An abnormal FBC: knowing when to refer

Dr Patrick Hayden
Consultant Haematologist
11th March 2023

Beacon Hospital
This is Modern Medicine

Disclaimer

While the information in this presentation is believed to be true and accurate, the author does not accept any legal responsibility for the content of this guidance and advises referral to specialist haematology services in all cases

Clinical cases

Microcytic anaemia

Macrocytic anaemia

Polycythaemia

Raised White Cell Count – neutrophilia, lymphocytosis

Low White Cell Count – neutropenia, lymphopenia

Thrombocytosis

Paraprotein

Raised Ferritin

Hb reference ranges

Neonates	14-24g/dL
2 months	8.9-13.2g/dL
9-12 years	11.5-15.4g/dL

Pregnancy

3rd trimester	9.8-13.7g/dL

Age 5th to 7th decade

Fall in men, rises in women

Exercise

Altitude

Smoking

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Changes in full blood count parameters with age and sex: results of a survey of almost 900 000 patient samples from primary care

The Full blood count (FBC) is a frequently requested blood test in both primary and secondary care. Given that the population in England is ageing, with 18·3% of the population aged ≥65 years in 2018,[1] it is important to ascertain how FBC parameters change in older patients. The aim of this study was to examine changes in FBC parameters with age and sex using a dataset of almost 900 000 primary care patients in England.

Methods

The reporting of routine blood tests in primary care for NHS England occurs electronically via the NHS spine data transfer service (DTS).[2] In July 2013, all blood test results were captured from the DTS over a 23-day period as part of an audit of data quality, sponsored by the UK Department of Health and overseen by the Royal College of Pathologists. Anonymised FBC data were made available for analysis in accordance with NHS coding standards. The data were restricted to

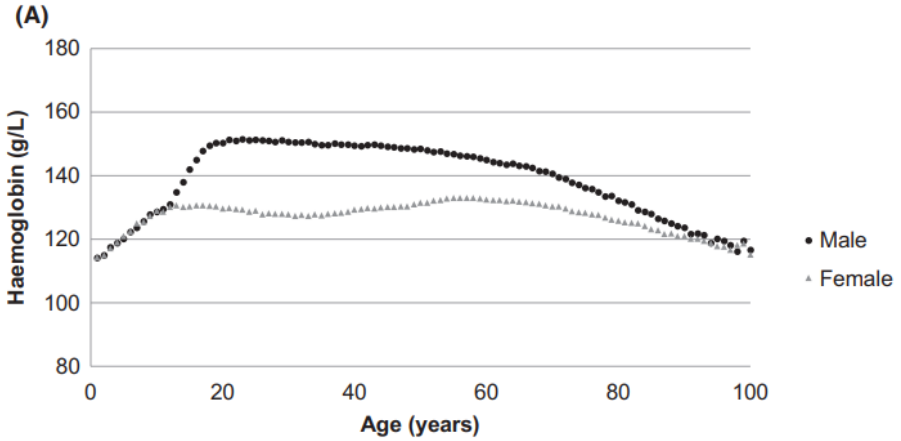
age 20 years. After this, it declines steadily until approximately age 70, when it starts to decline at an increasing rate (Fig 1A). In females, mean haemoglobin concentration increases until approximately age 14, when it starts to decline slowly until age 30, then increases again until age 60, and thereafter declining with age. Haemoglobin concentration in males and females begins to converge after age 60 and equalises by approximately 90 years.

In order to exclude common causes of anaemia, namely haematinic deficiency and renal impairment, haemoglobin concentrations were further assessed in a subset of patients over 18 years where concomitant test results for ferritin, B12, folate and creatinine were within their respective reference intervals (Fig 1B–F). For males with ferritin >30 μg/l, B12 > 200 ng/l, folate > 5 μg/l or creatinine <100 mmol/l, there were 6257, 6141, 4581 and 38 186 haemoglobin results respectively, and 1151 haemoglobin results where all four parameters were within range for a single blood test (Fig 1F).

Author Contributions

Rupert Phillips and Gary Weaving analysed the data. Rupert Phillips and Henry Wood researched the literature and wrote the paper. All authors critically revised the paper and approved the final manuscript.

Rupert Phillips[1]
Henry Wood[2]
Gary Weaving[1]
Timothy Chevassut[3]
[1]Brighton and Sussex University Hospitals NHS Trust, Brighton, [2]Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London and [3]Department of Haematology, Brighton



British Journal of Haematology, 2021, **192,** e99–e120

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Clinical cases

Microcytic anaemia

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Clinical cases

34 year old woman

Referred with ‘anaemia’ found on health screen for visa application
Some fatigue and menorrhagia

Had been on “iron supplements for two years without response”

No significant medical history
Medications – OCP and Galfer (ferrous fumarate)

Social history – Artist, two children, aged 4 and 1 years
Physical examination unremarkable

Parameter	Measurement
Hb	11.0 g/dL
MCV	65 fl
WCC	5.5 x 10*9/L
Plts	231 x 10*9/L

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Hb	11.0 g/dL
MCV	65 fl
WCC	5.5 x 10*9/L
Plts	231 x 10*9/L
Ferritin	466 ug/L (ref range 23-393)
Haemoglobinopathy screen	A2 6.2% (ref range 2.5-3.5)

Diagnosis: Beta Thalassaemia Trait

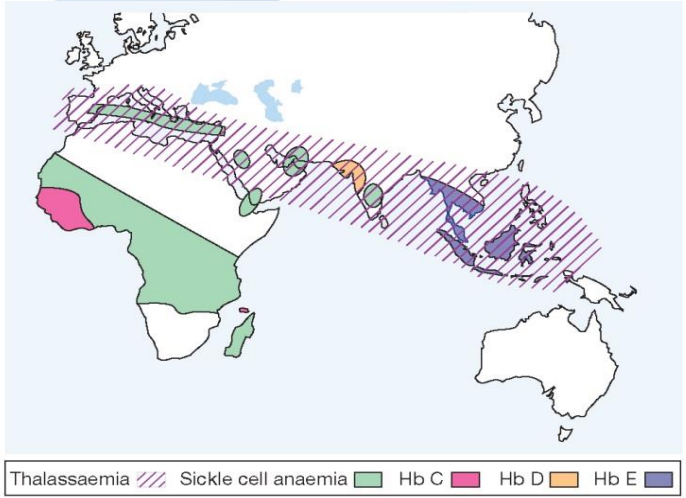
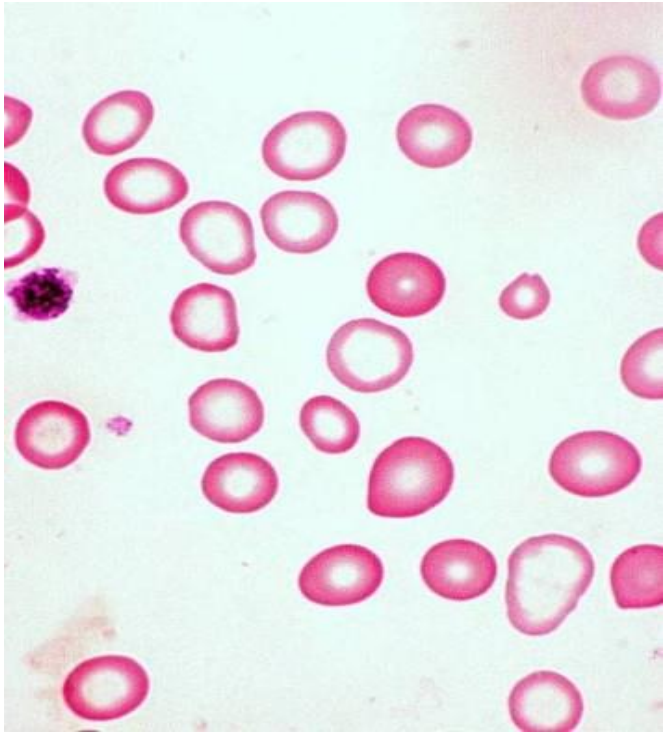
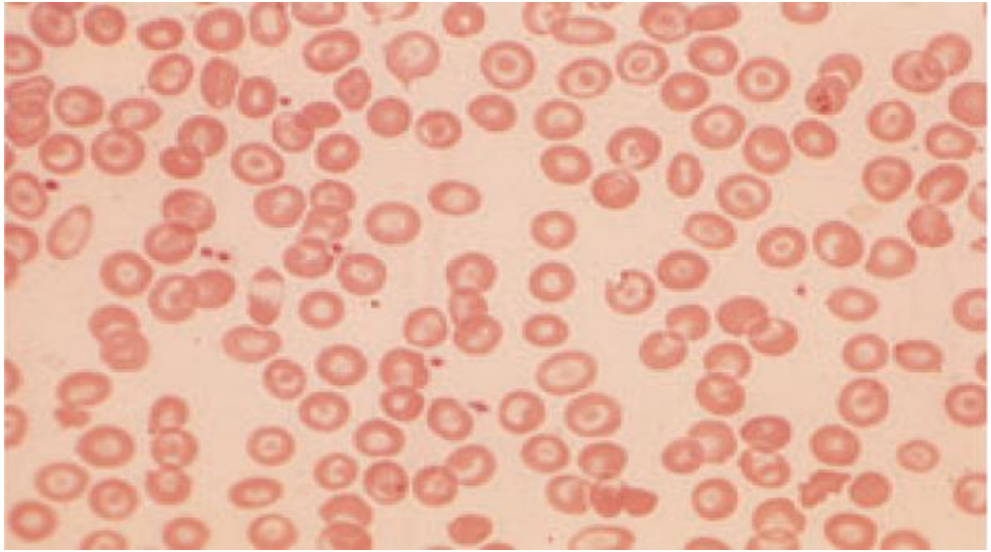


Figure 7.4 The geographical distribution of the thalassaemias and the more common, inherited, structural haemoglobin abnormalities.

Hoffbrand's Essential Haematology, Seventh Edition. By A. Victor Hoffbrand and Paul A. H. Moss. Published 2016 by John Wiley & Sons Ltd.



Blood film
Iron Deficiency Anaemia



Blood film
Beta Thalassaemia Trait

The Red Cell Distribution Width (RDW) is a measurement of the variation in size of Red Cells

Table 1a. Hematological Data on Patients with IDA and BTT

	Normal	IDA (n=81)	BTT (n=135)	p-value
Hematological data		Mean +/- SD	Mean +/- SD	
Hemoglobin	14-18 g/dL	9.34±1.6	10.4± 1.5	<.001
Red cell count	4.7-6.1×10^{12}/L	4.34± 0.8	5.6±0.7	<.001
Hematocrit	42-52%	34.1± 2.9	37.2 ±13.3	<.001
MCV	81-99fl	70.6±9.1	63.1±5.3	<.001
MCH	27-31pg	21.56 ±5.1	18.8 ±2.2	<.001
MCHC	32-36 g/dL	29.8± 3.4	29.6 ±1.2	<.001
RDW-CV	11-14%	17.9± 3.8	17.1± 2.1	<.003
RDW-SD	42-46fl	43.8 ±3.3	38.7± 3.4	<.010
Serum iron	6–37ug/dL	3.4 ± 1.2	36.54 ± 12.65	<.029
HbA2	< 3.5%	2 ± 0.4	5.97 ± 1.32	<.001

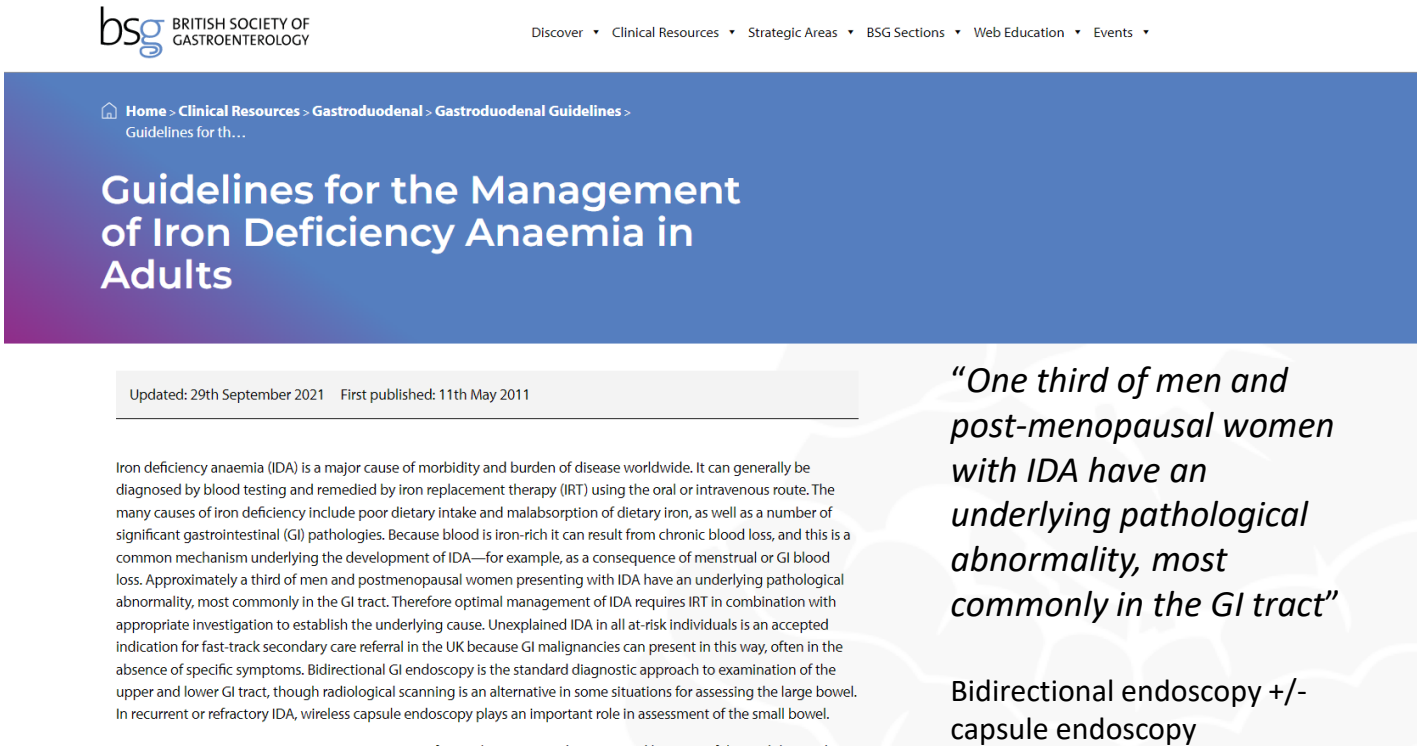
The percent of IDA and BBT was based on the total number of IDA and BBT diagnosed by serum iron, TIBC, response to iron therapy and Hgb A2 levels. Serum ferritin testing was not available.

Comparison of haematological parameters between patients with iron deficiency anaemia (IDA) and Beta Thalassaemia Trait (BTT) highlights value of MCV and HbA2

T P, S A. *Discriminant Functions In Distinguishing Beta Thalassemia Trait and Iron Deficiency Anemia: The value of the RDW-SD*. The Internet Journal of Hematology. 2010 Volume 7 Number 2.

Age-specific causes of iron deficiency

	Female	Male
1-5 years	Nutrition	Nutrition
6-15 years	Increased utilisation/growth	Increased utilisation/growth
16-40 years	Menstruation/ Pregnancy	Coeliac disease (Malabsorption) - tTG
>40 years	Gastrointestinal blood loss	Gastrointestinal blood loss



"One third of men and post-menopausal women with IDA have an underlying pathological abnormality, most commonly in the GI tract"

Bidirectional endoscopy +/- capsule endoscopy

https://www.bsg.org.uk/clinical-resource/guidelines-for-the-management-of-iron-deficiency-anaemia/

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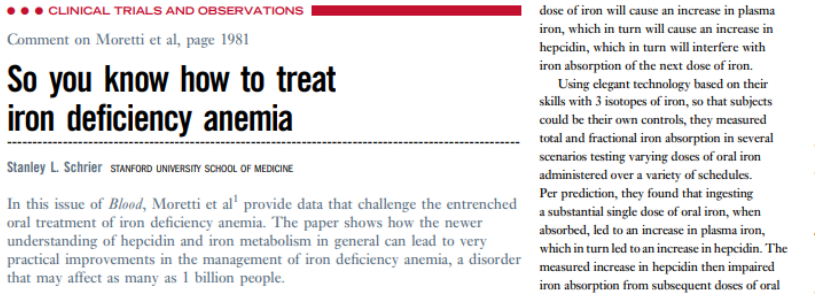
inside blood commentary
22 OCTOBER 2015 | VOLUME 126, NUMBER 17



CLINICAL TRIALS AND OBSERVATIONS

Comment on Moretti et al, page 1981

So you know how to treat iron deficiency anemia

Stanley L. Schrier STANFORD UNIVERSITY SCHOOL OF MEDICINE

In this issue of *Blood*, Moretti et al[1] provide data that challenge the entrenched oral treatment of iron deficiency anemia. The paper shows how the newer understanding of hepcidin and iron metabolism in general can lead to very practical improvements in the management of iron deficiency anemia, a disorder that may affect as many as 1 billion people.

dose of iron will cause an increase in plasma iron, which in turn will cause an increase in hepcidin, which in turn will interfere with iron absorption of the next dose of iron.

Using elegant technology based on their skills with 3 isotopes of iron, so that subjects could be their own controls, they measured total and fractional iron absorption in several scenarios testing varying doses of oral iron administered over a variety of schedules. Per prediction, they found that ingesting a substantial single dose of oral iron, when absorbed, led to an increase in plasma iron, which in turn led to an increase in hepcidin. The measured increase in hepcidin then impaired iron absorption from subsequent doses of oral

It may be that our orthodox treatment of iron deficiency anemia is all wrong. It results in an ~12% to 15% absorption of iron and produces unpleasant side effects. Rather than administering 1 large iron pill 3 times per day, maybe we should treat iron deficiency anemia by giving a single substantial dose of elemental ferrous iron before breakfast on Monday, Wednesday, and Friday. Recall that we need to absorb only ~180 mg of iron per week to meet and beat the best current program.

https://ashpublications.org/blood/article/126/17/1971/34416/So-you-know-how-to-treat-iron-deficiency-anemia

Take Home Messages on Microcytic Anaemia

Iron deficiency is the most common cause of a microcytic anaemia in the developed world

The first line test is a serum ferritin to assess iron stores

Other serum iron studies (serum iron, TIBC, transferrin saturation) less useful in the evaluation of iron deficiency anaemia

Menstrual loss is the commonest cause in pre-menopausal women

Gastrointestinal blood loss is the commonest cause in all other adults

If serum ferritin is low, consider direct referral to endoscopy, esp. if GI symptoms

If Hb relatively preserved and MCV very low (discrepant microcytosis), consider haemoglobinopathy e.g. thalassaemia trait – order a haemoglobinopathy screen

Anaemia of chronic disease (AOCD), though usually normocytic, can present with microcytic indices

Treatment of Iron Deficiency Anaemia

Oral iron preparations - Take one tablet three-to-five times weekly

Galfer	305mg Hard Capsules - ferrous fumarate 305mg (equivalent to 100mg elemental iron)
Ferrograd C	325mg/500mg Prolonged release Tablets Dried Ferrous Sulphate 325.0 mg (elemental iron 105 mg)

Many other OTC iron preparations contain significantly less iron

IV iron an option in selected patients clearly intolerant of oral iron supplements

Limited evidence for the treatment of a low serum Ferritin if Hb remains normal

Treatment options for menorrhagia include tranexamic acid and hormonal contraception

Serial monitoring of FBC (Hb) and Ferritin can be useful following iron repletion

Online resources

How to Interpret and Pursue an Abnormal Complete Blood Cell Count in Adults
Mayo Clinic Proceedings 2005
https://www.mayoclinicproceedings.org/action/showPdf?pii=S0025-6196%2811%2961568-1

UK guidelines on the management of iron deficiency in pregnancy - 2019
https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.16221

Guidelines for the management of iron deficiency anaemia
British Society of Gastroenterology - 2021
https://gut.bmj.com/content/gutjnl/70/11/2030.full.pdf

Investigating abnormal uterine bleeding in reproductive aged women - 2022
https://www.bmj.com/content/378/bmj-2022-070906

Clinical cases

Macrocytic anaemia

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Clinical cases

54 year old woman

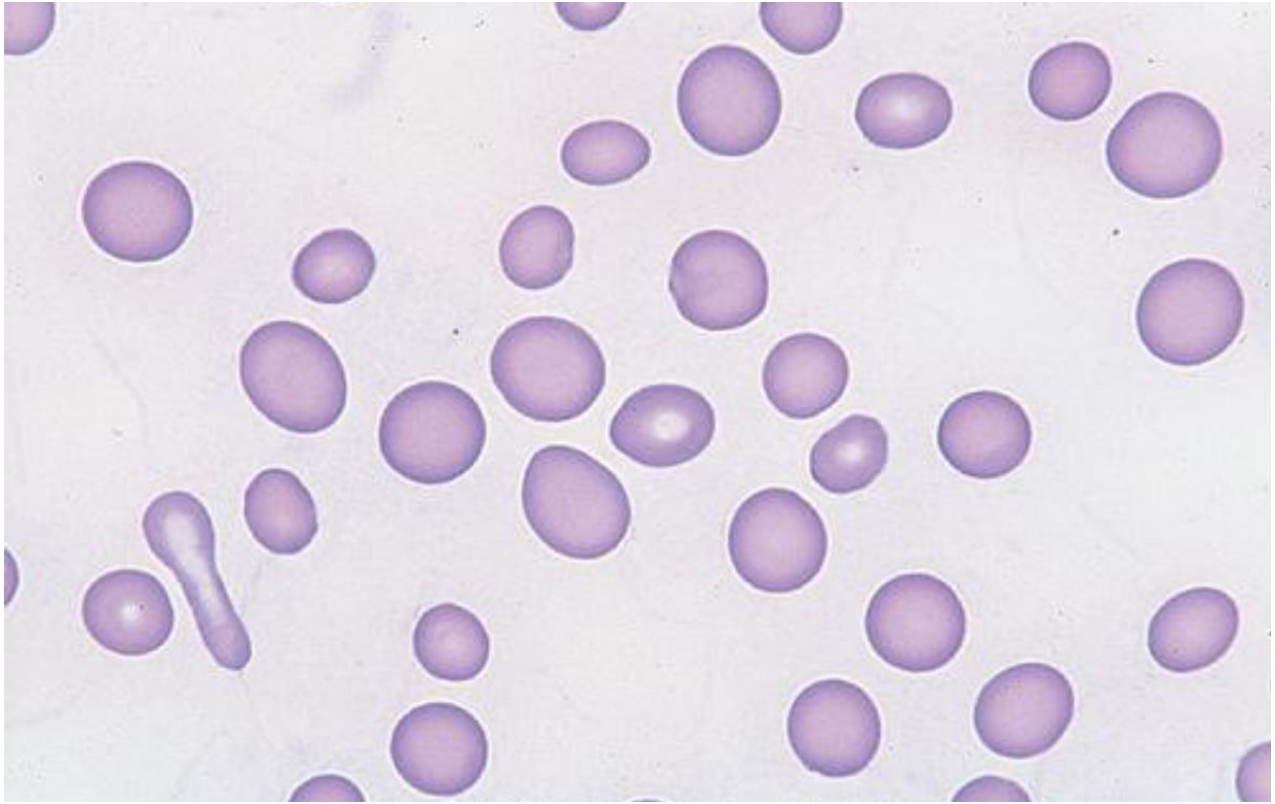
‘Severe fatigue and bruising’

Type I IDDM, Hypothyroidism
Multiple medications

Social history
Businesswoman, self-employed, three adult children

Physical examination
Pale, bruises on thigh, laparotomy scars

Parameter	Measurement
Hb	4.9 g/dl
MCV	118 fl
WCC	3.5 x 10*9/l
Plts	67 x 10*9/l
Reticulocyte (%)	0.1% (ref range 0.5-2%)
Bilirubin	25 (ref range 5-17)
LDH	1120 (ref range 190-320)



Macro-ovalocytes and anisocytosis

Parameter	Measurement
Vitamin B12	22 ng/l (ref range 200-1200)
Folate	2.7 ug/l (ref range 2-9)
Ferritin	59 ug/l (ref range 23-393)
Anti-intrinsic factor antibodies	Positive
Anti-gastric parietal cell antibodies	Positive

Diagnosis: Pernicious Anaemia

Parameter	Measurement
Vitamin B12	22 ng/l (ref range 200-1200)
Folate	2.7 ug/l (ref range 2-9)
Ferritin	59 ug/l (ref range 23-393)
Anti-intrinsic factor antibodies	Detected in 50% (highly specific to PA)
Anti-gastric parietal cell antibodies	Detected in 80-90% (not specific)

Treatment of Pernicious Anaemia

Hydroxycobalamin (Vitamin B12) 1mg IM or SC

Always give Folic acid 5mg once daily aswell

Never treat a macrocytic anaemia with Folic acid alone

Hypokalaemia is occasionally observed within days due to rapid rebound in haematopoiesis

Reticulocytosis within five days

Often a subjective improvement within 24 hours

Give five B12 injections during the first two weeks

Then three monthly for life

Follow-up - check FBC and TFTs

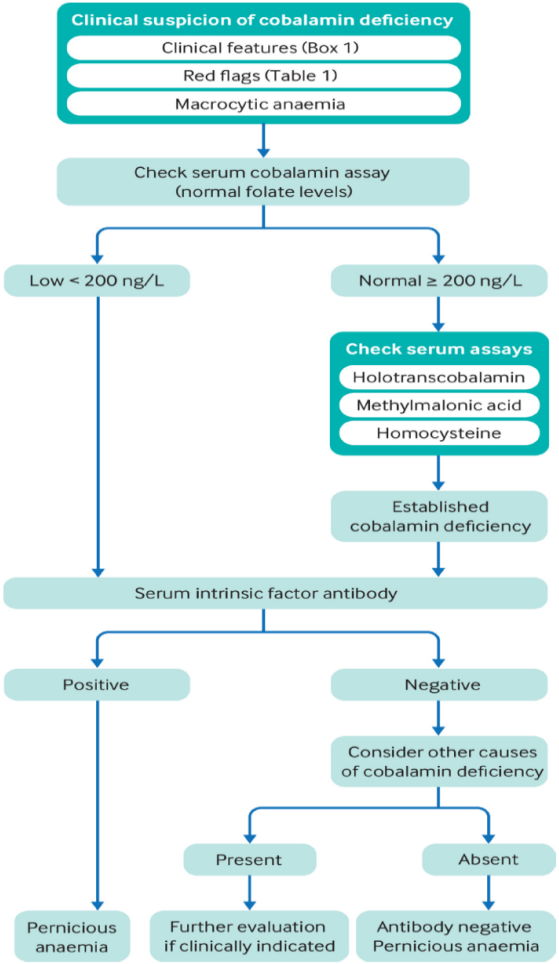


Fig 3 | Algorithm for investigating suspected pernicious anaemia

1 Department of Medicine, Launceston General Hospital, Australia
2 University of Tasmania, Launceston Clinical School, Launceston, Australia
3 Department of Medicine, Launceston

EASILY MISSED?

Pernicious anaemia

Muhajir Mohamed, [1,2] Joel Thio, [3] Remy Susan Thomas, [4] Jehan Phillips [5]

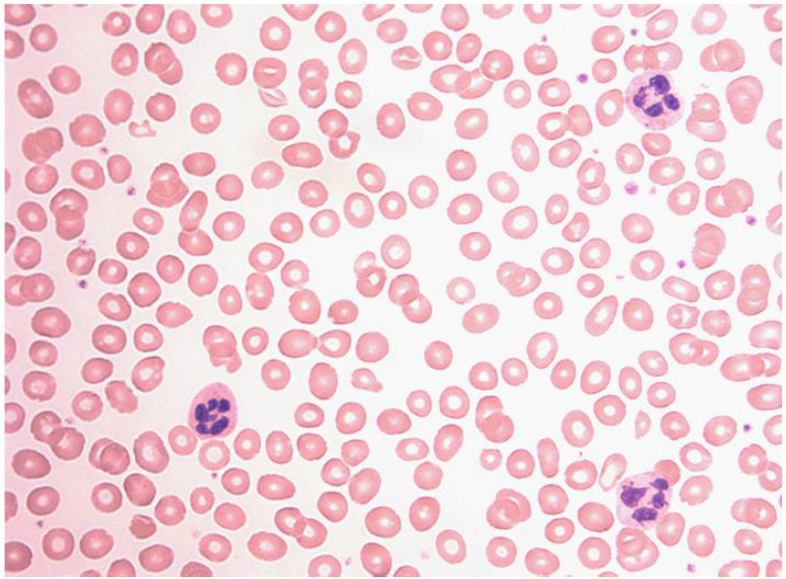


Fig 2 | Blood film in a patient with pernicious anaemia showing the presence of macro-ovalocytes and hypersegmented neutrophils

the bmj | BMJ 2020;369:m1319 | doi: 10.1136/bmj.m1319

Causes of Macrocytic anaemia

Megaloblastic anaemia – B12 or folate deficiency

B12 Deficiency

Malabsorption e.g. Pernicious Anaemia, Crohn's disease

Dietary e.g. vegan

Folate Deficiency

Poor diet e.g. homeless, alcoholism

Increased demand e.g. pregnancy, haemolysis

Malabsorption e.g. coeliac disease

Drugs e.g. anti-epileptics, methotrexate

Causes of Macrocytic anaemia

Non-Megaloblastic macrocytic anaemia –

Liver Disease
Infiltration of the bone marrow
Haemorrhage or haemolysis – increased reticulocyte count
Check Direct Antiglobulin Test (DAT) or Direct Coombs Test –
Positive in Autoimmune Haemolytic Anaemia (AIHA)
Drug therapy esp. hydroxycarbamide (good to check compliance - ↑MCV if taking hydrea)
Hypothyroidism
Myelodysplasia

Macrocytosis with or without anaemia
Alcohol

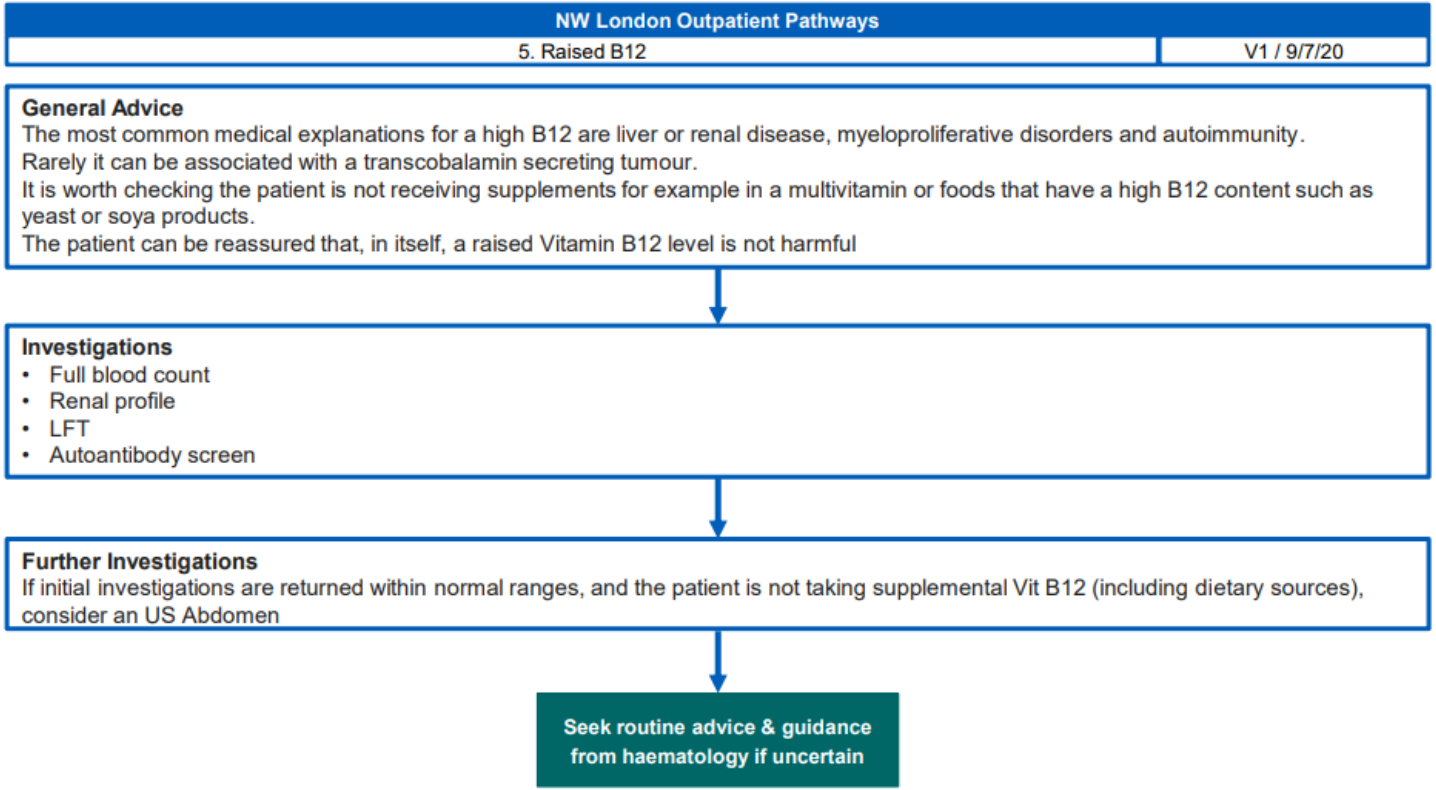
Take Home Messages on Macrocytic Anaemia

Pernicious Anaemia is an autoimmune disease with systemic effects due to low B12 levels
Folate deficiency is associated with social deprivation or malnutrition more generally
The LDH is usually raised in megaloblastic anaemia, consider possibility of acute leukaemia
Treat with Vitamin B12 and folic acid
Beware of over-interpreting mild abnormalities in the B12 assay result (>160) in well patients

Myelodysplasia not uncommon in an elderly population
However, may not warrant referral until there are significant cytopenias

Isolated Macrocytosis may be due to alcohol, liver disease or smoking
Macrocytosis found in 8.4% of adults >45 years in a UCC study
Associations with an elevated GGT and smoking; seldom warrants referral if sole abnormality

Raised B12 level



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Online resources

British Society for Haematology Guidelines for the diagnosis and treatment of cobalamin and folate disorders

https://b-s-h.org.uk/guidelines/guidelines/diagnosis-of-b12-and-folate-deficiency/

"serum cobalamin level can be affected by many variables i.e. diet, pregnancy, vitamin supplements, contraceptive pill, metformin etc."

Investigating vitamin B12 deficiency (2019)

https://www.bmj.com/content/365/bmj.l1865

Easily missed? Pernicious anaemia (2020)

https://www.bmj.com/content/369/bmj.m1319

Clinical cases

Polycythaemia

Clinical cases

46 year old man referred following an episode of transient expressive dysphasia

Medical history – Hypertension, obesity (BMI 32)

Medications – HCTZ

Social history – Businessman, three young children, non-smoker

Physical examination – normal

Laboratory investigations….

Parameter	Measurement
Hb	19.1 g/dl
RCC	5.9 (ref range 4.2-5.4)
Hct	0.56
WCC	11.5 x 10*9/l
Plts	982 x 10*9/l

Causes of Polycythaemia

Hypoxic lung disease

Heavy smoking whether or not a patient has established COPD

Cyanotic congenital heart disease (e.g. Down's syndrome & VSD shunt)

Residence at high altitude

Gross obesity and hypoventilation (Pickwickian syndrome)

Erythropoietin-secreting tumours

Pseudopolycythaemia or Gaisbock's syndrome

Relative polycythaemia due to plasma depletion (diuretics)

Polycythaemia Vera (PV) or Primary Proliferative Polycythaemia (PV) –
Different names for this myeloproliferative neoplasm (MPN)

Work-up

MRI Brain – no evidence of CVA

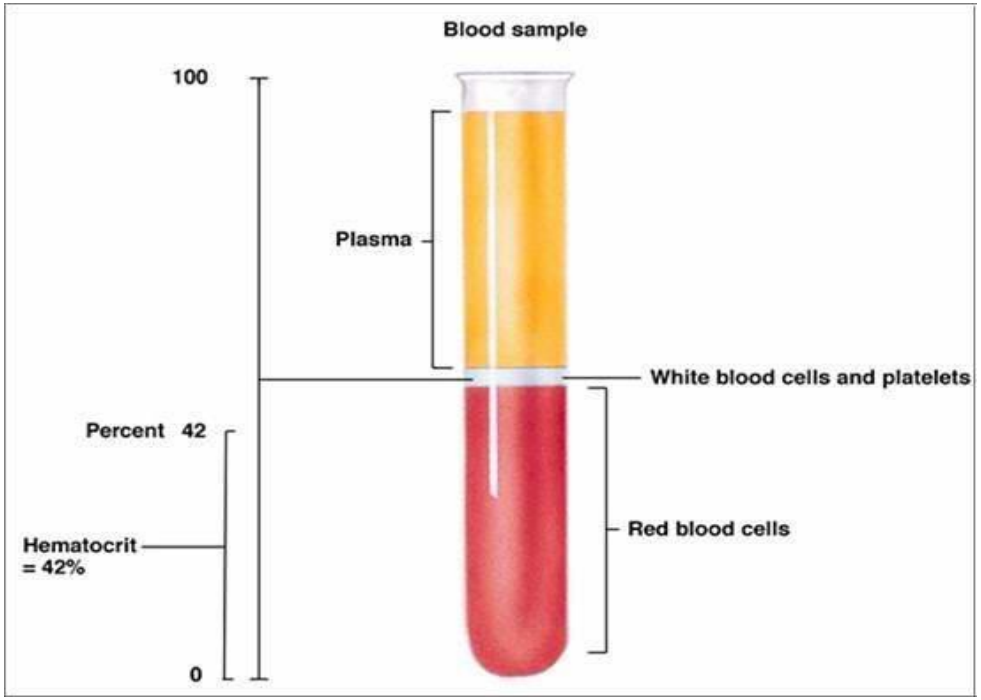
CT Abdomen – 15cm splenomegaly

BM Biopsy – hypercellular with panmyelosis

MPN mutation screen – JAK2 V617F positive

Diagnosis: JAK2 positive Polycythaemia Vera

Haematocrit



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Symptoms of Polycythaemia Vera

Erythrocytosis

Headache, decreased mental acuity, weakness

More specific to PRV/MPD

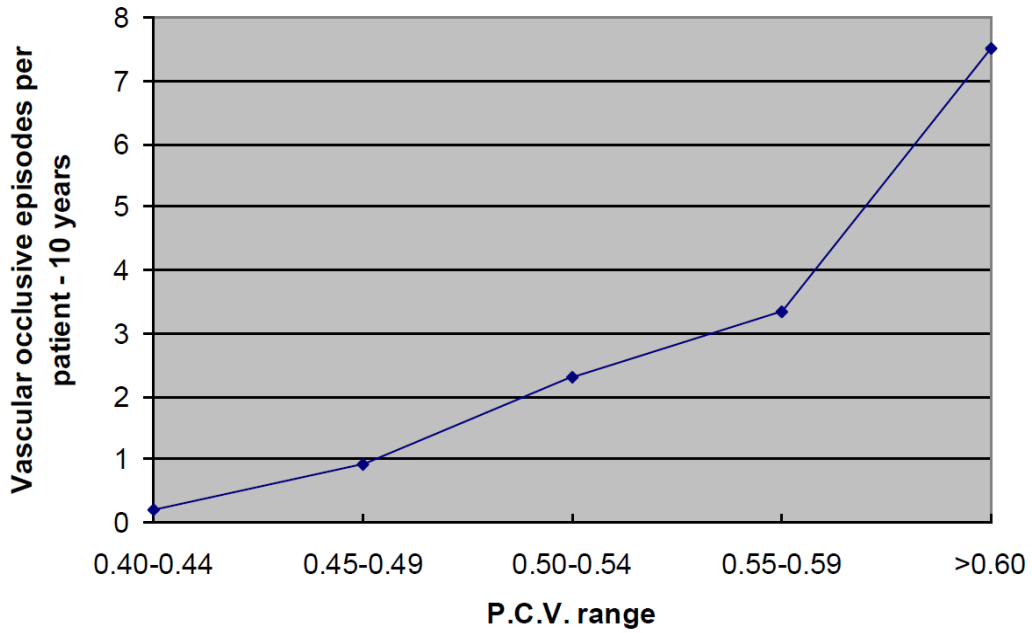
Pruritis after bathing – aquagenic pruritis

Erythromelalgia (tingling in fingers)

Hypermetabolic symptoms (sweats, weight loss)

Arterial or venous thrombosis (why we treat MPN)

Haemorrhage



Relation of PCV range to number of vascular occlusive episodes per 10 patient-years
In patients with primary proliferative polycythaemia.

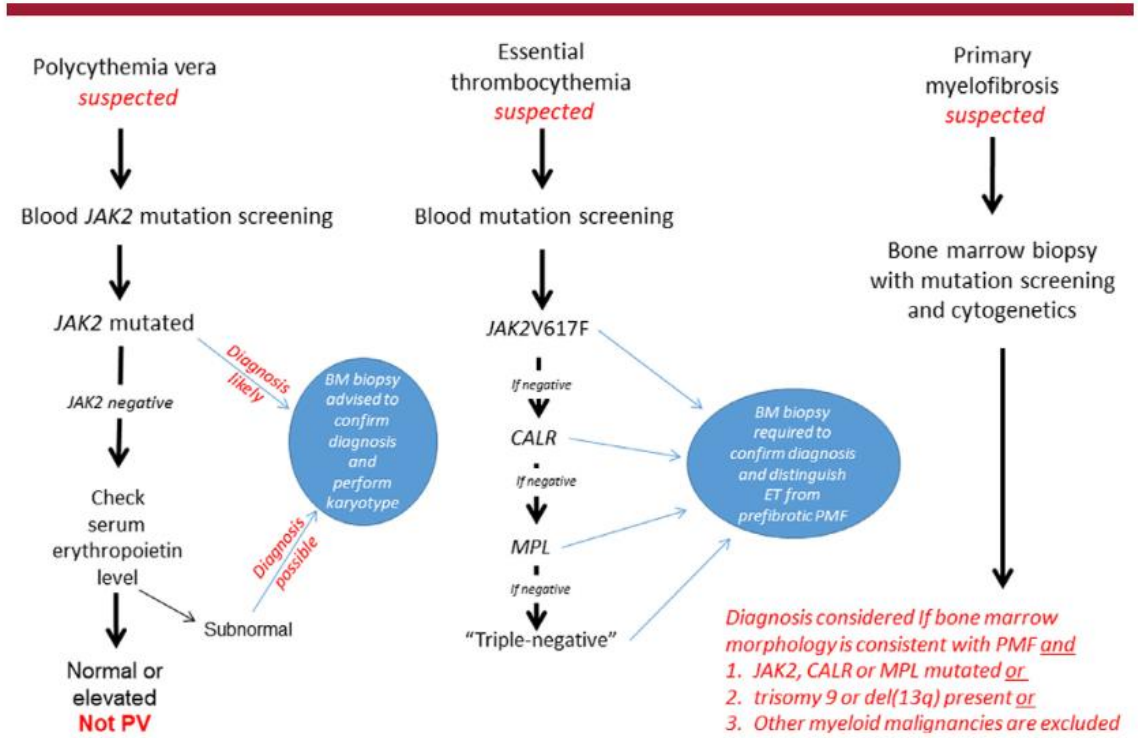


FIGURE 1 Practical diagnostic algorithm for myeloproliferative neoplasms

Am J Hematol.2020;95:1599–1613

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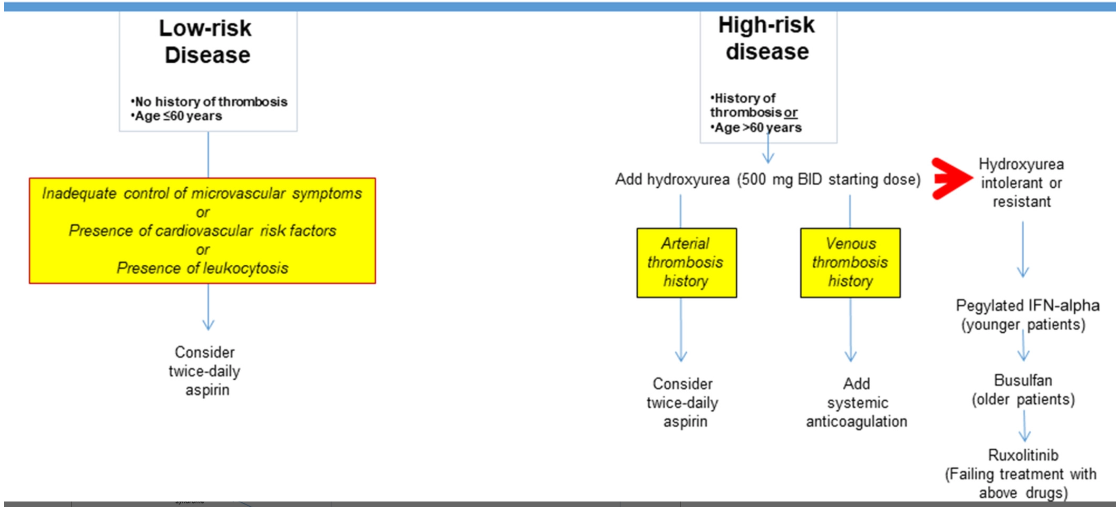
Current Treatment Recommendations in Polycythemia Vera

Phlebotomy to hematocrit <45% in both males and females

+

Once-daily low-dose aspirin (40-100 mg)



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Management in Primary Care

Repeat Full Blood Count (uncuffed, if possible)

Modify lifestyle factors – stop smoking
reduce alcohol consumption
stop thiazide diuretics if for BP control

Consider OPD referral if repeatedly raised Hct (>0.52 in men, >0.48 in women) in absence of chronic hypoxia

The following findings are often seen in myeloproliferative disease –

Arterial or venous thromboembolism, pruritis, splenomegaly, elevated white cell or platelet counts

Urgent referral if raised Hct (>0.52 in men, >0.48 in women) and -

Acute thrombosis or bleeding, visual loss or any neurological symptoms

Take Home Messages on Polycythaemia

Most polycythaemia is an appropriate response to hypoxia
There is no proven benefit to venesection for patient with chronic compensatory polycythaemia (e.g. cyanotic heart disease)

The JAK2 mutation is a sensitive and specific test for Polycythaemia Vera
Refer to haematology OPD clinic for this assay

The major risk of untreated Myeloproliferative Disease (MPD) is arterial or venous thrombosis
Aspirin 75mg od reduces the risk of thrombosis in MPD
The response of erythromelalgia to aspirin is characteristic of an MPD

Be suspicious of a high Hb with a low MCV and high RCC! Possible PV

The diagnosis and management of erythrocytosis

Clodagh Keohane *research fellow in myeloproliferative neoplasms*[1], Mary Frances McMullin *professor of clinical haematology*[2], Claire Harrison *professor of haematology*[1]

[1]Haematology Department, Guy's and St Thomas' NHS Foundation Trust, London SE1 9RT, UK; [2]Haematology Department, Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK

Summary points

- Erythrocytosis is a common reason for referral to haematology services and is usually secondary in origin
- Referral thresholds for iron replete patients are packed cell volume persistently >0.52 in men and >0.48 in women
- The cause can often be elucidated from a detailed medical and drug history
- Common secondary causes include smoking, hypoxia, and diuretics
- Intervention is not always indicated, and the decision to venesect is often made on a case by case basis after a risk-benefit assessment
- True polycythaemia vera is rare. It carries an increased risk of thrombosis and progression to myelofibrosis or leukaemia and requires specialist management

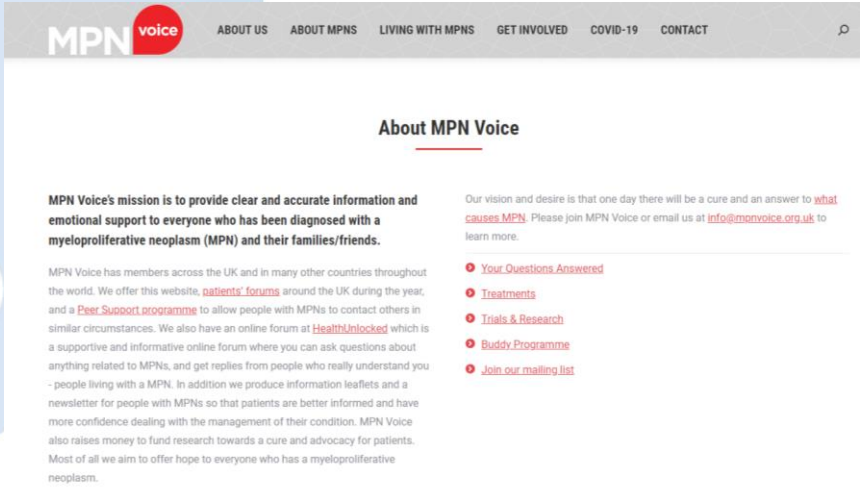
Cite this as: *BMJ* 2013;347:f6667

Online resources

Polycythemia vera and essential thrombocythemia: 2021 update
https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.26008

The diagnosis and management of erythrocytosis
https://www.bmj.com/content/347/bmj.f6667

https://www.mpnvoice.org.uk/
Excellent patient support site



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Clinical cases

Raised White Cell Count

Beacon Hospital

Clinical cases

71 year old man referred with persistent mild lymphocytosis found at annual screening visits

No symptoms, Weight stable

Medical History

Prostate cancer diagnosed in 2016 and treated with radiotherapy

Hyperlipidaemia – statin

Social history

Lives with wife, adult children

Does not smoke, ETOH – 12 units/week

Normal exam – no palpable adenopathy

Parameter	Measurement
Hb	13.5 g/dL
MCV	89 fl
WCC	12.7 x 10*9/L
Neutrophils	6.4 x 10*9/L
Lymphocytes	4.7 x 10*9/L (1.0-3.5) ↑
Platelets	411

Causes of Leucocytosis

Reactive neutrophilia

Very common; usually mild-moderate (10-20 x 10*9/L)

Variable rise in neutrophil count, lymphocytes and monocytes

Occasional immature forms (‘left shift’); platelets may be normal or elevated

- Infection, usually bacterial
- Drugs e.g. corticosteroids
- Inflammatory conditions
- Pregnancy
- Smoking
- Trauma/surgery/burns (“leukaemoid reaction”)

Rarely, CML or CMML (Chronic Myelomonocytic Leukaemia) in an older population

Causes of Lymphocytosis

Lymphocytosis is defined as a lymphocyte count >3.5 x 10*9/L

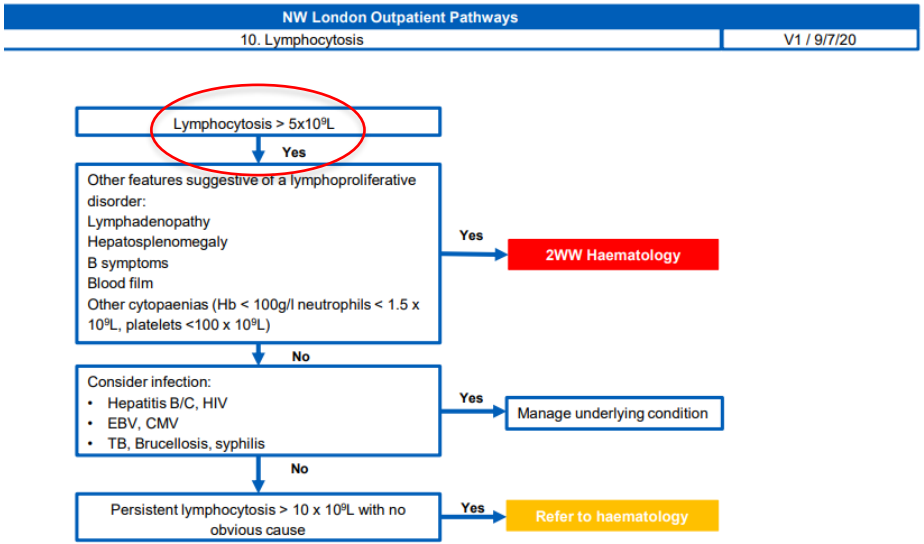
Common causes - smoking (often with a mild neutrophilia), viral infections, Post-splenectomy

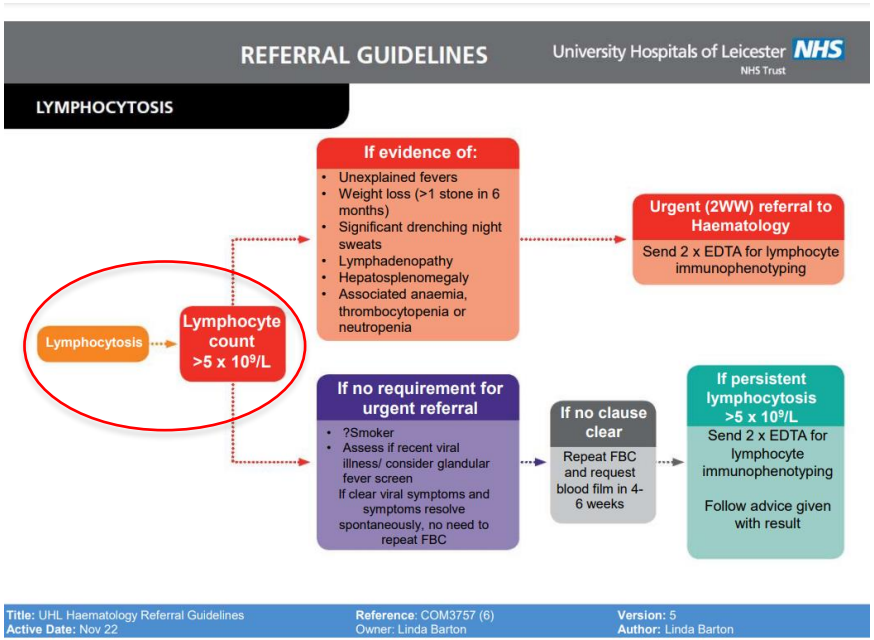
A transient, reactive lymphocytosis is frequently seen in acute viral infection, particularly infectious mononucleosis (EBV) – 'atypical' or 'reactive' lymphocytes

A chronic lymphocytosis is characteristic of chronic lymphoproliferative disorders, by far the most common of which is chronic lymphocytic leukaemia (CLL)

The most useful discriminant is AGE (>55 years)

Monoclonal B lymphocytosis: precursor state to CLL in which monoclonal B-cells are present in the peripheral blood, count < 5x10*9/L, no symptoms or physical signs





Lymphocytosis of 5x10*9/L the threshold for referral in many current guidelines

Clinical cases

Low White Cell Count

Beacon Hospital

Clinical cases

32 year old man, originally from Nigeria

Referred with low white cell count

No fever, chills, sweats, weight loss, bruising or bleeding

No hospital admissions as a child or as an adult
Medications – none

Social History – Dublin Bus Driver, non-smoker, no alcohol

Physical exam – unremarkable

Parameter	Measurement
Hb	15.0 g/dl
WCC	3.6 x 10*9/l
Neutrophils	1.2 x 10*9/l
Plts	266 x 10*9/l

Diagnosis: Constitutional Neutropenia

Normal variants < 1.5x10*9/L — Some individuals have an ANC <1.5 with no recurrent or severe infections, other cytopenias, or associated illnesses.

Most commonly, this inherited condition is associated with the Duffy null [Fy(a-b-)] red blood cell phenotype (which is protective against malaria), but other causes have been identified.

These variants are most often encountered in individuals of African descent and in Sephardic Jews, West Indians, Yemenites, Greeks, and Arabs.

This condition may also be called constitutional neutropenia and was formerly described as "benign ethnic neutropenia," but the preferred designation is "**Duffy-null associated neutrophil count (DANC)**" as there is an effort to move away from the older term because it implies an abnormality when it is in fact a normal variant.

UpToDate®

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Neutropenia

An absolute neutrophil count less than 2.0 x 10^9/L

Mild	1.0-2.0 x 10^9/L
Moderate	0.5-1.0 x 10^9/L
Severe	<0.5 x 10^9/L
Agranulocytosis	<0.2 x 10^9/L

The risk of bacterial infection only increases when the neutrophil count is below 1.0 x 10^9/L and correlates with the depth of the neutropenia

Causes of Neutropenia

Infection – bacterial sepsis (children, elderly), viral

Drugs – Beta-lactam antibiotics, Cotrimoxazole, anti-thyroid medications, anticonvulsants, psychiatric (clozapine), NSAIDs (trial off agent, if possible)

Immune - primary (infants) or secondary (RA, Felty's, SLE) neutropenia

Splenomegaly (patients with chronic liver disease)

BM failure - Leukaemia, MDS, Large Granular Lymphocytic Leukaemia

Rituximab can be associated with a delayed neutropenia

Nutritional deficiencies - B12 or folate, hypothyroidism, hyperthyroidism

Rare – congenital – Cyclical and Severe Congenital Neutropenia (SCN)

Finally and commonly, Chronic Idiopathic Neutropenia (CIN) – can have subtle BM Abnormalities

RATIONAL TESTING

Neutropenia in primary care

Deborah Hay *specialist registrar in haematology*[1], Matilda Hill *clinical medical student*[2], Tim Littlewood *consultant haematologist*[1]

[1]Department of Haematology, Oxford University Hospitals NHS Trust, Oxford, UK; [2]Oxford University Clinical Medical School, Oxford, UK

Learning points

- Isolated neutropenia is a common incidental finding in primary care. It is most often drug induced or caused by acute viral infection
- Benign ethnic neutropenia is common in people of black African and Afro-Caribbean ethnicity
- It is rare for primary haematological malignancy to present with isolated neutropenia because other haemopoietic cells lines are usually also affected
- The initial investigation of persistent isolated neutropenia should include a peripheral blood film, haematinics, and chronic viral serology
- No formal diagnosis can be reached in many adults with isolated neutropenia
- Referral for haematological assessment is warranted if anaemia or thrombocytopenia is also evident, or when persistent neutropenia is moderate or severe ($<1\times10^9$/L)

Cite this as: *BMJ* 2014;349:g5340

Work-up of neutropenia

Examine for splenomegaly, especially if associated thrombocytopenia

Repeat Full Blood Count (? Aged sample)

Blood film

Biochemistry profile including LDH

Vitamin B12 and folate

Consider stopping medications which may be responsible

Repeat FBC in 4-to-6 weeks

Transient neutropenia in association with viral infection is common

Refer to haematologist if persistent unexplained neutropenia (ANC <1.0, if isolated finding)

Some points on Neutropenia

Danish GP study in 370,000 individuals

Identified and followed neutropenic subjects for the next four years

Neutropenia was observed in 4.9% of children and in 1.9% of adults

Among neutropenic children, unspecified viral infections pre-dominated, followed by mononucleosis

In adults, Hepatitis, followed by HIV, were the most common infections

Acute Myeloid Leukemia (AML) and myelodysplastic syndromes (MDSs) the predominating hematological malignancies

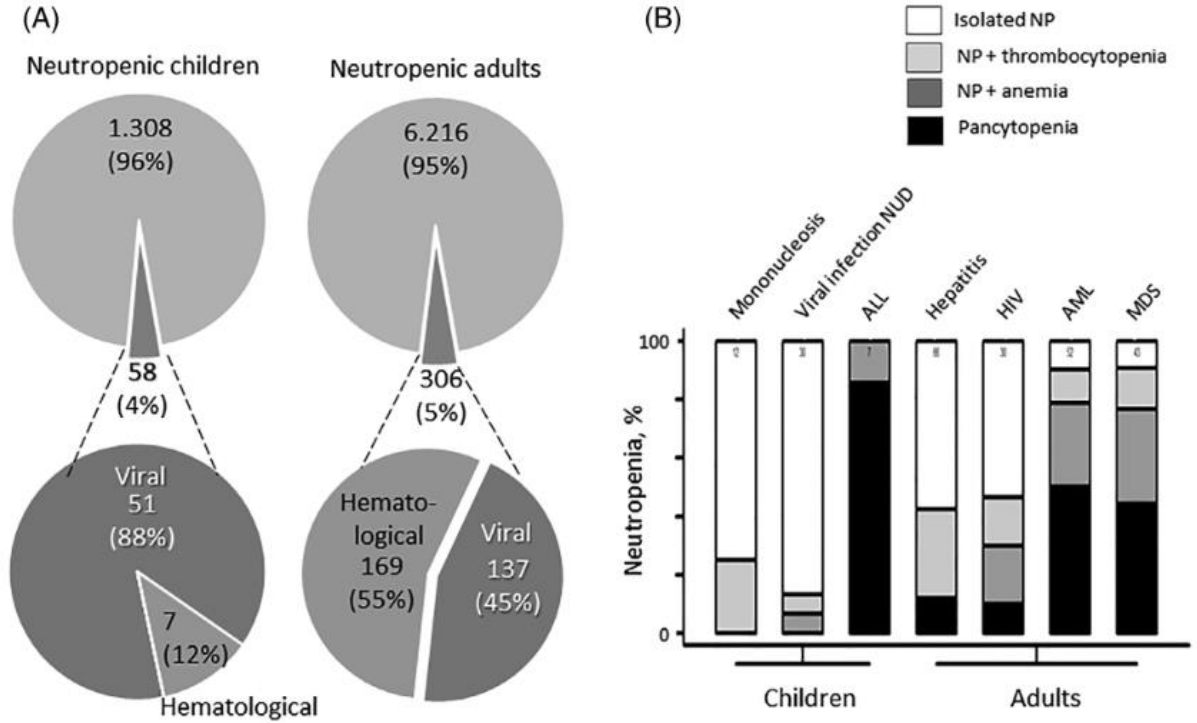

FIGURE 1 A, Cases of de novo viral and hematological disease in neutropenic children/adolescents and adults, respectively, during the 4 years of follow-up after identification of NP. Upper circles: light gray denotes individuals with NP who were not diagnosed in secondary care in the ensuing 4 years. Dark gray denotes individuals diagnosed with de novo NP-associated conditions. Lower circles: The proportion of viral and hematological diseases diagnosed in secondary care among neutropenic individuals. B, Proportion of neutropenic individuals with concomitant anemia and/or thrombocytopenia. Only disease groups constituting the majority of disease cases are shown. Please refer to Tables (S5-S10) for all details. ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; MDS, myelodysplastic syndrome; NUD, non-ultra descriptus

Take Home Message

Isolated neutropenia
in adults
very rarely
progressed to a
haematological
malignancy

The key risk factor is
AGE

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Lymphopenia

Lymphopenia is seldom of significance

Reference range 1.5-3.5

Common causes

Corticosteroids

Autoimmune diseases (RA, SLE)

Sarcoidosis, liver failure, renal failure

HIV

Lymphoproliferative diseases

Work-up in severe lymphopenia

Autoimmune screen, HIV and T-cell subsets

RATIONAL TESTING

Investigating an incidental finding of lymphopenia

Dawn Brass *specialty trainee in haematology*[1], Pam Mckay *consultant haematologist*[2], Fiona Scott *consultant haematologist*[3]

[1]Department of Haematology Ninewells Hospital, Dundee, UK; [2]Department of Haematology, Beatson Oncology Centre, Gartnaval General Hospital, Glasgow, UK; [3]Department of Haematology, Western General Hospital, Edinburgh EH4 2XU, UK

Learning points

- Lymphopenia is a common finding from a full blood count, especially in elderly patients, where it is usually of no clinical significance. No further investigation is advised in an elderly patient with a lymphocyte count >0.5×10^9/L in the absence of any concerning symptoms
- Most cases are reversible and do not require specialist evaluation. The lymphopenia may reflect a response to stress such as acute infection or recent surgery or be iatrogenic secondary to medication, especially immunosuppressant drugs such as steroids
- Symptomatic patients with persistent lymphopenia should be referred to the most appropriate specialty based on clinical and laboratory features
- In those with unexplained moderate to severe lymphopenia (lymphocyte count <1×10^9/L) offer HIV testing
- Persistent lymphopenia that remains stable over a six month period and in the absence of symptoms, clinical findings, or abnormal results from investigations does not require further investigation

Cite this as: *BMJ* 2014;348:g1721

Online resources

Neutropenia in primary care (2014)

https://www.bmj.com/content/349/bmj.g5340

Age-related prevalence and clinical significance of neutropenia, isolated or combined with other cytopenias: Real world data from 373 820 primary care individuals (2020)

https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.25756

Investigating an incidental finding of lymphopenia 2014)

https://www.bmj.com/content/348/bmj.g1721

Clinical cases

Thrombocytosis

Beacon Hospital

Clinical cases

41 year old woman with a raised platelet count

490 in 2019

510 in 2021

(2023) Hb 13.6 Hct 0.42 WCC 6.1 Plts 543

Medical history – nil of note

Medications – OCP

Social history – smoker

Physical examination – normal BMI

Refer?

Causes of thrombocytosis

A raised platelet count (>450) is almost always reactive –

Iron deficiency

Infection

Inflammation

Malignancy

Post-splenectomy

If persistent and unexplained, rule out a myeloproliferative disease (MPD)

Essential Thrombocythemia (ET) (JAK2/CALR/MPL), Myelofibrosis, Chronic Myeloid Leukaemia

Low risk ET: <60 years, No history of thrombosis – Aspirin only

High risk ET: either of above features – cytoreductive therapy recommended

Beware of pseudohyperkalaemia

Pt with known Essential Thrombocythaemia (Plts 710)

Attends GP Practice for cholesterol check

K 6.3 Creatinine 72umol/L referred to ED Treated with insulin

Developed Arrhythmia – CCU – Blood Gas K 2.4

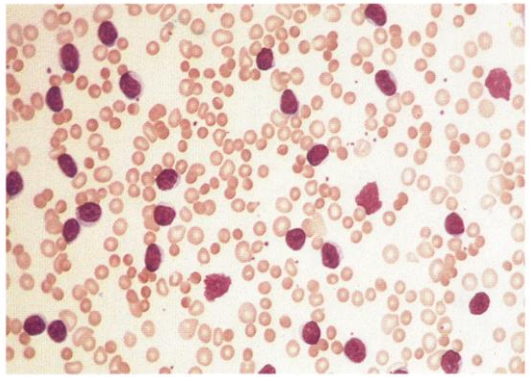
Remember – All biochemistry samples get spun in centrifuge

Artefactually raised potassium from leak of cellular contents

Pseudohyperkalaemia - MPD (↑ Platelets) and CLL (↑ lymphocytes)

General Haematology	
WCC	(H) 320.0
NEUT	(H) 11.0
LYMP	(H) 307.8
MONO	(H) 1.1
EOSINO	0.0
BASO	0.1
RCC	(L) 3.78
HB	12.6
HCT	0.420
MCV	(H) 111.1
MCH	(H) 33.3
MCHC	(L) 30.0
RDW	(H) 20.7
Plat	203
NRBC	* 0.0
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Blood Film Comment	
Retic. Count	
Abs. Retic. Count	
Biochemistry	
Sample Integrity	* MildHaemolysis
Urea Level	6.7
Sodium	(L) 132
Potassium	(H) 6.7
Creatinine	* 55
Bicarbonate	
eGFR	* >90
Total Protein	(L) 62

Lymphocytosis



Pseudohyperkalaemia

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Clinical cases

Paraprotein

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Clinical cases

64 year old man

Health screen on retirement

IgG kappa paraprotein detected 6.7g/L

No immune paresis

Normal FBC, renal function and corrected calcium

Referral? Myeloma work-up?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevalence of Monoclonal Gammopathy of Undetermined Significance

Robert A. Kyle, M.D., Terry M. Therneau, Ph.D., S. Vincent Rajkumar, M.D., Dirk R. Larson, M.S., Matthew F. Plevak, B.S., Janice R. Offord, B.S., Angela Dispenzieri, M.D., Jerry A. Katzmann, Ph.D., and L. Joseph Melton III, M.D.

N ENGL J MED 354;13 WWW.NEJM.ORG MARCH 30, 2006

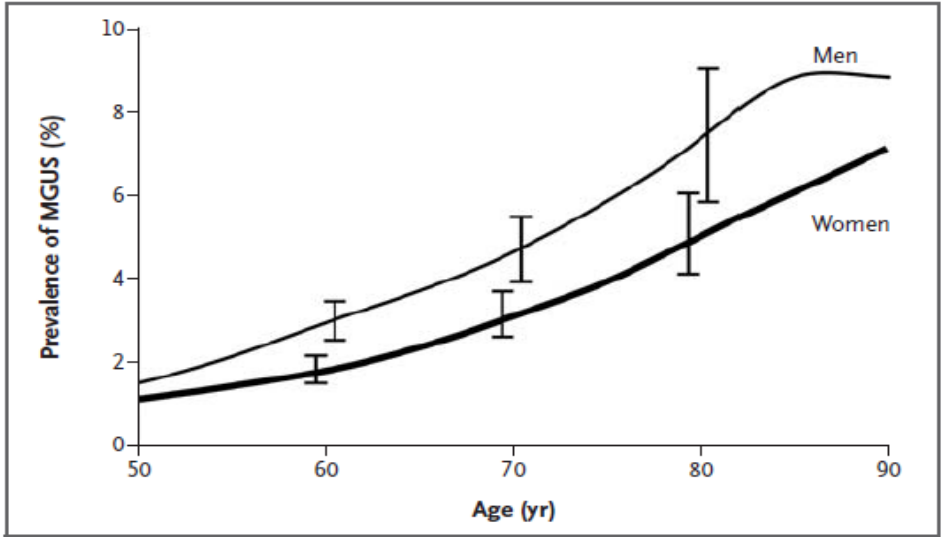


Figure 1. Prevalence of MGUS According to Age.

The I bars represent 95 percent confidence intervals. Years of age greater than 90 have been collapsed to 90 years of age.

A LONG-TERM STUDY OF PROGNOSIS IN MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Robert A. Kyle, M.D., Terry M. Therneau, Ph.D., S. Vincent Rajkumar, M.D., Janice R. Offord, B.S., Dirk R. Larson, M.S., Matthew F. Plevak, B.S., and L. Joseph Melton III, M.D.

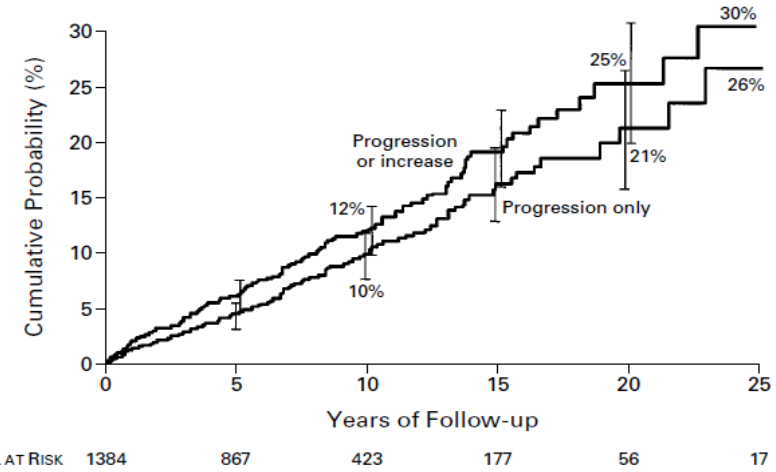


Figure 2. Probability of Progression among 1384 Residents of Southeastern Minnesota in Whom Monoclonal Gammopathy of Undetermined Significance (MGUS) Was Diagnosed from 1960 through 1994.

Prognosis in MGUS

Low risk MGUS – 40% of cohort

IgG isotype

Less than 15g/l

Normal serum free light chain Kappa: Lambda ratio

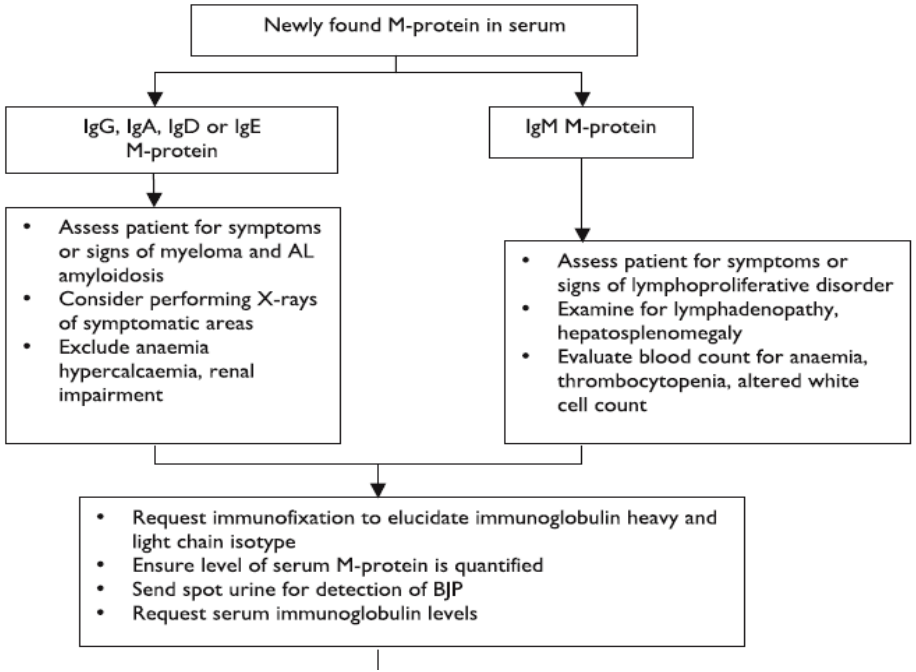
(The Serum free light chain assay is an expensive test requiring specialist interpretation, suggest perform in Haematology service)

Low risk MGUS - 5% risk of progression at 20 years

Lifetime risk of 2% when competing causes of death are taken into account

75-90% of patients with MGUS will not develop myeloma or a related disorder in their lifetime

Suggested algorithm for the investigation of a newly detected M-protein



Management of MGUS – British Society for Haematology 2009

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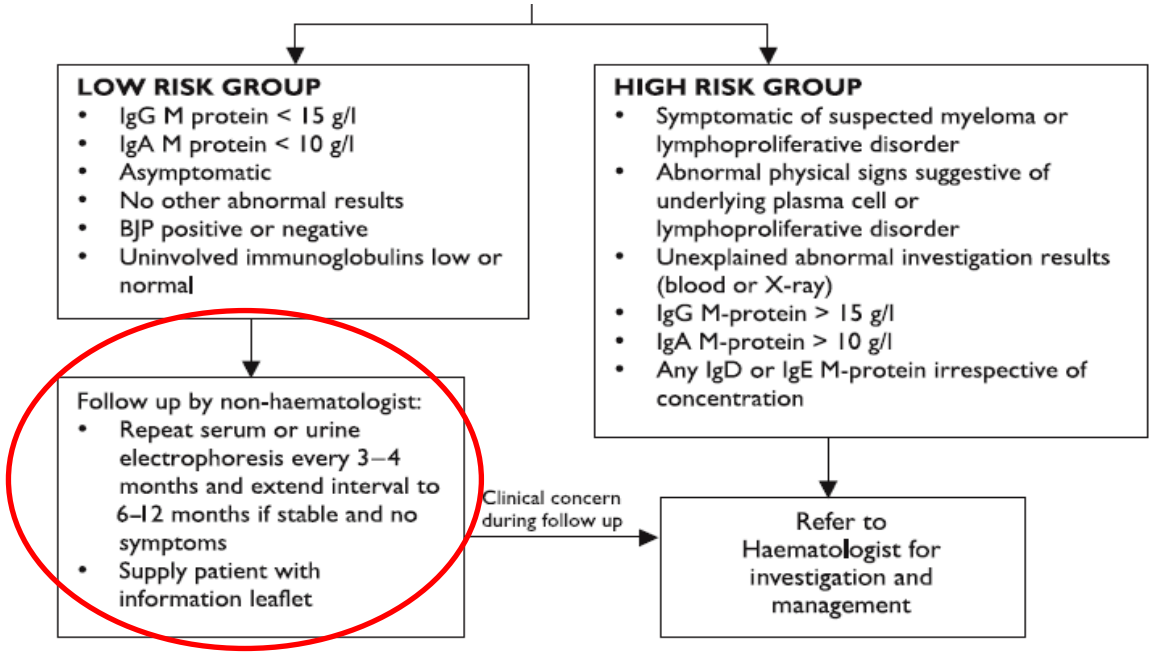

Investigation of MGUS – British Society for Haematology 2009

Beacon Hospital

Take Home Messages on Paraproteins

Elevated immunoglobulins in absence of paraprotein do not require referral to haematology – Polyclonal hypergammaglobulinaemia

A non-specific immune response, often see in rheumatological or liver diseases

A raised Total IgG, IgA or IgM does not require referral if no monoclonal band is detected

New test in recent years – serum free light chain assay

Measures the ratio between kappa and lambda light chains (normal ~3:2)

The levels of both light chains will be raised in renal impairment, this is normal

New reference ranges based on renal function have been developed

Online resources

Patient information on MGUS from Myeloma UK (Patient Support Group)
https://www.myeloma.org.uk/understanding-myeloma/related-conditions/mgus/

What Are MGUS, Smoldering Myeloma, and MM?
International Myeloma Foundation (Patient Support Group)
https://www.myeloma.org/what-are-mgus-smm-mm

Myeloma and MGUS - A Guide for GPs (2019)
https://www.myeloma.org.uk/wp-content/uploads/2021/09/Myeloma-UK-Myeloma-and-MGUS-A-Guide-for-GPs.pdf

University Hospital Limerick Guidance on Management of MGUS in Primary Care
https://healthservice.hse.ie/filelibrary/ulh/uhl-guidance-management-of-mgus-in-primary-care.pdf

Clinical cases

Raised Ferritin

Clinical cases

64 year old woman

Recurrent attendee with fatigue

Elevated BMI, NIDDM, osteoarthritis

Noted to have an elevated ferritin of 740

Transferrin saturation of 35%

Referred to haematology clinic…….

CLINICAL

Elevated serum ferritin

What should GPs know?

Katie Goot
Simon Hazeldine
Peter Bentley
John Olynyk
Darrell Crawford

Reprinted from AUSTRALIAN FAMILY PHYSICIAN VOL. 41, NO. 12, DECEMBER 2012 945

Objective

This article aims to outline the role of the Australian Red Cross Blood Service Therapeutic Venesection program, to clarify the interpretation of the HFE gene test and iron studies, and to describe the steps in evaluating a patient with elevated serum ferritin.

The most useful tests in the evaluation of iron overload due to HH are transferrin saturation and serum ferritin.[15] Transferrin saturation >45% is sensitive and fairly specific for diagnosing HH, with increasing specificity when the threshold is increased to >55%. Serum ferritin is most useful in monitoring venesection requirement and venesection response in patients already diagnosed with HH.

https://www.racgp.org.au/getattachment/b1e3ebee-8518-4ba1-a1a7-bfff76fe48c8/Elevated-serum-ferritin.aspx

Beacon Hospital

Table 5. Interpretation of iron studies

Iron study test name	Explanation	Iron as an analogy to money	Abnormal values (vary from laboratory-to-laboratory)	
			Suggestive of low iron stores	Suggestive of high iron stores
Serum iron	Unbound serum iron	'Loose change in your pocket'	<10 µmol/L	>30 µmol/L
Total iron binding capacity	Ability to bind even more iron	'Greediness for more money'	>70 µmol/L	<45 µmol/L
Transferrin saturation	• Iron absorbed from duodenum bound to a transport protein • One molecule of transferrin binds two atoms of iron	'Money kept in your wallet'	<16%	>45%
Serum ferritin	• Iron within a storage protein • One molecule of ferritin binds 4500 atoms of iron	'The savings you have in your bank'	<30 µg/L	• >200 µg/L pre-menopausal women • >300 µg/L men and postmenopausal women • >1000 µg/L refer to gastroenterologist, haematologist or physician with an interest in iron overload

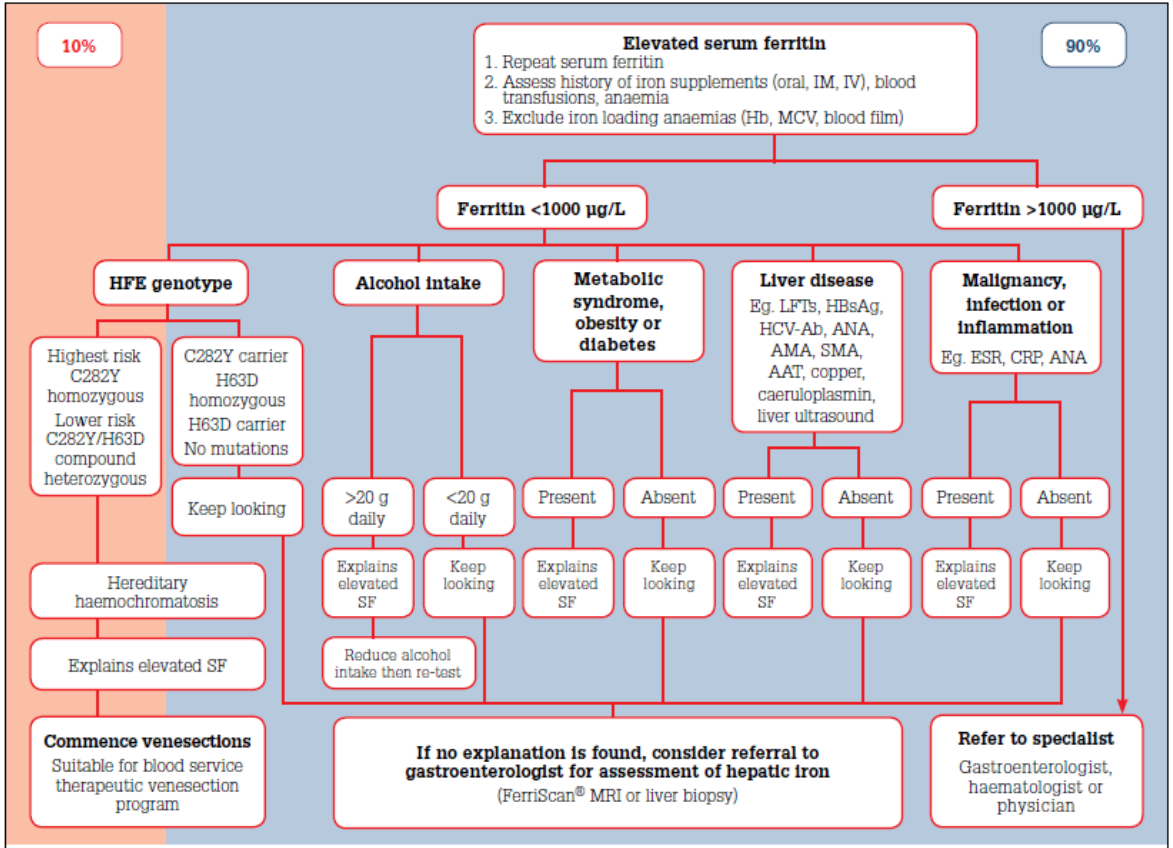

Figure 1. Algorithm for the investigation and management of elevated serum ferritin in general practice

Table 6. Comparison between elevated serum ferritin in haemochromatosis and in metabolic syndrome

Feature	Elevated serum ferritin due to hereditary haemochromatosis	Metabolic hyperferritinaemia due to metabolic syndrome/fatty liver/ insulin resistance/diabetes/obesity
Genotype	C282Y homozygous	Not C282Y homozygous
Ancestry	Usually Caucasian	Variable
Transferrin saturation	Usually >45%	Usually normal (20–45%)
Serum ferritin	Elevated	Elevated
C-reactive protein	Normal	Normal
Hepcidin levels (not commercially available)	Reduced hepcidin levels	Normal or elevated hepcidin levels
Serum ferritin over time	Progressively more elevated	Fluctuations from one test to another
Total body iron levels	Raised	Normal
Response to weekly 500 mL venesections	Patient tolerates >16 weekly venesections without becoming anaemic	Patient becomes anaemic after <16 weekly venesections
Hepatic iron concentration (FerriScan® MRI or liver biopsy)	Raised	Normal
Pattern of iron deposition on liver biopsy	Parenchymal deposition in hepatocytes	Nonparenchymal deposition in sinusoidal and Kupffer cells
Management	• Iron depletion – venesections – iron chelation therapy	• Lifestyle modifications – weight control – correction of insulin resistance

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BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology

Guideline | Free Access

Investigation and management of a raised serum ferritin

Jonathan O. Cullis, Edward J. Fitzsimons, William JH Griffiths, Emmanouil Tsochatzis, D. Wayne Thomas, on behalf of the British Society for Haematology

First published: 19 April 2018 | https://doi.org/10.1111/bjh.15166 | Citations: 87

Summary

Serum ferritin level is one of the most commonly requested investigations in both primary and secondary care. Whilst low serum ferritin levels invariably indicate reduced iron stores, raised serum ferritin levels can be due to multiple different aetiologies, including iron overload, inflammation, liver or renal disease, malignancy, and the recently described metabolic syndrome. A key test in the further investigation of an unexpected raised serum ferritin is the serum transferrin saturation. This guideline reviews the investigation and management of a raised serum ferritin level. The investigation and management of genetic haemochromatosis is not dealt with however and is the subject of a separate guideline.

Scope

The objective of this guideline is to provide healthcare professionals with guidance on the management of patients with a raised serum ferritin. The guidance may not be appropriate to every patient and in all cases individual patient circumstances may dictate an alternative approach.

Online resources

Elevated serum ferritin - What should GPs know?

https://www.racgp.org.au/getattachment/b1e3ebee-8518-4ba1-a1a7-bfff76fe48c8/Elevated-serum-ferritin.aspx

Investigation and management of a raised serum ferritin

Cullis JO, et al. Br J Haematol. 2018. Review.

https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.15166

Beacon Haematology Service

General and Malignant Haematology

Special interest in Myeloma and plasma cell disorders

Inpatient and dayward-based services in Beacon

Dedicated Haematology Nurse: Tracy MacNamara

Haematology Clinic Administrator: colette.gallagher@beaconhospital.ie

Recommend referral of specialist haemostasis and thrombosis to Dr. Niamh O'Connell or Dr. Kevin Ryan, National Coagulation Centre, St. James's Private Clinic, St. James's Hospital

Thank you