Haematology in Primary Care

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Topics covered

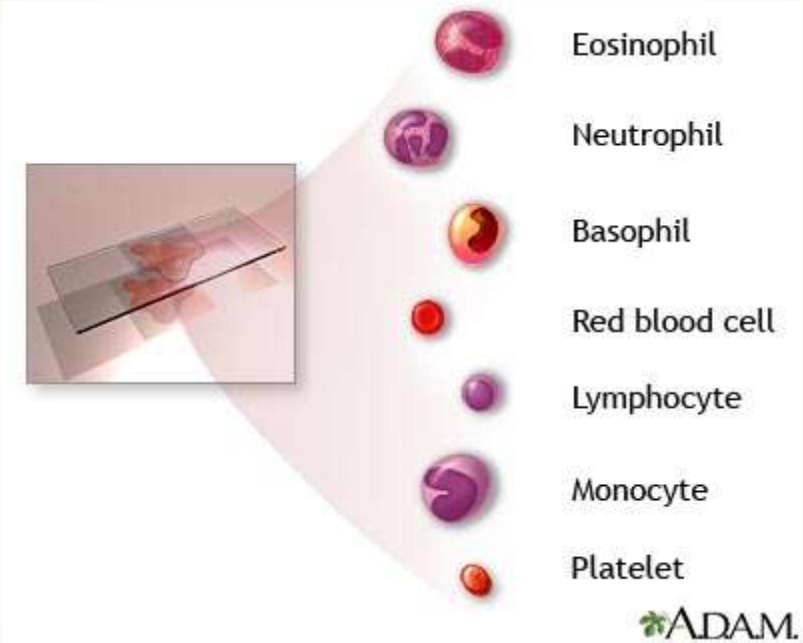
- Anaemia
- Macrocytosis & B12 deficiency
- Polycythaemia
- Neutropenia
- Thrombocytosis
- Lymphocytosis
- Thrombocytopenia
- Paraproteinamia

Anaemia

- <130g/l in males & <115g/l in females
  - Hx of diet, bleeding , drug and family hx
  - Normocytic / microcytic / macrocytic
- Investigations in primary care:
  - Blood film & reticulocyte count
  - Ferritin (include ESR / CRP)
  - Iron profile (Serum Fe, TIBC & Trans sat)
  - Renal and liver functions
  - Coeliac screen in iron deficiency not related to bleeding
  - Protein electrophoresis and serum free light chains

FBC

Blood film



Serum Levels That Differentiate Anemia of Chronic Disease from Iron-Deficiency Anemia.

Table 3. Serum Levels That Differentiate Anemia of Chronic Disease from Iron-Deficiency Anemia.*

Variable	Anemia of Chronic Disease	Iron-Deficiency Anemia	Both Conditions†
Iron	Reduced	Reduced	Reduced
Transferrin	Reduced to normal	Increased	Reduced
Transferrin saturation	Reduced	Reduced	Reduced
Ferritin	Normal to increased	Reduced	Reduced to normal
Soluble transferrin receptor	Normal	Increased	Normal to increased
Ratio of soluble transferrin receptor to log ferritin	Low (<1)	High (>2)	High (>2)
Cytokine levels	Increased	Normal	Increased

* Relative changes are given in relation to the respective normal values.
† Patients with both conditions include those with anemia of chronic disease and true iron deficiency.

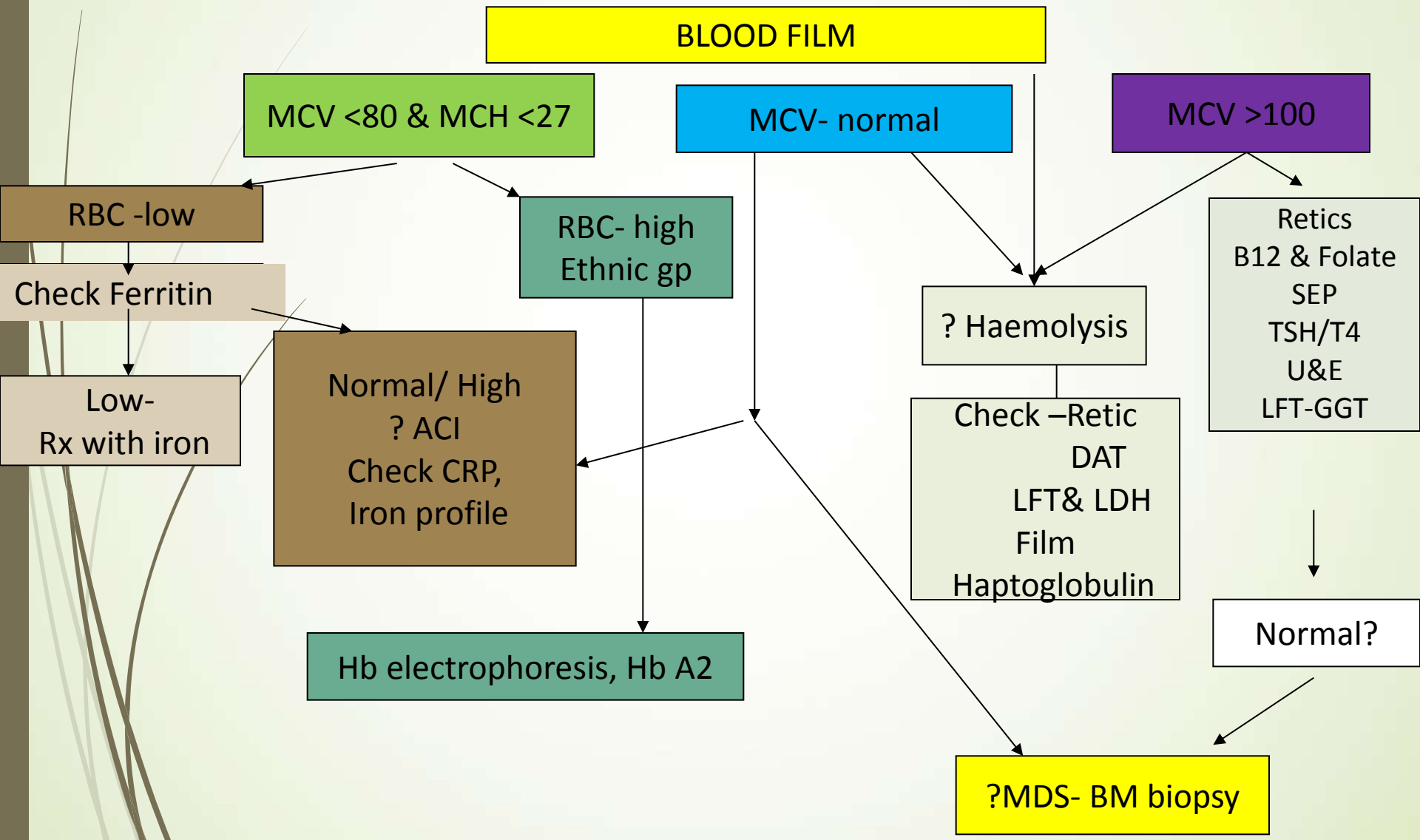
Weiss G, Goodnough LT. N Engl J Med 2005;352:1011-1023.

Anaemia contd..

- Urgent referral to Haematology if…
  - Leuco erythroblastic picture on film report
  - Unexplained progressive anaemia
  - Anaemia associated with organomegaly
- Routine referral
  - Unexplained anaemia
  - Sub optimal response to oral iron after 6-8 week trial
  - Try switching over to an alternate oral preparation
  - Consider referral to gastro / gynae

Algorithm for investigating anaemia in adults

Hb < 130g/l(males), <115g/dl (females)



Macrocytosis : MCV > 100fl

- B12 and folate deficiency
- Alcohol excess
- Hypothyroidism
- Hemolysis (associated with increased reticulocytes
- Drugs- Azathioprine, hydroxycarbamide, methotrexate, retroviral drugs etc.)
- Myelodysplasia
- Paraproteinaemia
- Pregnancy

Macrocytosis contd..

- Diet & alcohol hx
- Investigations;
  - B12, Folate & Reticulocyte count
  - Liver, renal and thyroid function test
  - Immunoglobulin, protein electrophoresis and SFLC
  - Anti intrinsic factor ab
  - Coeliac screen

Macrocytosis contd..

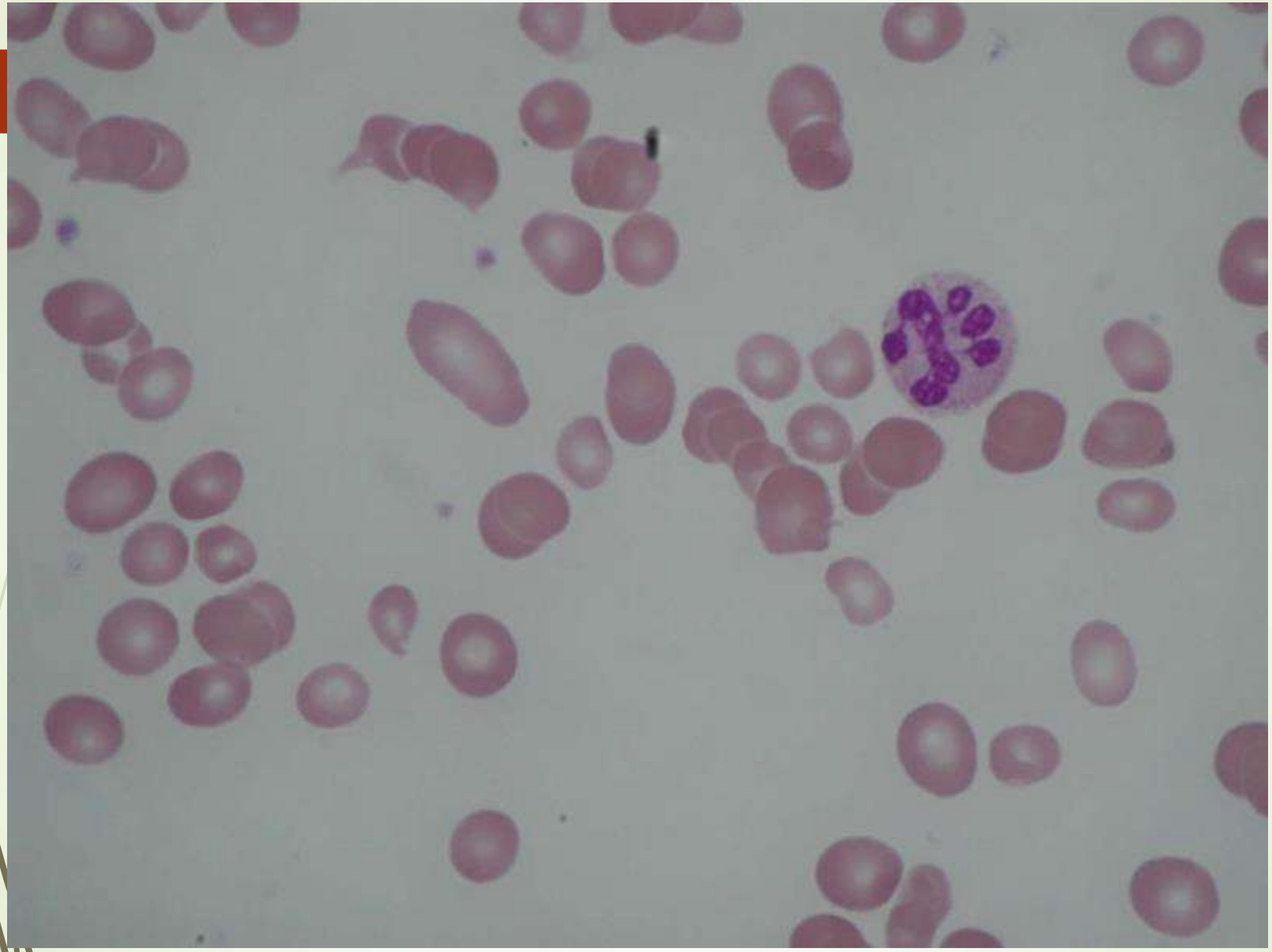
- Suspected myelodysplasia on blood film
- Co-existing abnormal white cell or platelet count
- Persistent unexplained MCV> 105fl

Case 1

- 78 year old man
- Presented to A&E with SOB
- Clinical examination: ?jaundiced, raised JVP, gallop rhythm, basal crackles in the lungs & ankle oedema, beefy tongue.
- Clinical diagnosis
- FBC: Hb 5.0g/dl, MCV 63, RDW 20,WBC 12 & Platelets 210 & Bilirubin 31.
- B12 <50 Folate 5.0, Ferritin 28
- Haematological diagnosis

Case 1

- Anti Intrinsic factor ab (35-40% positive)
- Anti parietal cell ab (less specific)
- Thyroid function test
- Serum Methyl malonic acid assay/ Homocysteine
- Test for Coeliac disease
- Endoscopy (co-existing iron deficiency)
- If in doubt TREAT



Causes of B12 deficiency

- Poor intake
  - Vegan
  - Anorexia
- Oral contraception
  - Not a true deficiency but apparent reduction in the b12 level due to low transcobalamin
- Malabsorption
  - Pernicious anaemia
  - Long term use of PPI and H2 blockers
  - Chronic alcoholism
  - Pancreatic insufficiency
  - Coeliac deficiency
  - Gastrectomy
  - Small bowel surgery / surgery

Treatment-Symptomatic

- B12 deficiency without neurological involvement:
  - 1mg Hydroxocobalamin 3 times a week for 2 weeks then every 3 months
- B12 deficiency with neurological involvement:
  - 1mg Hydroxocobalamin every other day until no further improvement then every 2 months
- Folic acid 5mg daily for 4 weeks

Treatment-Asymptomatic

- Serum B12> 150ng/l- Confirm test
- Significant proportion of these patients will go on to become symptomatic.
- Treat with oral vitamin B12 supplements + monitor level every 2-3months
- If no response then consideration given to parenteral B12 replacement

Pregnancy and B12 level

- Serum B12 tend to fall by 30% especially in last trimester
- Difficult to interpret B12 level as results are unreliable
- If in doubt Rx with parenteral B12 injections
- Three injections to cover pregnancy and re test 2 months post partum

Polycythaemia

Causes

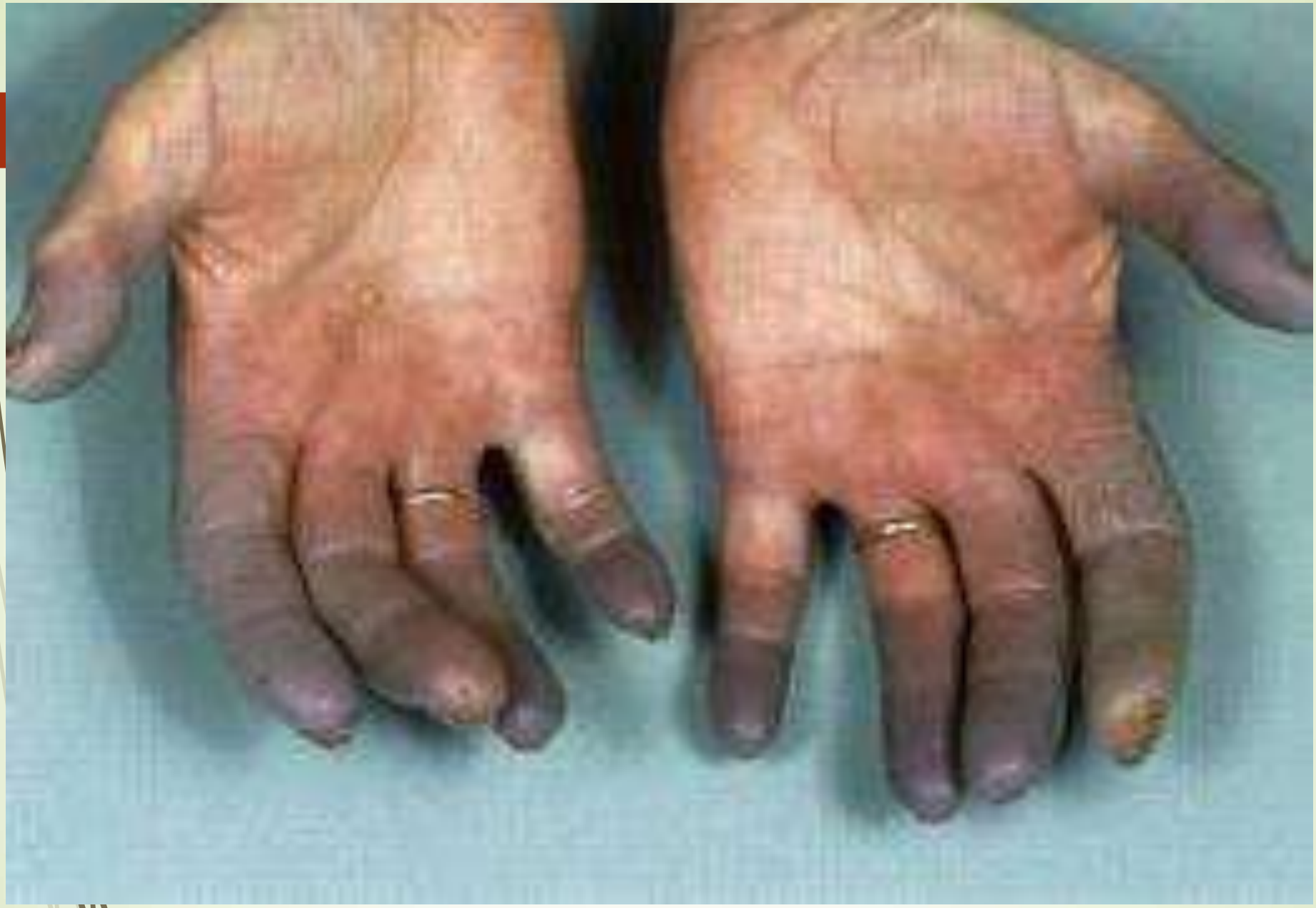
- Primary (PV)
- Secondary Polycythaemia
  - COPD
  - Cyanotic heart disease
  - Alcohol/ heavy smoking
  - Sleep apnoea
  - Testosterone replacement
  - Anabolic steroid use
  - Renal – tumours, hydronephrosis
  - Gynaecologic- fibromyoma!
- Relative/spurious (diuretics, dehydration
- High Affinity Haemoglobins

Polycythaemia- Investigations

- Repeat FBC (uncuffed blood sample)
- Review risk factors: hydration, smoking, alcohol, diuretic rx, testosterone replacement
- Screen for diabetes and dyslipidemia
- Risk factors for sleep apnoea?

Polycythaemia- when to refer

- Urgent referral of if..
  - Raised HCT (male >0.60 and females >0.56)
  - Raised HCT (male >0.52 and females> 0.48) in association with
    - Recent arterial or venous thrombosis
    - Neurological event suggestive of hyper viscosity
    - Visual disturbance
- Routine referral if persistently ↑Hct (male >0.52 and females> 0.48)
  - Pruritis
  - Splenomegaly
  - Elevated white cell and platelets
  - Co-existent cardiovascular risk factors
  - Unexplained polycythaemia



Neutropenia

- Defined as neutrophils <2.0 x10^9
- Risk of infection related to depth of neutropenia
- Major rise in infection when neuts are <0.5

Causes:

- Infections- Viral, severe bacterial sepsis
- Drugs
- Autoimmune
- Hematinic deficiency
- Ethnic
- Marrow dysfunction
  - Aplasia
  - MDS
  - Infiltration

Investigation in Neutropenia

- Viral serology- EBV, HIV, Hepatitis B & C & CMV
- Autoimmune screen- ANA, Rheumatoid factor
- Blood film
- Haematinic level
- Repeat FBC in 4-6 weeks

Referral in Neutropenia

- Urgent referral if..
  - Co-existing other cytopenia
  - Lymphadenopathy
  - Splenomegaly
  - If neutrophils <1.0 (and not ethnic neutropenia)
  - All neutropenia <1.0 associated with sepsis to be discussed with haematologist
- Routine referral
  - Persistent neutropenia
  - Progressive neutropenia (but well patient)

Leucocytosis

White cell count >10.5 x 10^9/l

- Immediate haematology assessment in:
  - Suspected acute leukaemia
  - New suspected chronic myeloid leukaemia with
    - White cell count >100 x 10^9/l
    - Hyper viscosity symptoms
- Urgent referral if
  - Leucoerythroblastic picture
  - Unexplained leucocytosis >20x 10^9/l
- Investigations
  - Careful history
  - Physical examination
  - Routine bloods including ESR, CRP.

Case 2

- 43 year old caucasian female
- Recurrent abdominal pain and aches and pain in the extremities
- Easy bruising
- ↑menstrual blood loss
- Previous hx of iron deficiency
- Examn - unrewarding
- FBC: Hb 11.2, WBC 15, Plts 1100, MCV 76, Retic 3%
- Blood film

Case 2

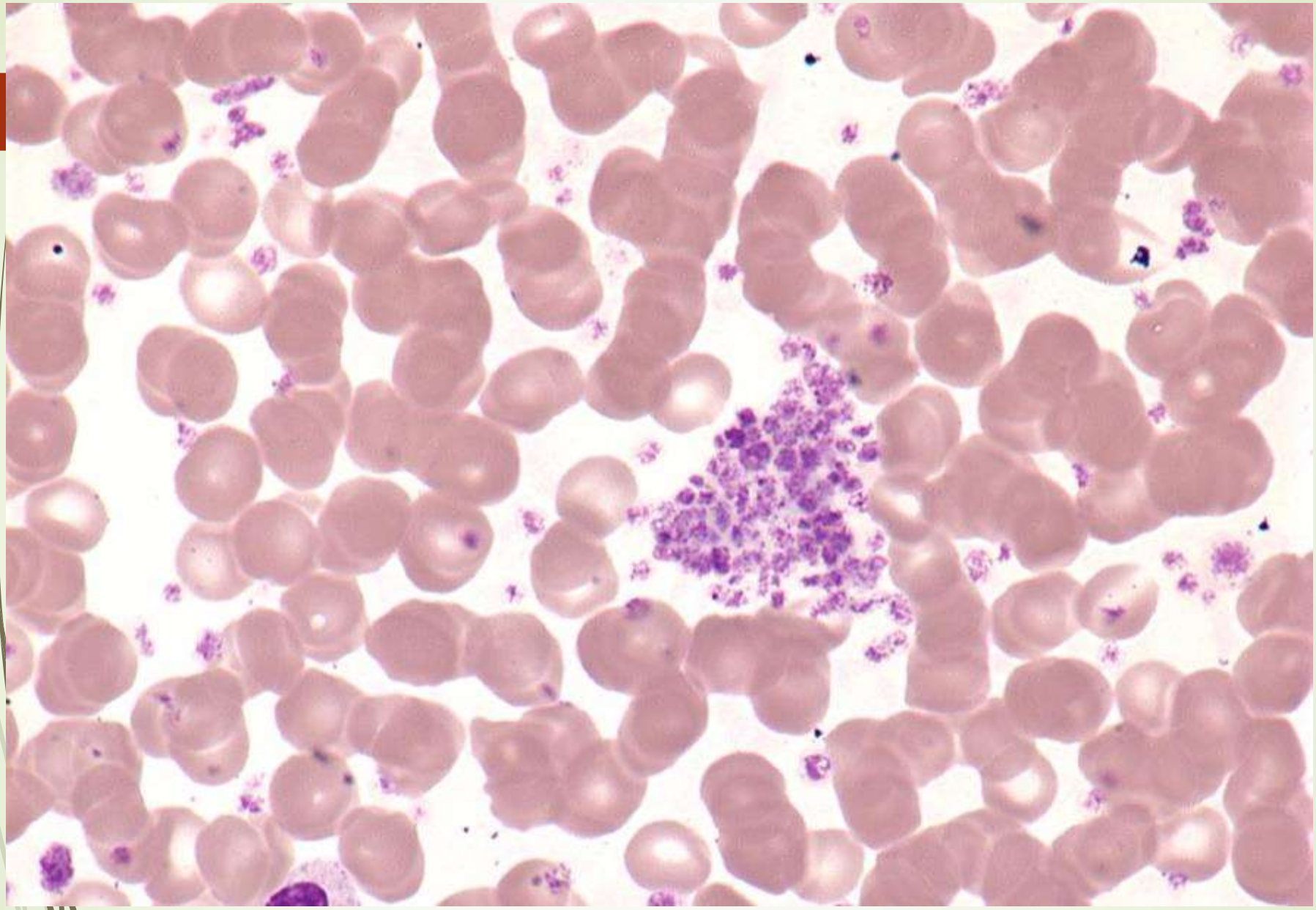
- Further Investigations:

  ↓Ferritin

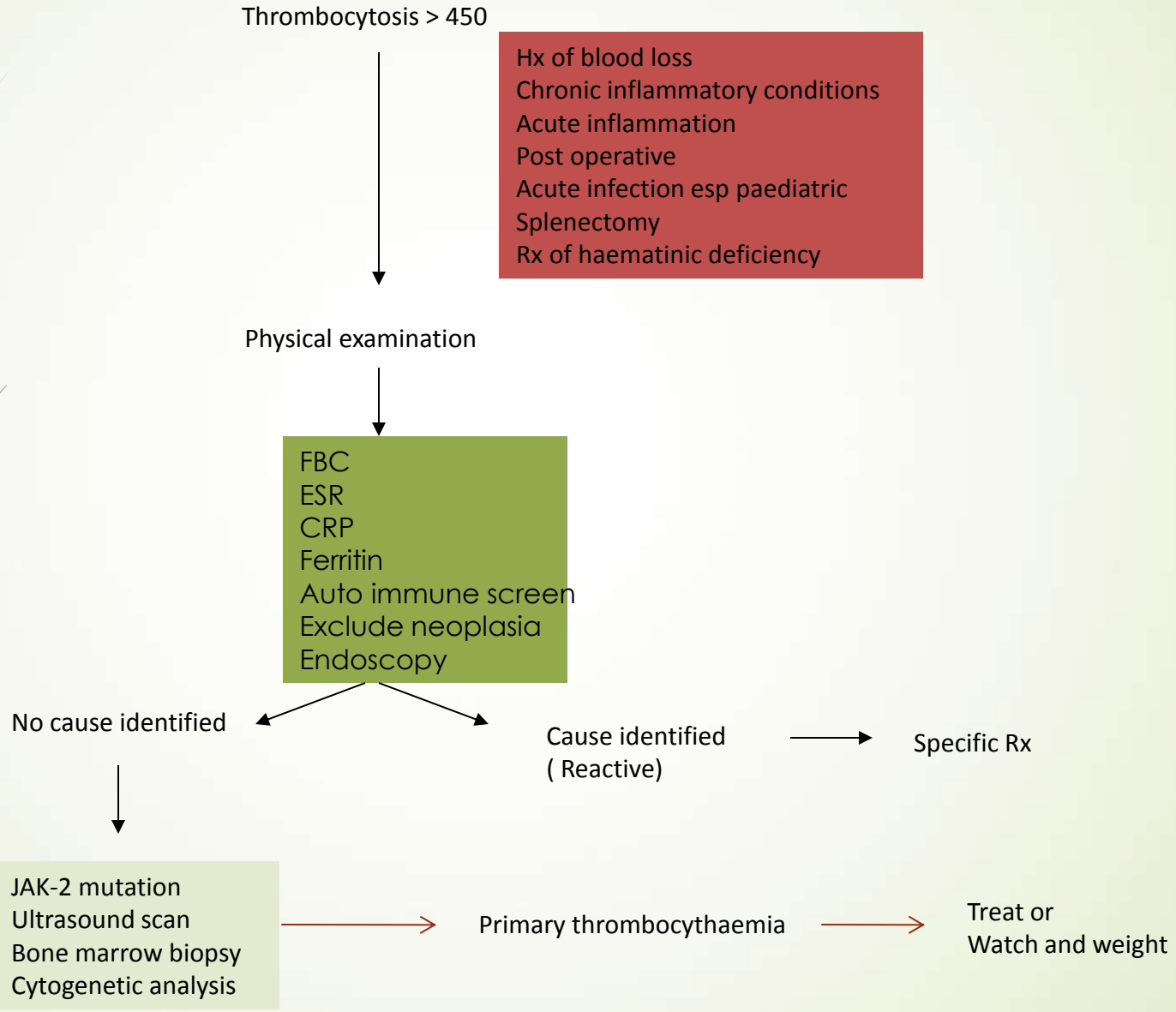
  B12 ↑

  Folate- normal

  CRP & ESR - normal
- Probable diagnosis
- Further tests
  - JAK-2 mutation
  - Bone marrow biopsy
  - Chromosomal analysis
- Final diagnosis:
  - Primary thrombocythaemia



Algorithm of investigations in thrombocytosis



Thrombocytosis- when to refer

- **The following should be referred urgently for outpatient assessment:**
  - Platelet count > 1000 x 10^9/l
  - Platelet count 600 - 1000 x 10^9/l in association with:
  - recent arterial or venous thrombosis (including DVT / PE, CVA / TIA, MI / unstable angina, PVD)
  - neurological symptoms
  - abnormal bleeding
  - age > 60 years

Lymphocytosis

Lymphocyte count > 4 x 10^9/l

- Causes
  - Acute viral infections eg. IMN
  - Chronic lymphocytic leukaemia
  - Monoclonal B cell lymphocytosis (<5 x 10^9/l)
  - Low grade lymphoma

Lymphocytosis

- Investigations in primary care
  - Glandular fever screen (acute lymphocytosis)
  - Other viral serologies- eg HIV
  - Repeat FBC in 4-6 weeks
  - Lifestyle changes – smoking can cause polyclonal B lymphocytosis
  - U&E
  - LFT
  - LDH
  - DAT (if there is co-existent anaemia)

Lymphocytosis- when to refer

Urgent referral if..

Lymphocytosis in association with:

- anaemia, thrombocytopenia or neutropenia
- splenomegaly
- painful or progressive lymphadenopathy
- B symptoms (weight loss >10%, soaking sweats, unexplained fever)
- Lymphocytosis in excess of 10 x 10^9/l (or rapidly increasing)

Routine referral

- Persistent lymphocytosis > 5 x 10^9/l

Thrombocytopenia

Platelets <150 x 10^9/l

- Most patients are asymptomatic >50 x10^9/l
- Spontaneous bleeding usually <20 x 10^9/l

- Causes
  - Acute viral infection
  - Immune
  - Marrow dysfunction
    - Aplasia
    - MDS
    - Infiltration
    - Haematinic deficiency
    - Drugs
    - Sepsis
    - Artefactual (clumps)
  - Hypersplenism
  - TTP/DIC

When to refer low platelets

Urgent referral

- Platelet count < 50 x 10^9/l
- Platelet count 50 - 100 x 10^9/l in association with:
- other cytopenia (Hb < 10g/dl, Neutrophils < 1 x 10^9/l)
- splenomegaly
- lymphadenopathy
- pregnancy
- upcoming surgery

Severe thrombocytopenia (<20 x 10^9/l) – discuss urgently with haematologist

Thrombocytopenia contd..

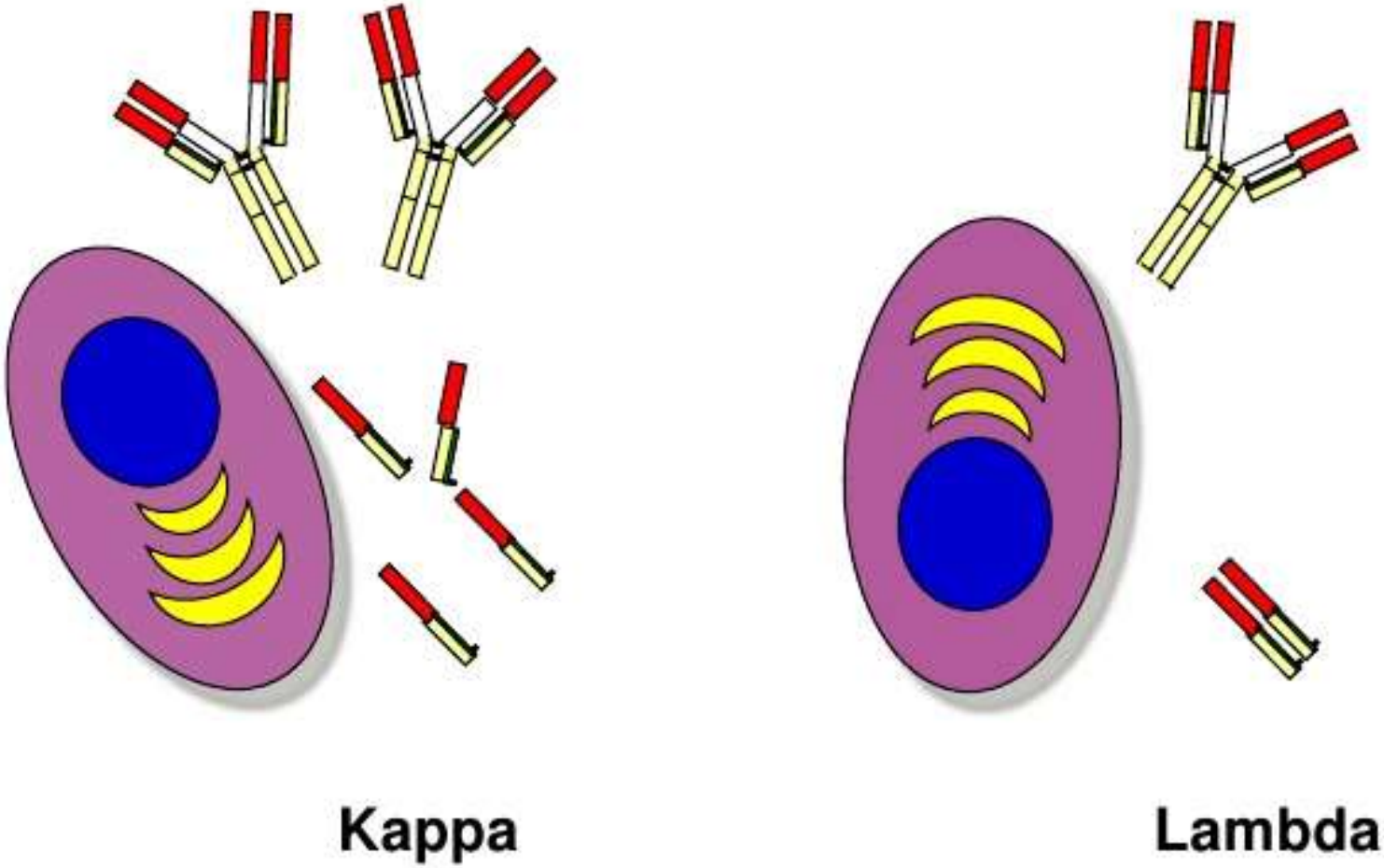
Investigations in primary care:

- Blood film examination - may exclude platelet clumping artefact
- Autoimmune profile
- Liver biochemistry
- Viral screening (HIV, Hep B, Hep C , EBV)
- Alcohol history
- Consider discontinuation of potentially precipitating medications
- Repeat FBC in 4-6 weeks

Case 3

- 78 y.o man
- 4 week history of severe back pain
- PMH- Hypertension on ACEI
- Precipitated by prolonged gardening in the summer
- Not responding to paracetamol, tramadol
- Physical examination – unremarkable
- Routine bloods- FBC: Hb 134, Wbc 6.8, Plts 380 & MCV 102
  - U&E: Creatinine 138, eGFR 48, K 4.8 & corrCa 2.3
  - SEP (Ig G kappa M band 10g/l)

PLASMA CELLS PRODUCE WHOLE IMMUNOGLOBULIN AND FREE LIGHT CHAINS



Paraproteinaemia

- What are Paraproteins?
- Types- Intact Ig

  IgG, IgA, IgM , IgD & IgE

  Light chain

  Kappa or Lambda

  Heavy chain

  μ, α and γ

Conditions associated with paraproteinaemia

- MGUS
- Myeloma
- Primary Amyloidosis
- Low grade - B cell NHL
- CLL

Non-Haematological causes

Connective tissue disorders

Inflammatory bowel disorder

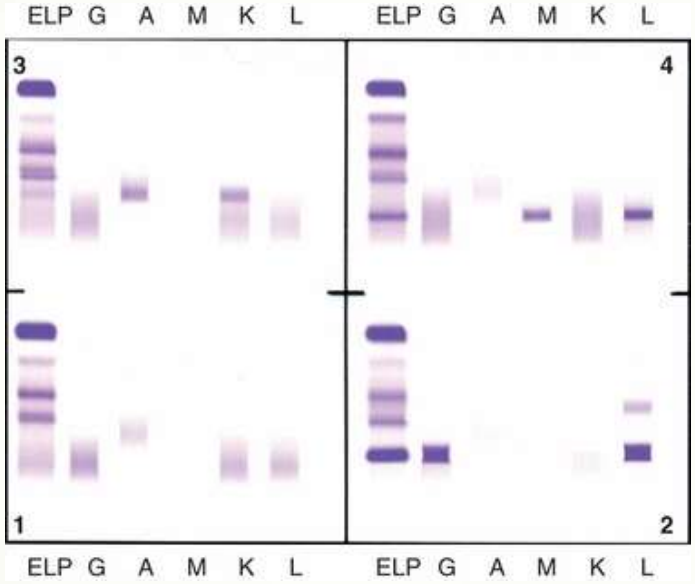
Pyoderma gangrenosum

Chronic infection

Prevalence

- 3.2% older > 50 years
- 5% older > 70 years
- 9% older > 85 years !!
  - Kylie et al 2006
- But most patients are asymptomatic
- Now constitute 5-8% of haematology referral

UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS)



British Journal of Haematology
Volume 147, Issue 1, pages 22-42, 10 AUG 2009 DOI: 10.1111/j.1365-2141.2009.07807.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2009.07807.x/full#f2

MGUS

Definition

- Paraprotein <30g/l

- No evidence of organ damage-
  - Renal
  - Skeletal
  - Haematological
  - Calcium

- Clonal plasma cells in the bone marrow < 10%

MGUS: RISK STRATIFICATION MODEL

Risk Group	Absolute risk of progression at 20 yrs.	20 yr. risk of progression after other causes of death
1. Low-risk Serum M protein <1.5 gm/dL, IgG subtype, normal FLC ratio	5%	2%
2. Low/Intermediate-risk Any 1 factor abnormal	21%	10%
3. Hi/Intermediate-risk Any 2 factors abnormal	37%	18%
4. High-risk All 3 factors abnormal	58%	27%

MGUS

Investigations:

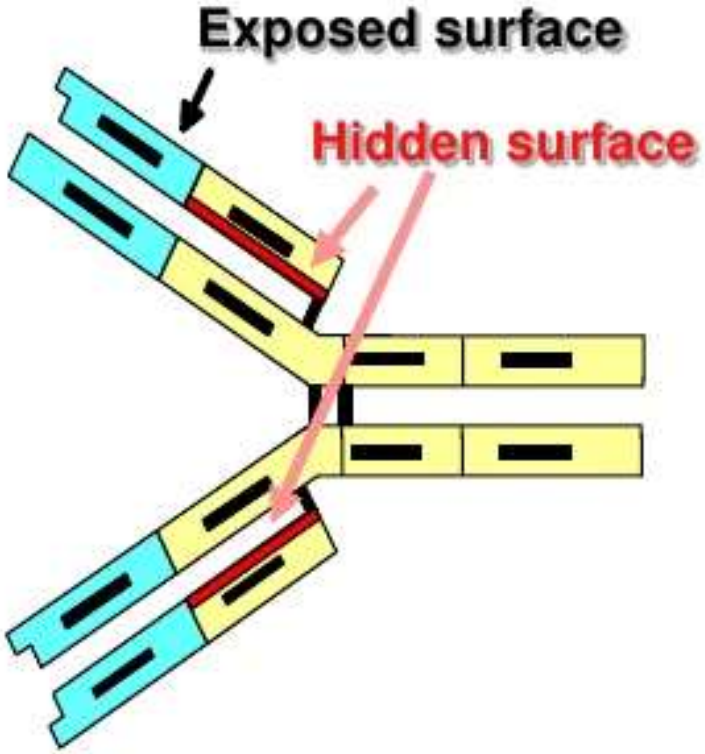
- FBC
- U&E
- Bone profile
- β2 microglobulin
- SPE
- Urine - Bence Jones Protein
- Serum Free light chain
- Bone marrow bx in suspected high risk cases

TOOLS FOR EVALUATION OF MONOCLONAL GAMMOPATHIES

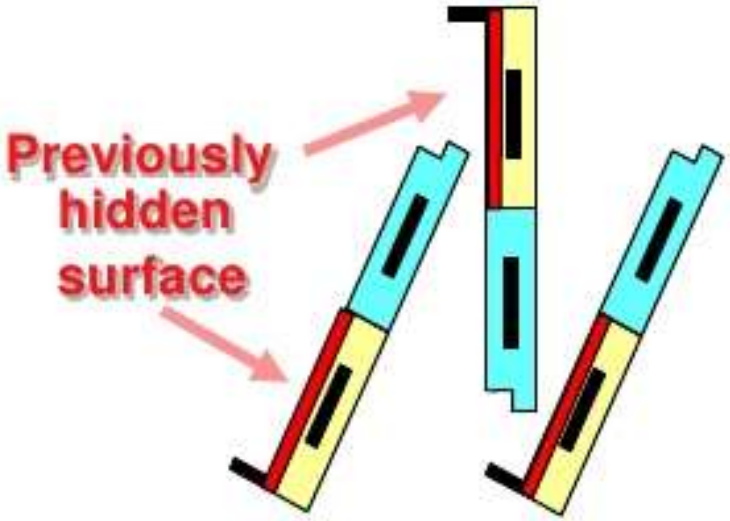
- SPEP
- Immunofixation
- UPEP on 24-hour urine
- **Serum free light chain assay**

SERUM FREE LIGHT CHAIN ASSAY

Intact Immunoglobulin



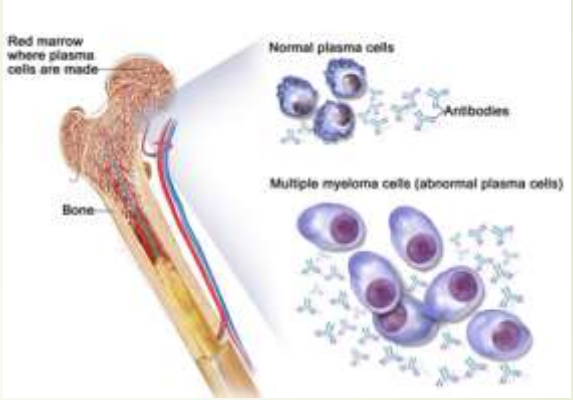
Free Light Chain



SERUM FREE LIGHT CHAIN ASSAY

- Serum assay
  - Eliminates need to collect urine specimen
- More sensitive than SPEP or SIFE
- Indications:
  - Diagnosis of Plasma Cell Disorders
  - Prognosis & Risk Stratification
  - Response Assessment on therapy
  - Disease Monitoring on follow up

MGUS - SFLC



Serum Free Light Chains:

- More accurate than uBJP
- Easily reproducible
- Avoids the sampling issue with urine
- Get a total amount for:Kappa (3.3 - 19.4)
  Lambda (5.7 - 26.3)
  K/L ratio (0.3 - 1.7)

- Additional comment added K/L ratio between 0.1-10 are unlikely to be of clinical consequence

When to refer paraproteinaemia

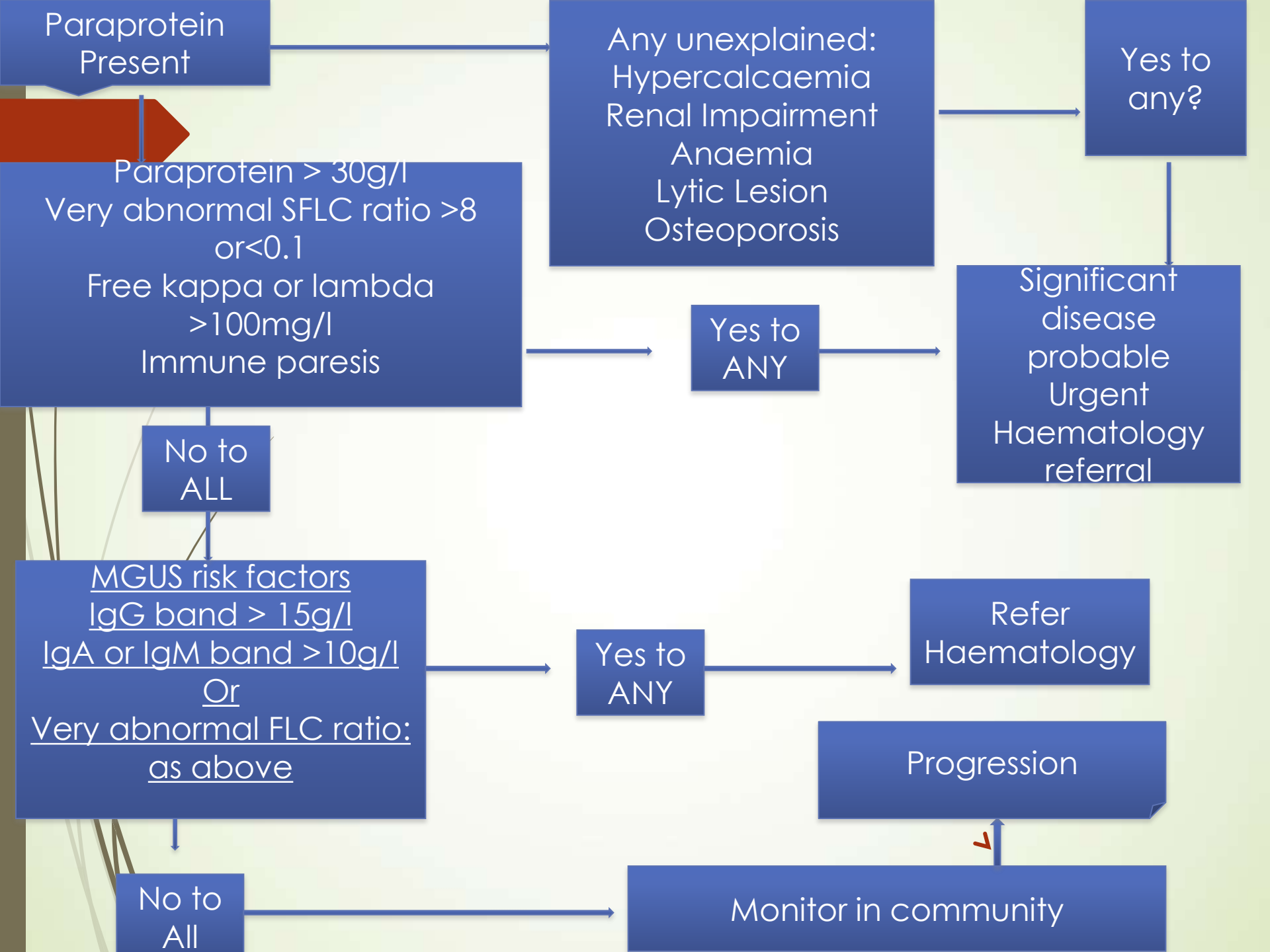
Urgent referral

- Any new paraprotein with accompanying features suggestive of multiple myeloma or other haematological malignancy, including:
  - hypercalcaemia
  - unexplained renal impairment
  - urinary Bence Jones proteins, increased urinary protein
  - bone pain or pathological fracture
  - radiological lesions reported as suggestive of myeloma
  - anaemia or other cytopenia
  - Hyper viscosity symptoms (headache, visual loss, acute thrombosis)
  - lymphadenopathy or splenomegaly
  - lymphocytosis

When to refer paraproteinaemia

Routine referral if

- Other newly-identified para proteins not meeting above criteria:
  - Any IgG PP >15g/L
  - Any IgA or IgM PP> 10g/L
  - Any IgD or IgE PP regardless of concentration

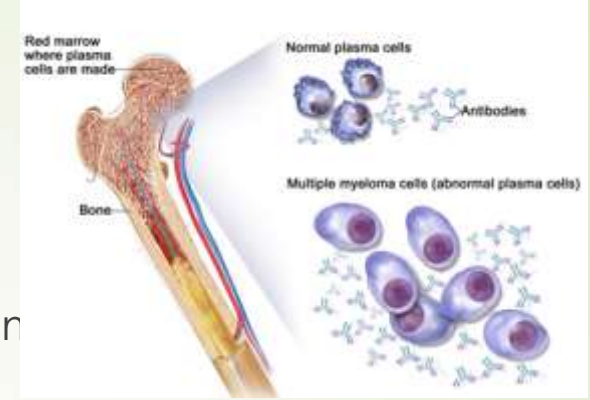

Paraprotein Present
Any unexplained:
Hypercalcaemia
Renal Impairment
Anaemia
Lytic Lesion
Osteoporosis
Yes to any?
Paraprotein > 30g/l
Very abnormal SFLC ratio >8 or<0.1
Free kappa or lambda >100mg/l
Immune paresis
Yes to ANY
Significant disease probable Urgent Haematology referral
No to ALL
MGUS risk factors
IgG band > 15g/l
IgA or IgM band >10g/l
Or
Very abnormal FLC ratio: as above
Yes to ANY
Refer Haematology
Progression
No to All
Monitor in community

Paraproteinaemia- monitoring in community

If IgG < 15g/L and IgA/M < 10g/L

- FBC, Calcium, U&E and SPE check every 3-4months for one year
- Intervals can be extended to 6 monthly if patient remains asymptomatic and paraprotein stable

MGUS - pathway



Signs of progression

- 25% increase in total paraprotein level (minimum of 5g/L)

  OR

- 25% increase total level of the affected light chain LC (Kappa or Lambda)
  - minimum absolute LC level >100 mg/L

  AND
  - ratio of >10.0 or <0.1

- Hypercalcaemia
  - (corrected Ca > 2.75 mmol/L)

- Otherwise unexplained renal failure
  - 25% increase in creatinine or creatinine >177 µmol/L

- Lytic bone lesions or compression fractures

- Severe bone pain

When to re-refer?

- New unexplained compression fracture
- Progressive unexplained anaemia (<10g/l or 2g/l below baseline)
- Deteriorating unexplained renal function (25% increase in creatinine)
- Hypercalcaemia
- >25% increased concentration from previous reading or rising trend
- In cases of IgM paraprotein- B symptoms or new onset lymphadenopathy
- https://www.myeloma.org.uk/wp-content/uploads/2014/05/Myeloma-UK-MGUS-Infosheet.pdf

Any Questions??????

Thank you!