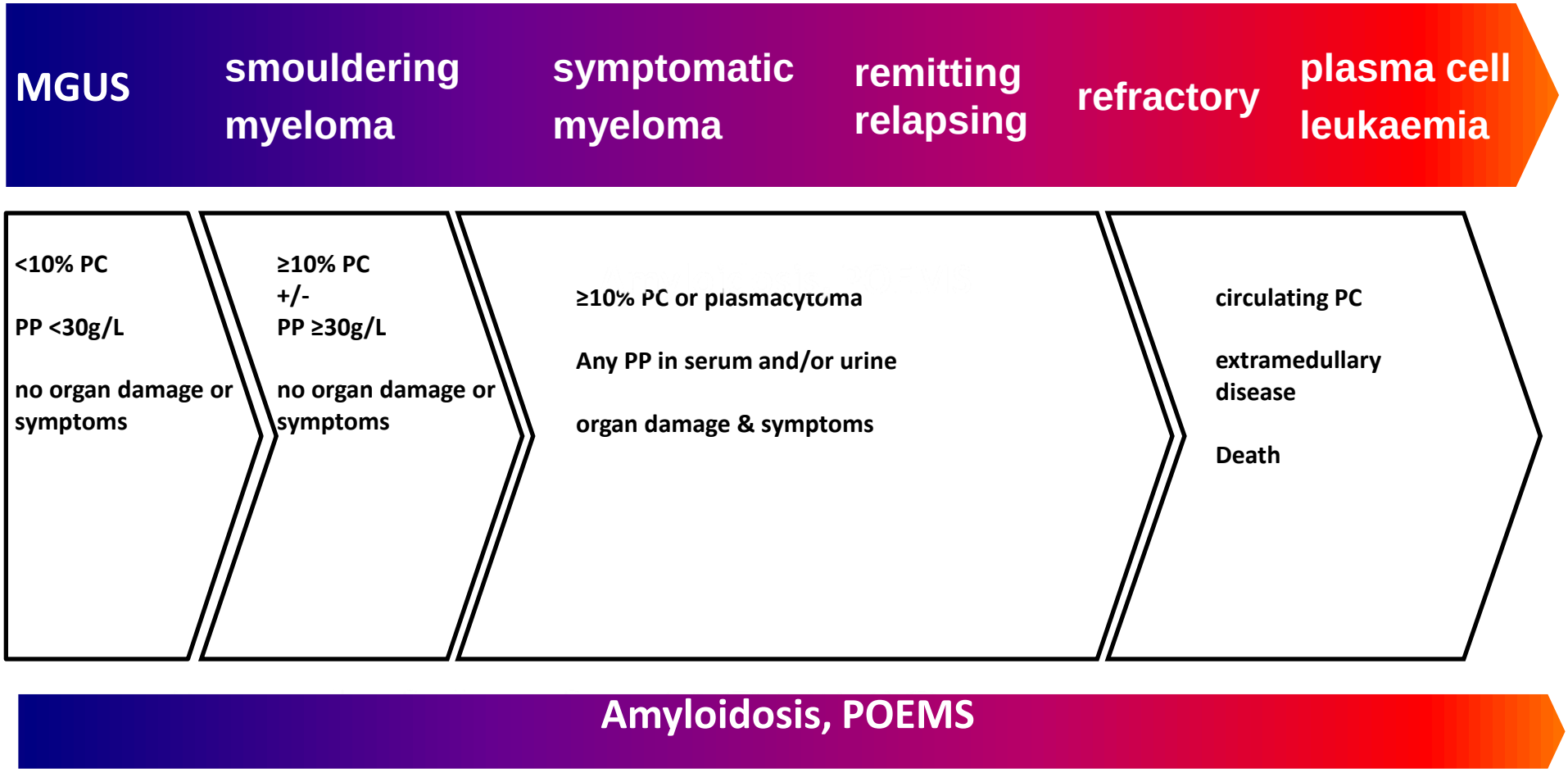
- **IgM PP >10g/L or**
- **Any size IgM PP and symptoms**

Patients with symptoms from a known underlying condition (eg Rheumatoid arthritis) and a small IgM PP may not require referral

Asymptomatic individuals with a small IgM PP <10g/L, if not referred to haematology they will require monitoring by their GP every 3-4 months initially, if stable every 6-12months

Increase of an IgM PP >25% (minimum 5g/L) may indicate progression and should trigger referral

IgA and IgG paraproteins and/or elevated serum FLC



IgG / IgA paraproteins and/or elevated serum FLC

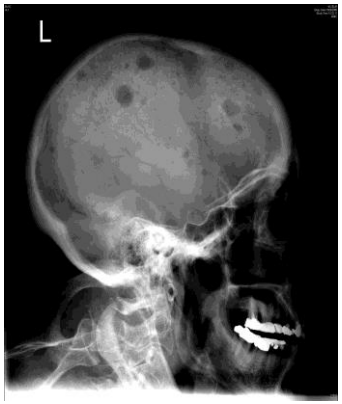
Clinical evaluation for MGUS or myeloma (any size PP)

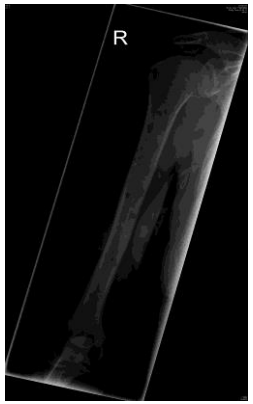
- **Anaemia (Hb <100g/L or drop by 20g/L from baseline)**
  - >70% of patients at presentation, normocytic
- **Bone disease (80%)**
  - Bone pain, lytic lesions, osteopenia, fractures
- **Hypercalcaemia**
- **Renal impairment (20 - 40%)**
  - Cast nephropathy, always check FLC not only PP
- **Infections**
  - Bacterial & viral

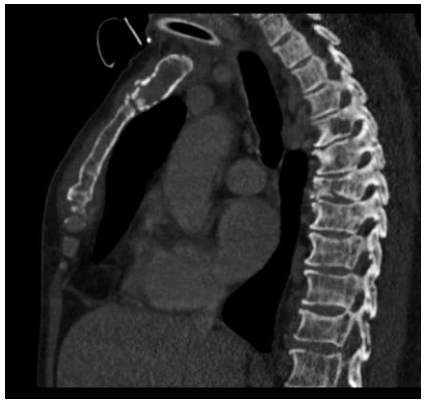
IgG / IgA paraproteins and/or elevated serum FLC

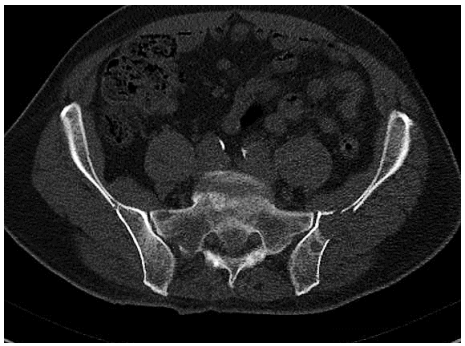
Imaging for MGUS or myeloma

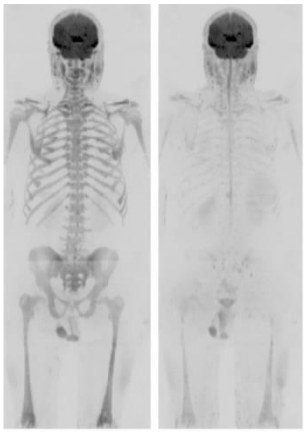
- Skeletal survey XR films: obsolete











- **Whole body low-dose CT scan**
- **CT PET scan**

Whole-body diffusion-weighted MRI

IgG / IgA paraproteins and/or elevated serum FLC

Clinical evaluation for possible amyloidosis (any size PP)

- **Macroglossia**
- **Unexplained heart failure**
- **Peripheral neuropathy**
- **Postural hypotension**
- **Carpal tunnel syndrome**
- **Erectile dysfunction**
- **Proteinuria – nephrotic syndrome**

  Tip: Always check a urine sample for proteinuria

IgG, IgA and light chain MGUS
(monoclonal gammopathy of undetermined significance)

The most common pre-malignant condition:
3.5% of individuals aged >50 years

Regression or progression

Risk for progression: 1% annually
- IgG and IgA → myeloma
- Light chain → light chain myeloma or renal disease

MGUS
M-protein in serum <30 g/l
Bone marrow clonal plasma cells <10% and low level of plasma cell infiltration in a trephine biopsy (if done)
No myeloma-related organ or tissue impairment (including bone lesions or symptoms)
No evidence of other B-cell LPD or light chain associated amyloidosis or other light chain, heavy chain or immunoglobulin-associated tissue damage‡

Adapted from International Myeloma Working Group. (2003)

MGUS risk stratification

Mayo Clinic criteria

TABLE 3. **Risk-Stratification Model to Predict Progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders**

Risk group	No. of patients	Relative risk	Absolute risk of progression at 20 y (%)	Absolute risk of progression at 20 y, accounting for death as a competing risk (%)
Low-risk (serum M protein, <1.5 g/dL; IgG subtype, normal; free light chain ratio, 0.26-1.65	449	1	5	2
Low-intermediate-risk Any 1 factor abnormal	420	5.4	21	10
High-intermediate-risk Any 2 factors abnormal	226	10.1	37	18
High-risk All 3 factors abnormal	53	20.8	58	27

From *Blood*,[34] the American Society of Hematology.

- **Tip:** normal range serum free light chains ratio is higher in renal failure

MGUS risk stratification

The association of PP level and progression risk

Table VIII. Association between the level of M-protein and risk of progression at 20 years.

M-protein level (g/l)	Risk of progression (%)
<5	14
<10	16
<15	25
<20	41
<25	49
<30	64

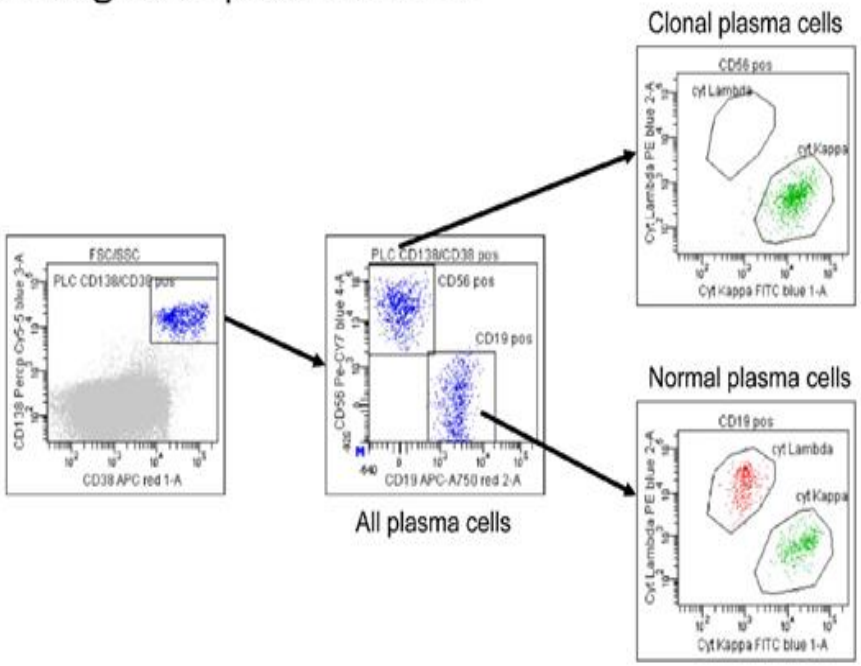
Gregersen *et al*, 2001a; Van De Donk *et al*, 2001; Rosiñol *et al*, 2007).

MGUS risk stratification

Spanish Group criteria

Perez-Persona *et al.* (n=311)[30] -≥95% aberrant bone marrow plasma cells -Evolving MGUS*		
Number of risk factors	Risk of progression at 7 years	% of total
0	2%	49%
1	16%	45%
2	72%	6%

Flow cytometry for normal and malignant plasma cells



Evolving MGUS: >10% PP increase in 6 months of progressive increase

MGUS management

Recommendations for referral to Haematology
BCSH guidelines, British Journal Haematology 2009

- **IgA PP >10g/L or IgG PP >15g/L**
- **Bence Jones proteinuria >500mg/L**
- **Any size PP and symptoms**

Recommendations from the International Myeloma Working Group
Leukemia 2010

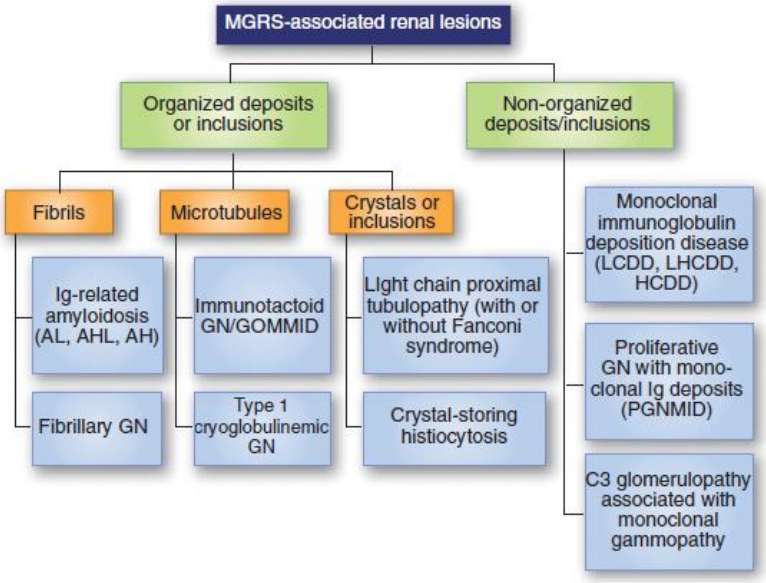
- **Cases should be risk stratified**
- **Adjust follow up to risk**
- **Low risk MGUS can be followed less frequently, every 2-3 years or if they develop symptoms**

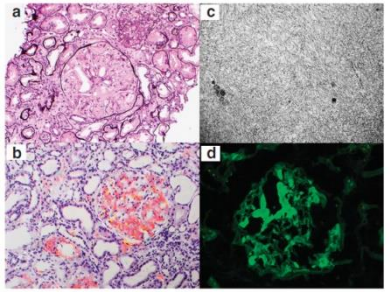
MGUS-related conditions

Monoclonal gammopathy of renal significance (MGRS)

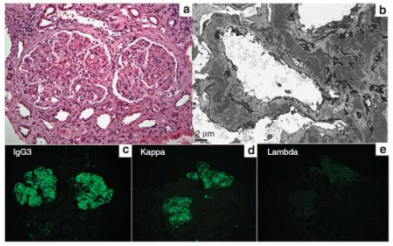
- Rare condition
- No symptoms or criteria of myeloma / lymphoma
- The physicochemical properties of the Ig and not the amount are important

Early treatment of the myeloma clone is required





renal Ig–related amyloidosis.



proliferative glomerulonephritis with monoclonal IgG deposits.

Smouldering myeloma

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

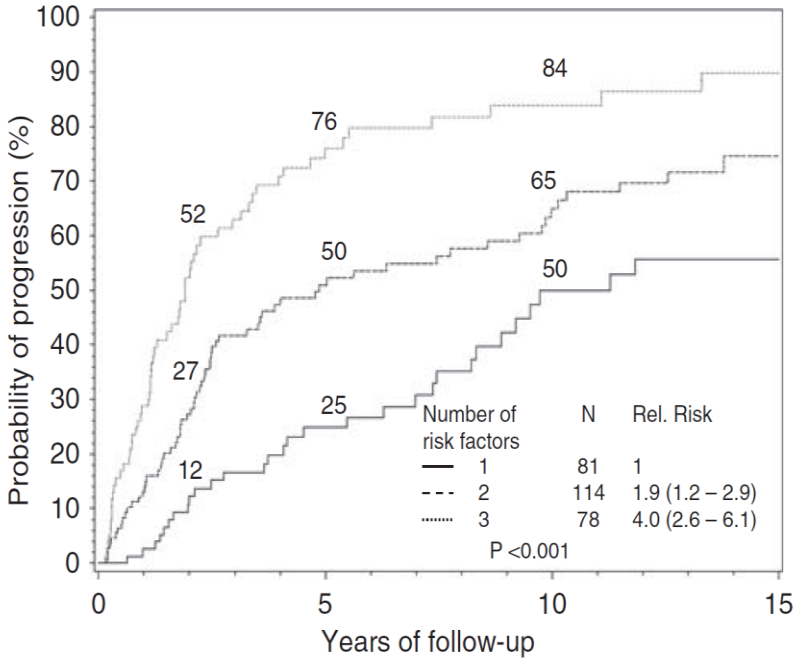
Lancet Oncol 2014; 15: e538–48

- **Mayo Clinic Risk Stratification:**
  - **Bone marrow plasma cells ≥10%**
  - **PP ≥30g/L**
  - **FLC ratio <0.125 or >8**

Tip:

FLC ratio >100 is a diagnostic criterion for myeloma

- Low, intermediate risk: observation
- High risk (3 factors): ?treatment



Serum PP and FLC in myeloma to measure response

Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease

- Modern therapies offer high rates of complete response and stringent complete response
- Deeper response → longer remission
- The aim of myeloma treatment should be stringent complete response with negative minimal residual disease in the bone marrow

Serum PP and FLC to diagnose myeloma progression

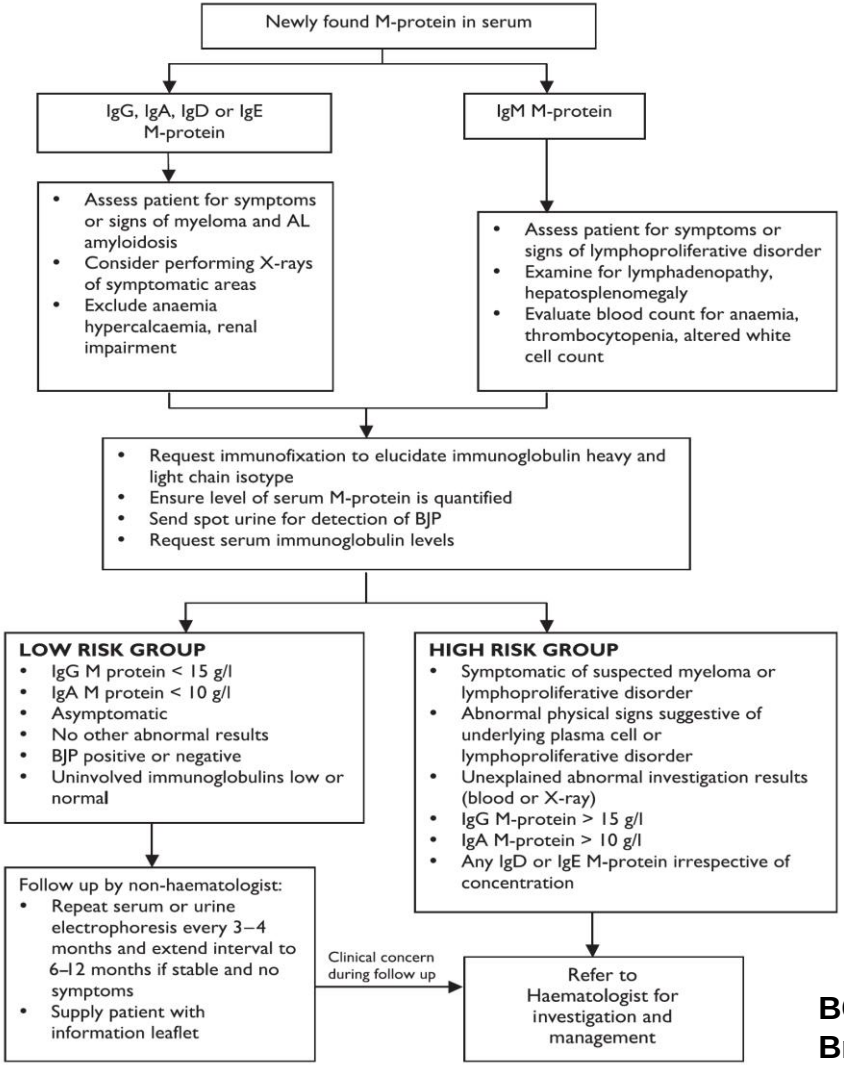
The prevalence of myeloma in the community increases with aging population and novel effective therapies leading to longer survival

Criteria for progressive myeloma

(Progressive disease ¶¶,||||	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease

- PP increase >25% from nadir (minimum 5g/L) defines progressive disease
- In light chain myeloma: > difference FLC by 25% (minimum >10mg/L)

Suggested algorithm for investigation of new PP



BCSH guidelines,
British Journal Haematology 2009

SUMMARY

- Increased polyclonal immunoglobulins rarely due to haematological disease
- Serum free light chain assay has changed the field, use together with protein electrophoresis and immunofixation
- IgM PP (MGUS, lymphoma) vs non-IgM PP (MGUS, myeloma)
- Clinical evaluation is of paramount importance
- Link symptoms with the presence of PP: myeloma & lymphoma but also amyloidosis, MGRS, neuropathy
- Risk stratification driven clinical management