An abnormal FBC: knowing when to refer

Dr Patrick Hayden
Consultant Haematologist
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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

HAEMATOLOGY REFERENCE RANGES

PARAMETER	UNITS	ADULT MALE	ADULT FEMALE
RCC	10^{12}/L	4.5-5.5	3.8-4.8
Hb:	g/L	13.0-17.0	12.0-15.0
HCT:	L/L	0.400-0.500	0.360-0.460
MCV:	fL	83-101	83-101
MCH:	pg	27-32	27-32
MCHC:	g/dL	31.5-34.5	31.5-34.5
RDW-CV:	%	11.6-14.0	11.6-14.0
RDW-SD:	fL	39-46	39-46
Platelets:	10^9/L	150-410	150-410
WBC:	10^9/L	4.0-10.0	4.0-10.0
Neutrophils (Abs):	10^9/L	2.0-7.0	2.0-7.0
Neutrophils %:	%	40-80	40-80
Lymphocytes (Abs):	10^9/L	1.0-3.0	1.0-3.0
Lymphocytes % :	%	20-40	20-40
Monocytes (Abs) :	10^9/L	0.2-1.0	0.2-1.0
Monocytes %:	%	2-10	2-10
Eosinophils (Abs):	10^9/L	0.02-0.5	0.02-0.5
Eosinophils %:	%	1.0-6.0	1.0-6.0
Basophils (Abs):	10^9/L	0.02-0.1	0.02-0.1
Basophils %:	%	0.0-2.0	0.0-2.0
Reticulocytes (Abs):	10^9/L	50-100	50-100
Reticulocytes % :	%	0.5-2.5	0.5-2.5

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

blood

2006 107: 1747-1750
Prepublished online September 27, 2005;
doi:10.1182/blood-2005-07-3046

The definition of anemia: what *is* the lower limit of normal of the blood hemoglobin concentration?

Ernest Beutler and Jill Waalen

BLOOD, 1 MARCH 2006 • VOLUME 107, NUMBER 5

Table 4. Proposed lower limits of normal for hemoglobin concentration of the blood for white and black adults

Group	Hemoglobin, g/dL
White men, y	
20-59	13.7
60+	13.2
White women, y	
20-49	12.2
50+	12.2
Black men, y	
20-59	12.9
60+	12.7
Black women, y	
20-49	11.5
50+	11.5

Based on Scripps-Kaiser data for the 5th percentiles given in Table 2. NHANES data are considered to be confirmatory.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Mayo Clin Proc. • *July 2005;80(7):923-936* • *www.mayoclinicproceedings.com*

How to Interpret and Pursue an Abnormal Complete Blood Cell Count in Adults

AYALEW TEFFERI, MD; CURTIS A. HANSON, MD; AND DAVID J. INWARDS, MD

TABLE 1. **Reference Ranges of Complete Blood Cell Count in Adult White Persons and Persons of African Ancestry***

Variable	White		African	
	Male	Female	Male	Female
Hemoglobin[9] (g/dL)	12.7-17.0 (13.5-17.5)	11.6-15.6 (12.0-15.5)	11.3-16.4	10.5-14.7
RBCs[9] ($\times 10^{12}$/L)	4.0-5.6 (4.3-5.7)	3.8-5.2 (3.9-5.0)	3.8-5.7	3.6-5.2
Mean corpuscular volume[9] (fL)	81.2-101.4 (81.2-95.1)	81.1-99.8 (81.6-98.3)	77.4-103.7	74.2-100.9
RBC distribution width (%)	(11.8-15.6)	(11.9-15.5)		
Platelets[8] ($\times 10^9$/L)	143-332 (150-450)	169-358 (150-450)	115-290	125-342
WBCs[8] ($\times 10^9$/L)	3.6-9.2 (3.5-10.5)	3.5-10.8 (3.5-10.5)	2.8-7.2	3.2-7.8
Neutrophils[8] ($\times 10^9$/L)	1.7-6.1 (1.7-7.0)	1.7-7.5 (1.7-7.0)	0.9-4.2	1.3-4.2
Lymphocytes[8] ($\times 10^9$/L)	1.0-2.9 (0.9-2.9)	0.95-3.3 (0.9-2.9)	1.0-3.2	1.1-3.6
Monocytes[8] ($\times 10^9$/L)	0.18-0.62 (0.3-0.9)	0.14-0.61 (0.3-0.9)	0.15-0.58	0.15-0.39
Eosinophils[8] ($\times 10^9$/L)	0.03-0.48 (0.05-0.50)	0.04-0.44 (0.05-0.50)	0.02-0.79	0.02-0.41
Basophils ($\times 10^9$/L)	(0-0.3)	(0-0.3)		

*Abstracted from population-based studies from Bain[8] and NHANES-II.[9] Mayo Clinic normal values, based primarily on white subjects, are in parentheses for comparison. RBC = red blood cell; WBC = white blood cell.

Clinical cases

Microcytic anaemia

Beacon Hospital

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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Ferritin	466 ug/L (ref range 23-393)

Parameter	Measurement
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

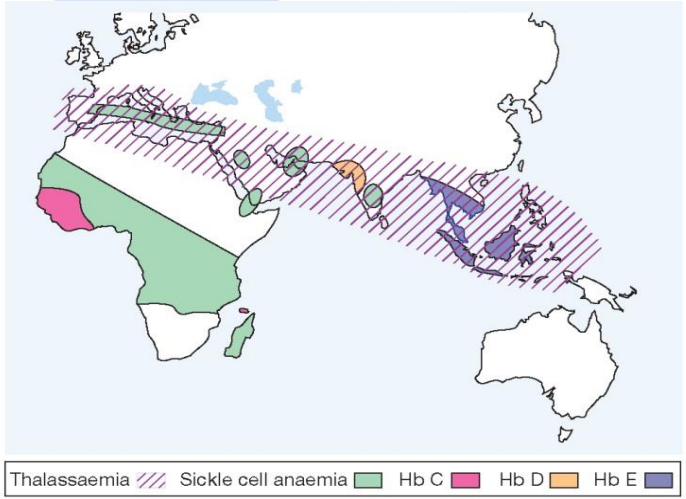
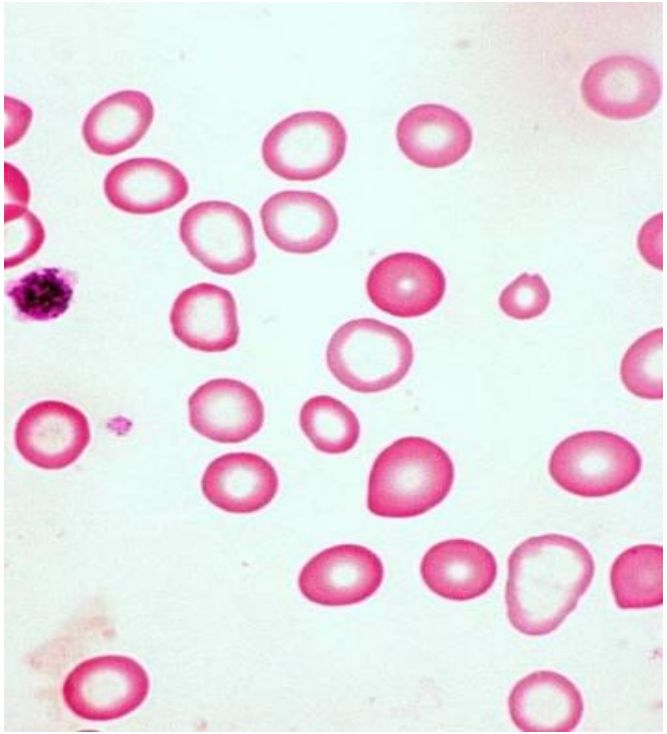
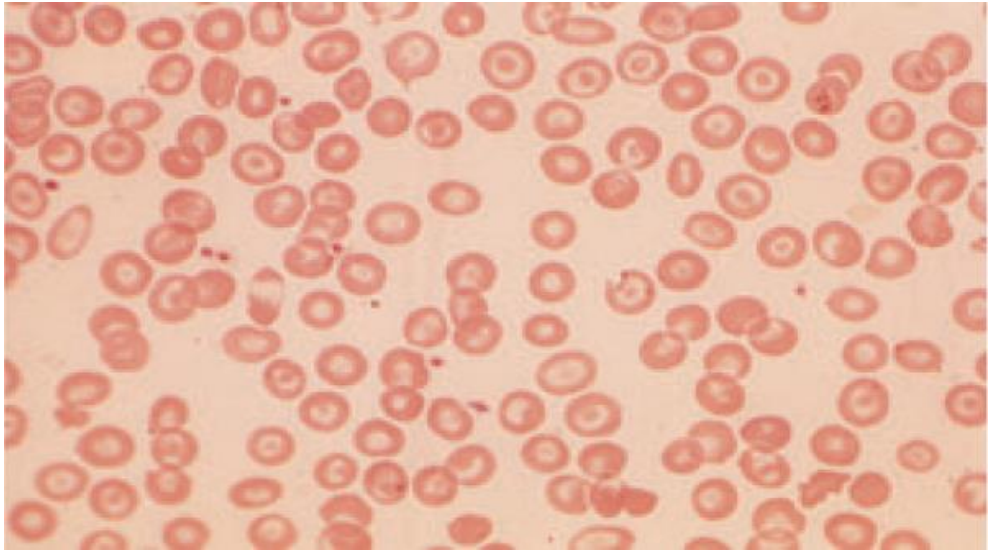


Figure 7.4 The geographical distribution of the thalassaemias and the more common, inherited, structural haemoglobin abnormalities.

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.

	Iron Deficiency	Thalassaemia Trait
RCC	low	normal
Hb	low	low/ normal
MCV	low	very low
RDW	high	normal

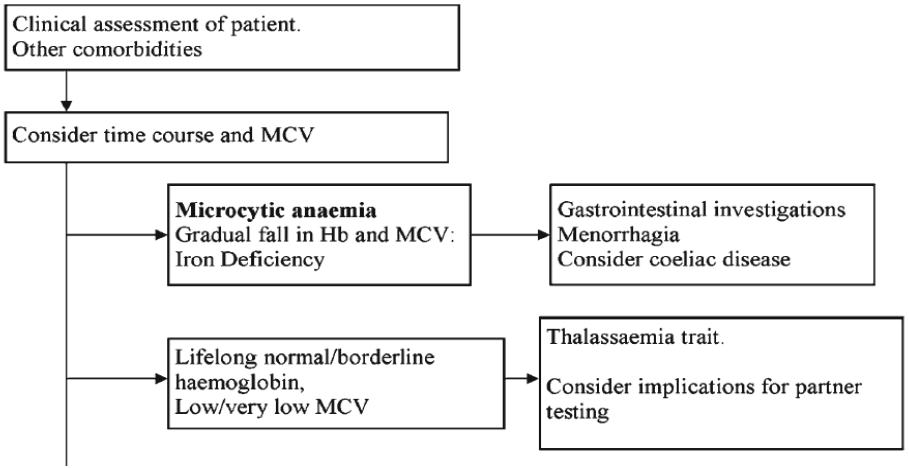
Comparison of haematological parameters between patients with iron deficiency anaemia (IDA) and Beta Thalassaemia Trait (BTT) highlights value of MCV and RDW

Age-specific causes of iron deficiency

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

Investigation of anaemia

A full blood count is one of the common blood tests requested by GPs. Anaemia is frequently found, whether suspected or incidental. This article aims to guide your thinking about how to assess and investigate anaemia in adults and when to refer.



Box 1. Causes of iron deficiency

- GI bleeding due to use of non-steroidal anti-inflammatory drug (NSAID)/aspirin
- Colonic polyps/malignancy
- Gastric ulcers/polyps/malignancy
- Angiodysplasia
- Oesophageal malignancy
- Other GI tract bleeding
- Urinary tract bleeding
- Menorrhagia
- Coeliac disease
- Gastrectomy
- Severe epistaxis

Investigation of Anaemia *InnovAiT: The RCGP Journal for Associates in Training March 2009 2: 148-157*

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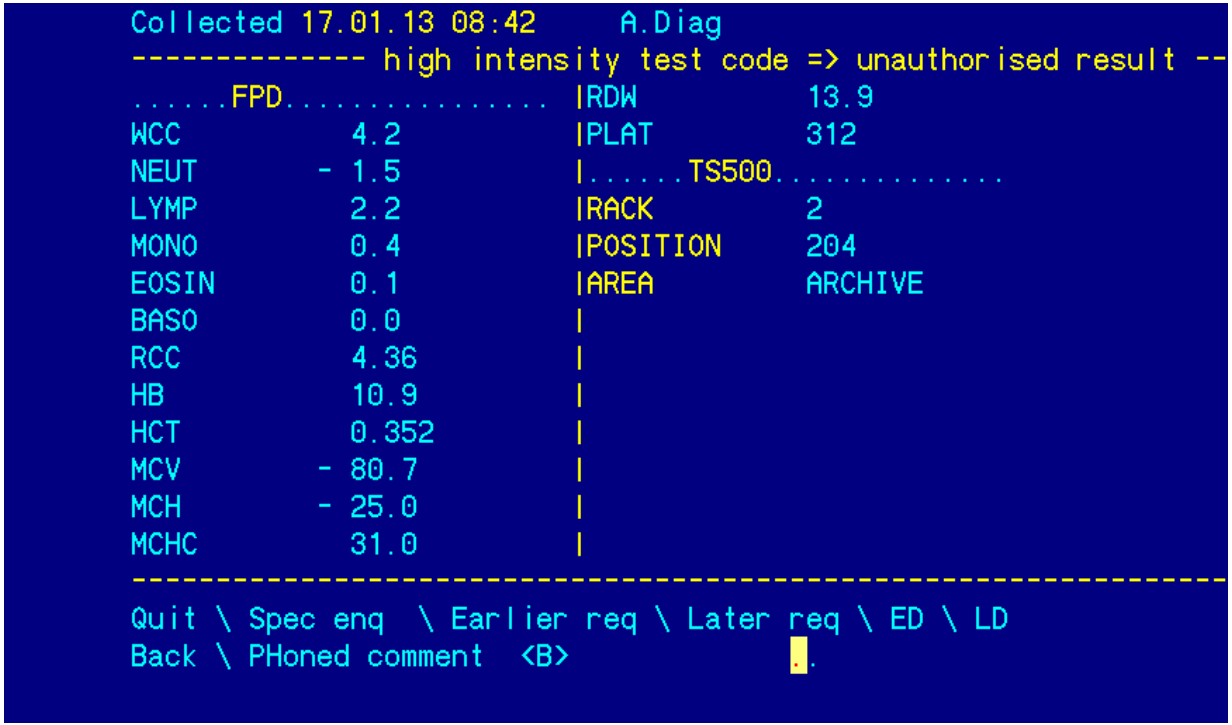
Guidelines for the management of iron deficiency anaemia

Table 1 Pathological contributors to iron deficiency anaemia in the UK with prevalence as percentage of total[4–9]

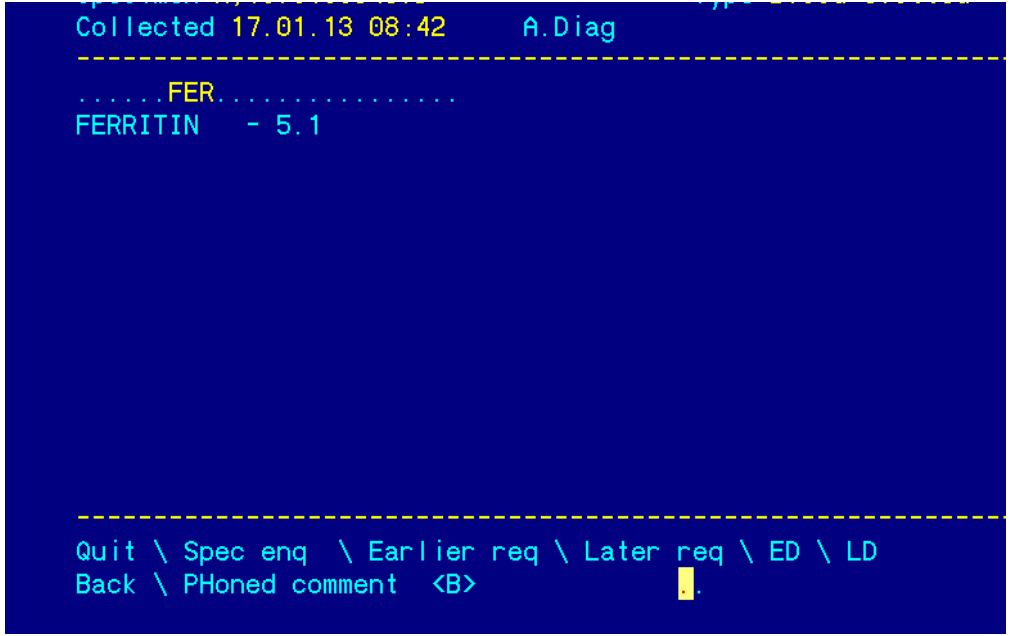
Contributor	Prevalence
Occult GI blood loss	
Common	
Aspirin/NSAID use	10–15%
Colonic carcinoma	5–10%
Gastric carcinoma	5%
Benign gastric ulceration	5%
Angiodysplasia	5%
Uncommon	
Oesophagitis	2–4%
Oesophageal carcinoma	1–2%
Gastric antral vascular ectasia	1–2%
Small bowel tumours	1–2%
Cameron ulcer in large hiatus hernia	<1%
Ampullary carcinoma	<1%
Ancylomasta duodenale	<1%
Malabsorption	
Common	
Coeliac disease	4–6%
Gastrectomy	<5%
Helicobacter pylori colonisation	<5%
Uncommon	
Gut resection	<1%
Bacterial overgrowth	<1%
Non-GI blood loss	
Common	
Menstruation	20–30%
Blood donation	5%
Uncommon	
Haematuria	1%
Epistaxis	<1%

GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug.

Goddard AF, James MW, McIntyre AS, *et al*. *Gut* (2011). doi:10.1136/gut.2010.228874



Patient referred to haematology clinic with neutropenia who was incidentally noted to have a mild microcytic anaemia – this result displays the usual relationship between the Hb and MCV in a case of iron deficiency anaemia as opposed to the more marked microcytosis seen in thalassaemia trait



Patient referred to haematology clinic with neutropenia who was noted to have a mild microcytic anaemia – This result confirms iron deficiency as the cause of the mild microcytic anaemia see on the previous slide

Causes of microcytic anaemia

Iron deficiency

Haemoglobinopathies

Anaemia of chronic disease

Rare inherited anaemias e.g. sideroblastic anaemia

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) seldom 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 groups

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

If Hb relatively preserved and MCV very low (discrepant microcytosis), consider thalassaemia trait; refer to Haematology service

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

Online resources

Guidelines for the management of iron deficiency anaemia

British Society of Gastroenterology 2011

https://www.bsg.org.uk/wp-content/uploads/2019/12/Guidelines-for-the-management-of-iron.pdf

UK guidelines on the management of iron deficiency in pregnancy 2019

https://b-s-h.org.uk/guidelines/guidelines/uk-guidelines-on-the-management-of-iron-deficiency-in-pregnancy/

Seminar on Iron deficiency

www.thelancet.com Vol 397 January 16, 2021

https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2932594-0

Clinical cases

Macrocytic anaemia

Beacon Hospital

Clinical cases

54 year old woman

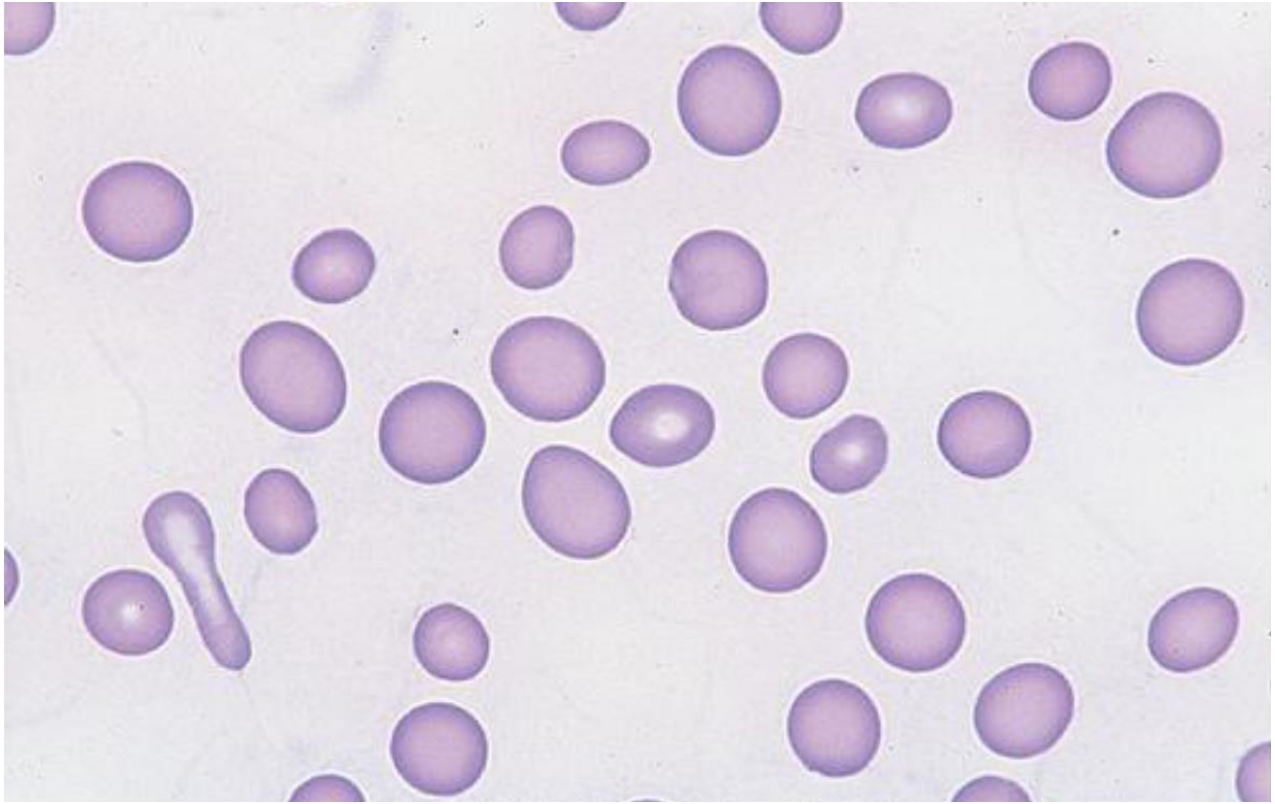
‘Severe fatigue and bruising’

Type I IDDM, Hypothyroidism
Medications – multiple

Social history – businesswoman, self-employed, three adult children

Physical examination – pallor, 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% (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

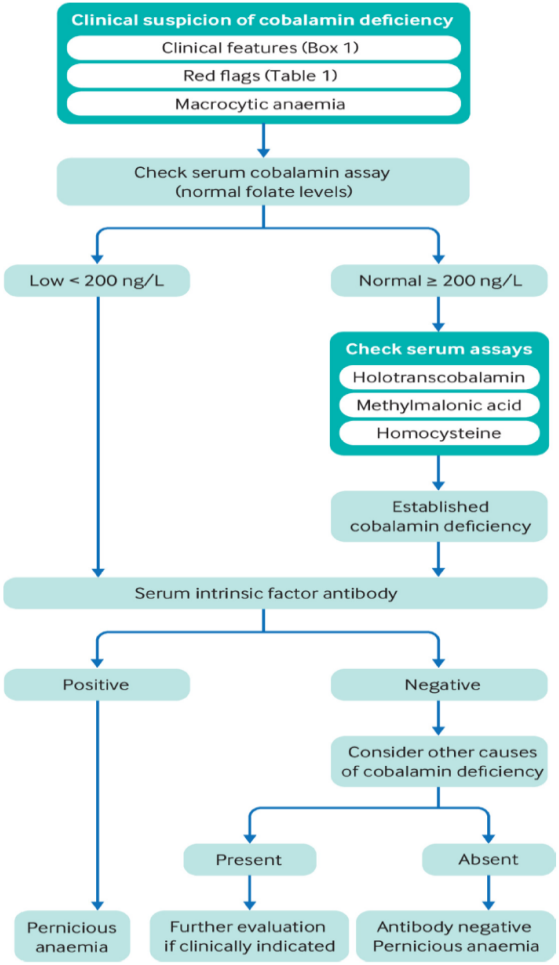


Fig 3 | Algorithm for investigating suspected pernicious anaemia

Check for updates

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]

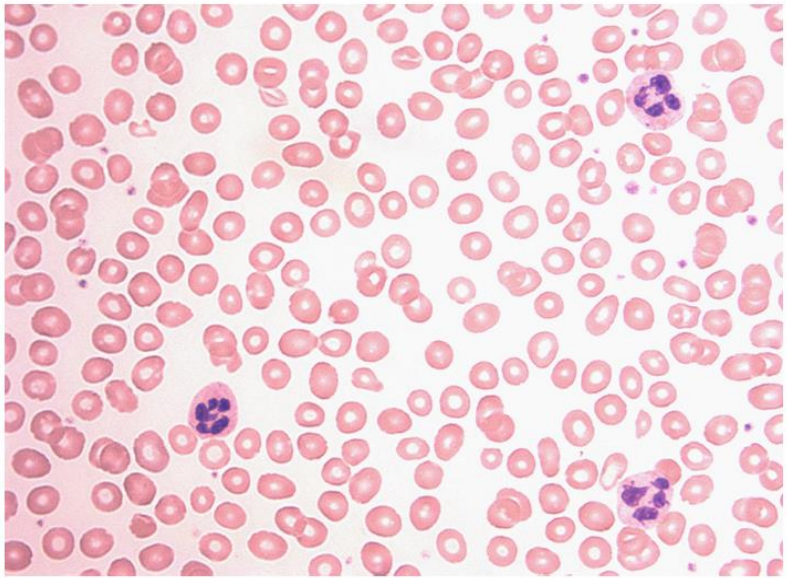


Fig 2 | Blood film in a patient with pernicious anaemia showing the presence of macro-ovalocytes and hypersegmented neutrophils

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

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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 reticulocytes
Drug therapy esp. hydroxycarbamide (good to check compliance)
Hypothyroidism
Myelodysplasia

Macrocytosis with or without anaemia
Alcohol

Clinical cases

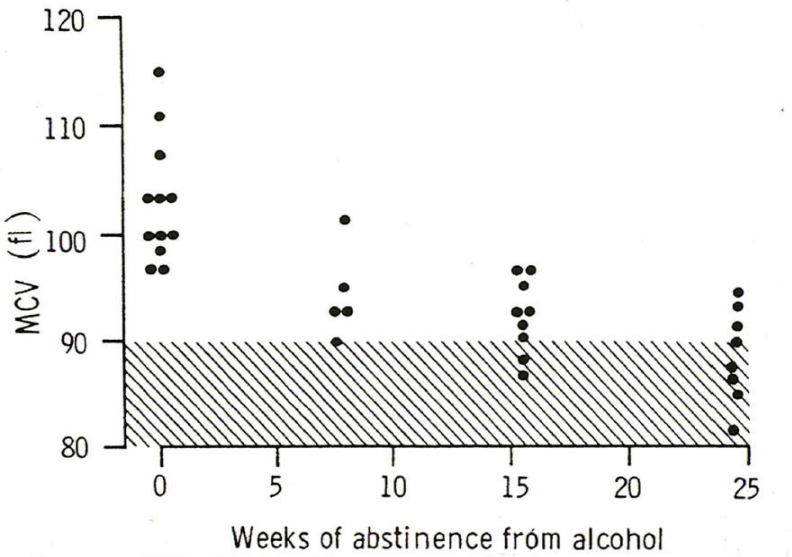
48 year old man with elevated MCV

FBC performed as part of Health Screen

Hb 14.5 MCV 103
WCC 6.5 ANC 3.4
Plts 144

'Social Drinker' – a bottle of red wine four evenings each week
Physical examination – 2cm hepatomegaly
LFTs – GGT raised at 154

FIG. 1. Serial mean corpuscular volumes (MCVs) in patients following cessation (?) of alcohol consumption



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
The LDH can be raised in megaloblastic anaemia, also consider possibility of acute leukaemia
Treat with Vitamin B12 and folic acid

Myelodysplasia not uncommon in an elderly population
Advances in treatment options justify referral for diagnosis
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 recent UCC study
Associations with an elevated GGT and smoking

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/

Investigating vitamin B12 deficiency

BMJ 2019;365:l1865 doi: 10.1136/bmj.l1865 (Published 10 May 2019)

Easily missed? Pernicious anaemia

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

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	1.4 x 10*9/l
Plts	266 x 10*9/l

Diagnosis: Benign Ethnic Neutropenia

Benign ethnic neutropenia (BEN; also called constitutional neutropenia) is an inherited cause of mild/moderate neutropenia (absolute neutrophil count [ANC] <1500/µL) that is not associated with increased infections

BEN is most commonly encountered in people of African descent, West Indians, Sephardic Jews, Yemenites, Greeks, and Arabs, but it may be seen in patients with any ancestry

The diagnosis of BEN is based on detection of persistent ANC <1.5x10*9/L in an individual with no history of frequent or unusual infections and no history or physical findings that suggest an alternative explanation. No treatment is required, and once the individual is diagnosed with BEN, no further follow-up is needed.

(Up-to-date 19/01/2021)

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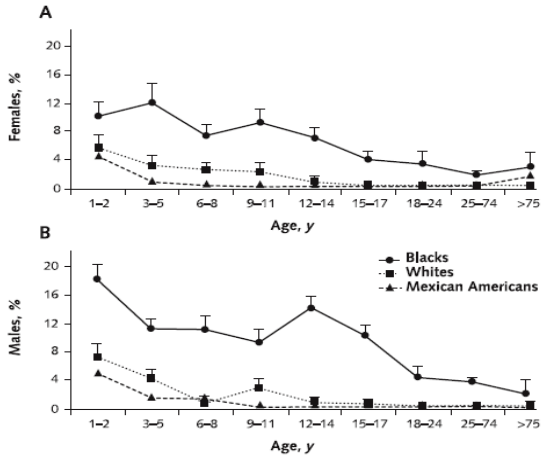
Annals of Internal Medicine | ARTICLE

Prevalence of Neutropenia in the U.S. Population: Age, Sex, Smoking Status, and Ethnic Differences

Matthew M. Hsieh, MD; James E. Everhart, MD, MPH; Danita D. Byrd-Holt; John F. Tisdale, MD; and Griffin P. Rodgers, MD

Figure 2. Percentage of females (*top*) and males (*bottom*) with neutrophil counts less than 1.5×10^9 cells/L.



The error bars refer to the standard errors. **Appendix Table 4** (available at www.annals.org) shows the actual percentages and number of participants.

Table 3. Prevalence of a Neutrophil Count Less than 1.5×10^9 Cells/L

Variable	Prevalence, %* (95% CI)
Ethnicity	
White	0.79 (0.57–1.01)
Black	4.47 (3.92–5.02)
Mexican American	0.38 (0.24–0.52)
Sex	
Female	0.97 (0.77–1.17)
Male	1.50 (1.25–1.76)
Age	
1–2 y	7.24 (5.24–9.24)
3–5 y	3.70 (2.6–4.8)
6–8 y	2.25 (1.51–2.99)
9–11 y	2.73 (1.63–3.83)
12–14 y	2.21 (1.64–2.78)
15–17 y	1.51 (1.0–2.02)
18–24 y	0.66 (0.31–1.01)
25–74 y	0.72 (0.54–0.9)
≥75 y	0.50 (0.17–0.83)

* Prevalence is estimated as the predicted marginals in the logistic regression analysis. The estimates for white, black, and Mexican-American participants are adjusted for age and sex.

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 (<1.0)

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

Clinical cases

Erythrocytosis and/or Thrombocytosis

Beacon Hospital

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

Work-up

MRI Brain – no evidence of CVA

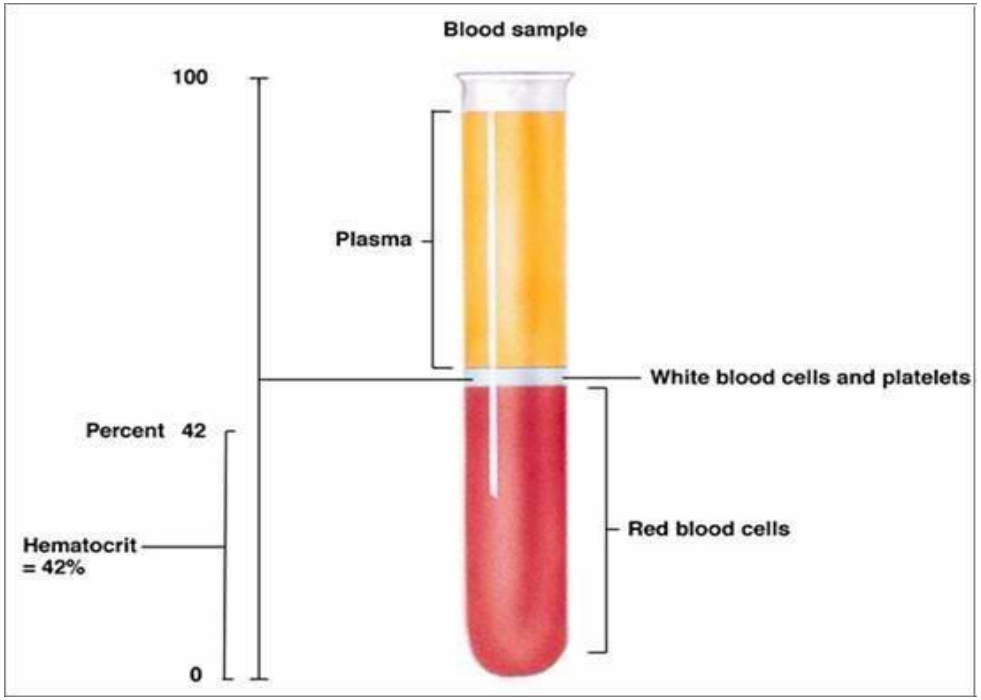
CT Abdomen – 15cm splenomegaly

BM Biopsy – hypercellular with panmyelosis

MPN mutation screen – JAK2 V617F positive

Diagnosis: JAK2 positive Polycythaemia Vera

Haematocrit



Beacon Hospital

Symptoms of Polycythaemia Vera

Erythrocytosis

Headache, decreased mental acuity, weakness

More specific to PRV/MPD

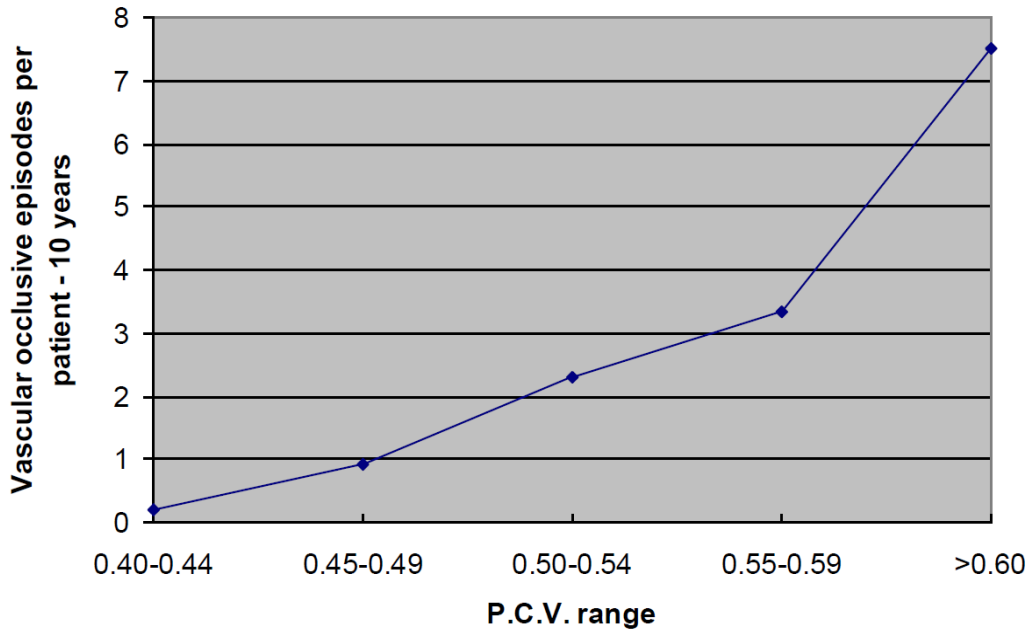
Pruritis after bathing – aquagenic pruritis

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.

Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management

Ayalew Tefferi[1] | Tiziano Barbui[2]

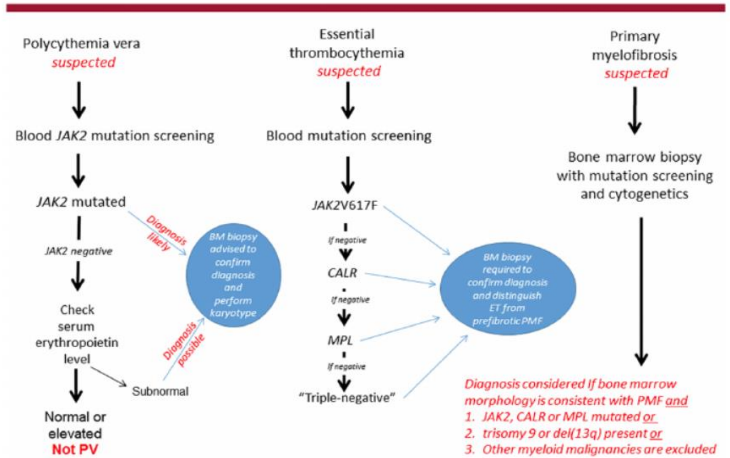


FIGURE 1 Practical diagnostic algorithm for MPNs [Color figure can be viewed at wileyonlinelibrary.com]

Am J Hematol. 2019;**94**:133–143.

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)

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 (>0.48 in men, >0.45 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 (>0.48 in men, >0.45 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

Clinical cases

Raised Platelets

Beacon Hospital

Clinical cases

41 year old woman with a raised platelet count

490 in 2010
510 in 2014

FBC Hb 13.6 Hct 0.42 WCC 6.1 Plts 510

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

Myeloproliferative Neoplasms online patient resources

Information on MPN Voice, UK charity run by volunteers comprising MPN patients and healthcare professionals

https://www.mpnvoice.org.uk/

Other MPN Support Groups

https://mpninfo.org/support/other-mpn-support-groups/

Clinical cases

Paraprotein

Beacon Hospital

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

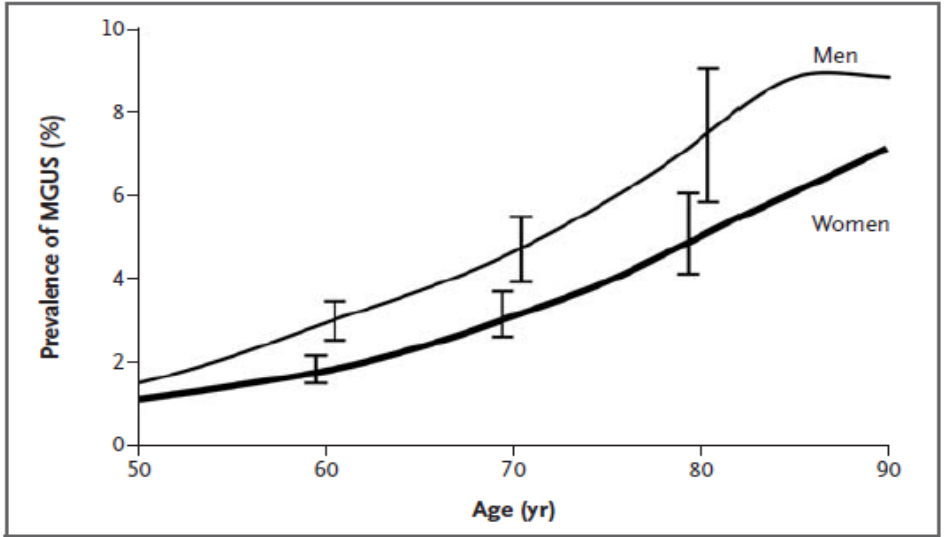


Figure 1. Prevalence of MGUS According to Age.

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.

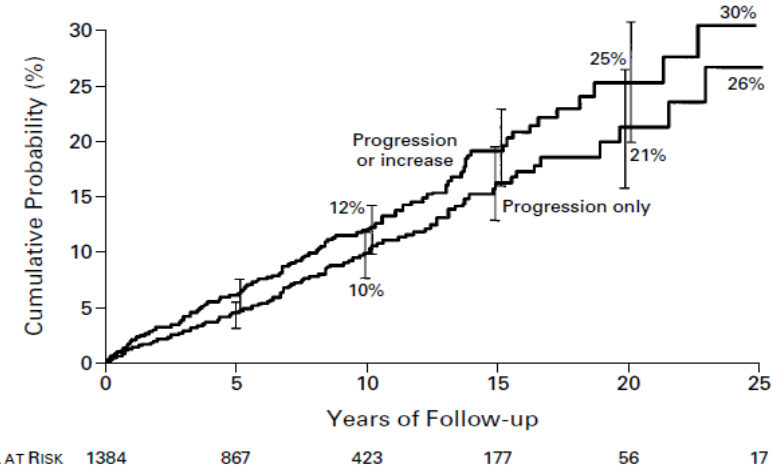


Figure 2. Probability of Progression among 1384 Residents of Southeastern Minnesota in Whom Monoclonal Gammopathy of Undetermined Significance (MGUS) Was Diagnosed from 1960 through 1994.

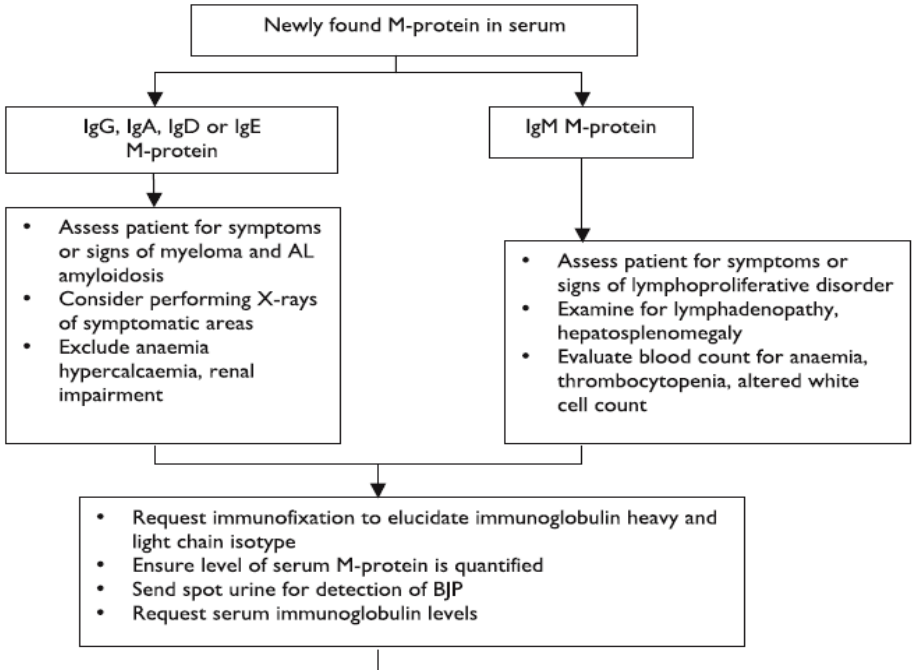
Prognosis in MGUS

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

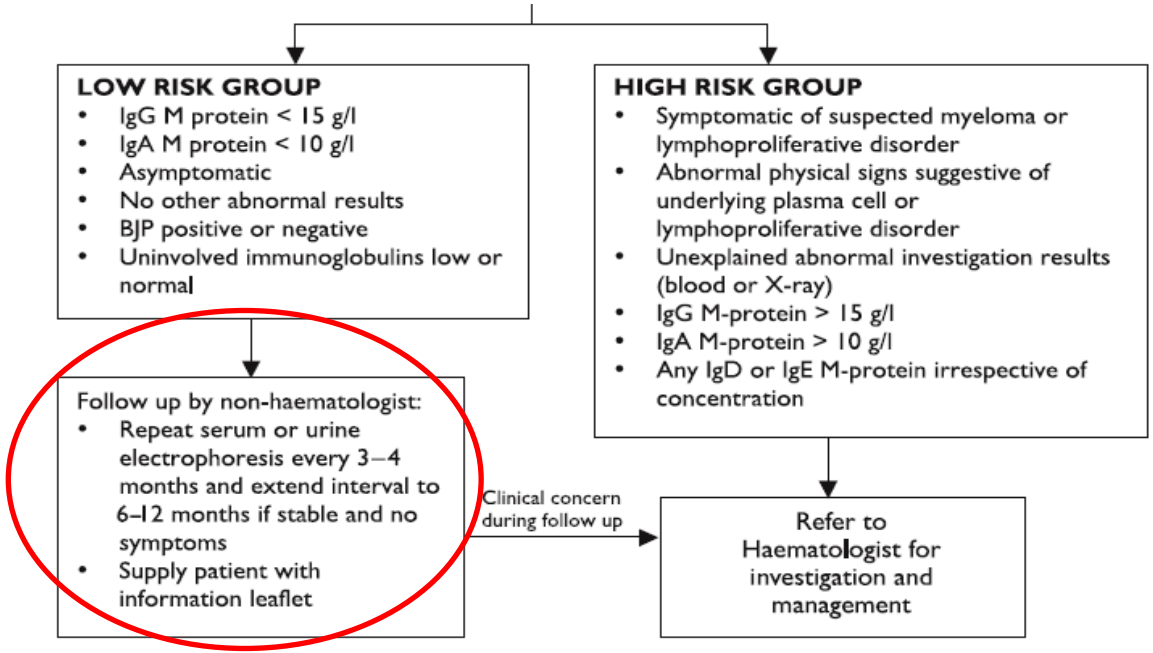
75-90% of patients with MGUS will not develop myeloma or a related disorder in their lifetime

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



Management of MGUS – British Society for Haematology 2009

Beacon Hospital



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; they reflect a non-specific immune response, often see in rheumatological or liver diseases

The diagnosis of myeloma is largely based on end-organ damage –

C hypercalacemia

R renal impairment

A anaemia

B bone disease

If suspected spinal cord compression, refer to Emergency Department

Discharge policy – IgG, less than 15g/L, normal SFLC ratios

Long term follow up - FBC, RLB, Calcium, dipstick urine for protein

Online resources

Patient information on MGUS

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

https://b-s-h.org.uk/guidelines/guidelines/investigation-of-newly-detected-m-proteins-and-the-management-of-mgus/

Guidelines from 2009 though still useful

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