National University Cancer Institute, Singapore

NUHS National University Health System

Too much or too little red cells

What should you do?

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GP CME Symposium 2017

What can affect the red cell results?

Answer:

Haemoglobin: spurious increase	
Lipids	WBC↑, Hb↑, MCH↑
High WBC counts	MCH↑, RBC↑
Immunoglobulins (and cryglobulins)	WBC↑, PLT↑, MCH↑,
In vitro haemolysis	MCH↑
Carboxyhaemoglobin (high amount)	
Bilirubin (>250–300 mg/l)	MCH↑
Haemoglobin: spurious decrease	
Coagulation within the sample	All parameters
Overfilling vaccum tube	All parameters
Veinipuncture near a drip	MCV↑ (glucose drip)
Sulfhaemoglobin	

RBC: spurious decrease
- Cold agglutinins, warm agglutinins
- Very small RBC
- Cryoglobulins (↓ flow, inadequate aspiration)
- *In vitro* haemolysis
- Coagulation

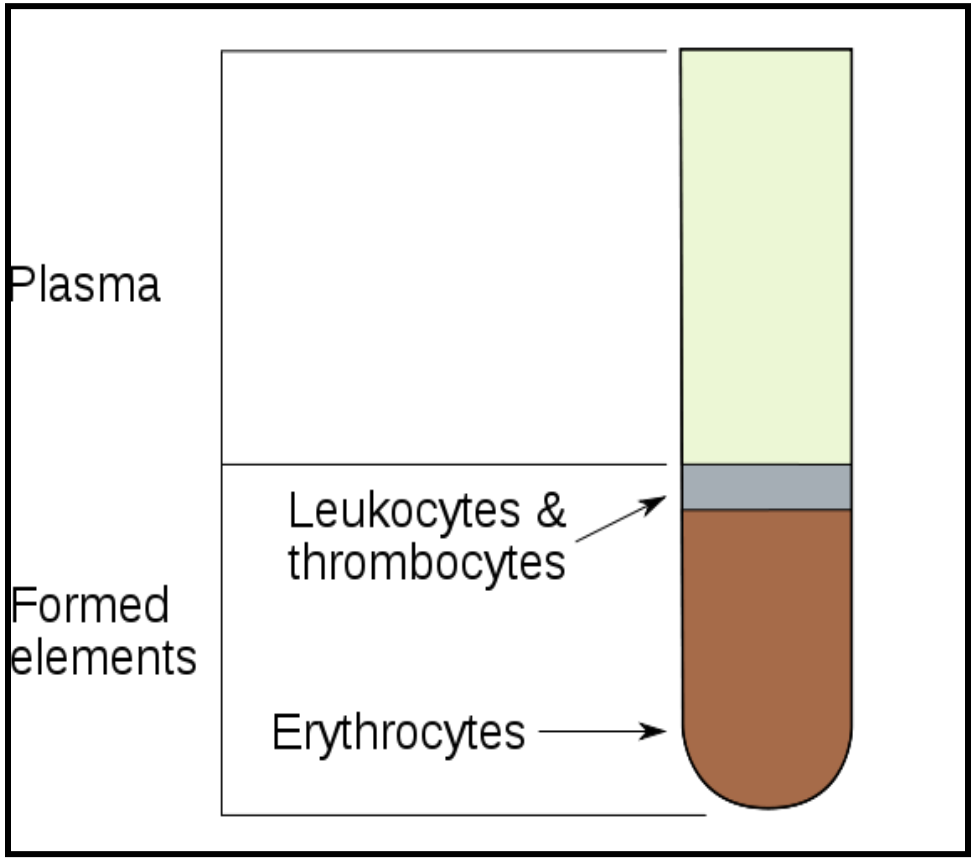
RBC: spurious increase
- High WBC counts
- Giant PLT

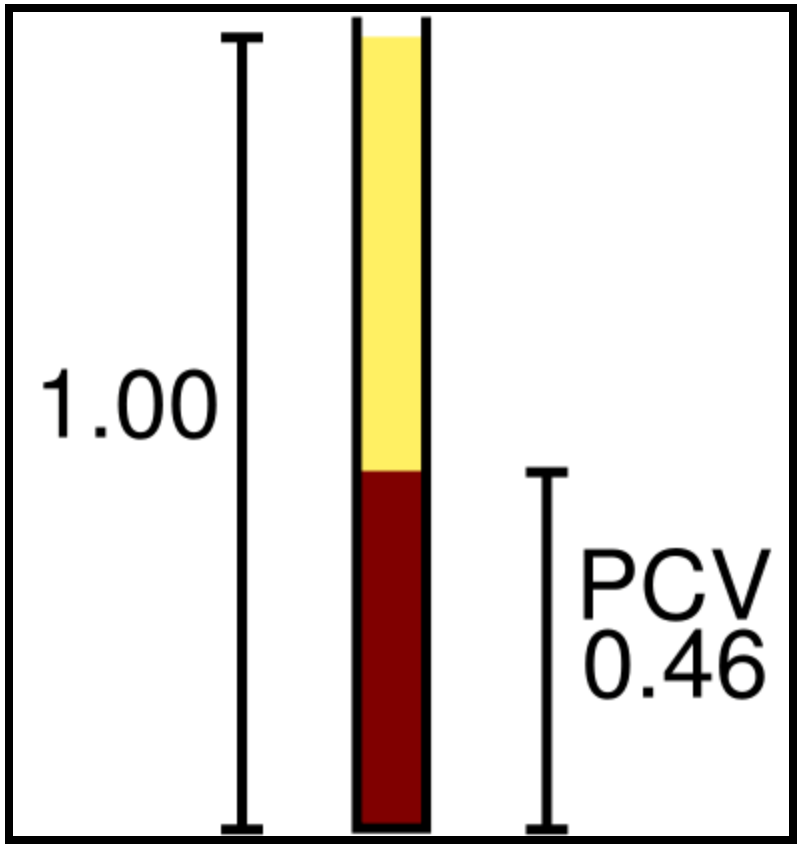
Too many red cells

Polycythaemia

- Polycythaemia indicates increased red blood cells, white blood cells and platelets
- But most of the time, when this term is used, we mean erythrocytosis

Hematocrit: Proportion of the blood volume that is occupied by RBCs.



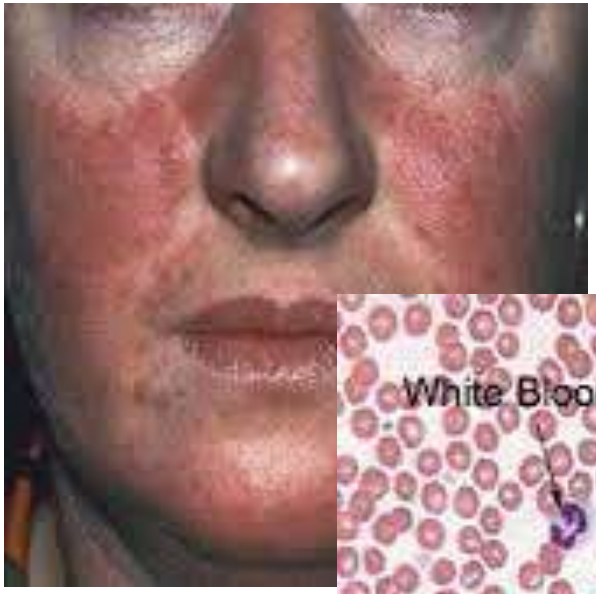


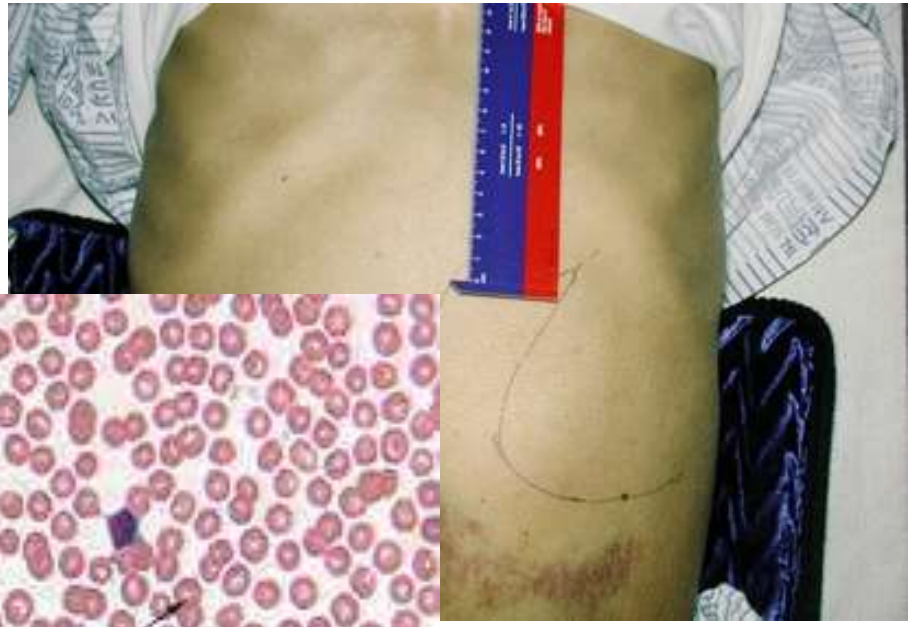
History

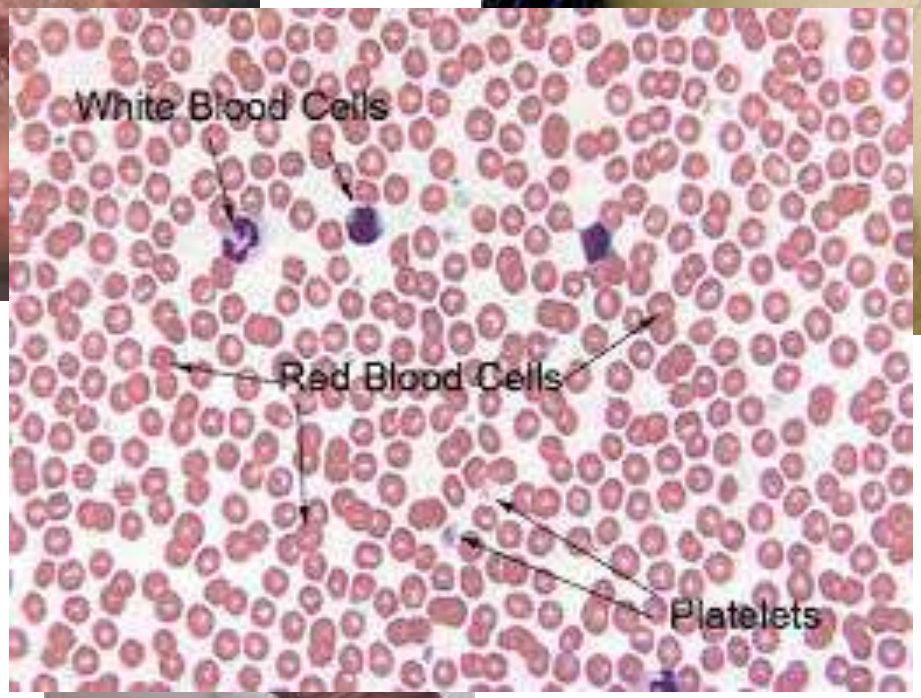
- Constitutional symptoms (weight loss, night sweats, fevers)
- Vasomotor symptoms (Headache, dizziness, tinnitus, paresthesias, erythromelalgia)
- Lethargy
- Confusion
- Chronic pruritus
- Stroke
- Thrombosis

In relation to	Factors
Personal/medical history	Work exposure, past diseases, including neoplasia, surgical interventions, past cardiovascular events and hemorrhage, if menopausal (woman), and altitude (where you live)
Family	Relatives with a diagnosis of MPN , with other hematologic neoplasia or disorders; relatives with unexplained erythrocytosis ; and relatives with thrombotic events in unusual sites and/or at an unusual age
Lifestyle	Smoking, physical activity, dietary habits, and nocturnal apnea (ask the spouse)
Concomitant comorbidities	Other diseases, in general; and in particular, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, and gout
Medications	Use of antihypertensive agents, especially diuretics; use of androgens; chronic use of corticosteroids; use of antiplatelet aggregants or anticoagulants

Physical

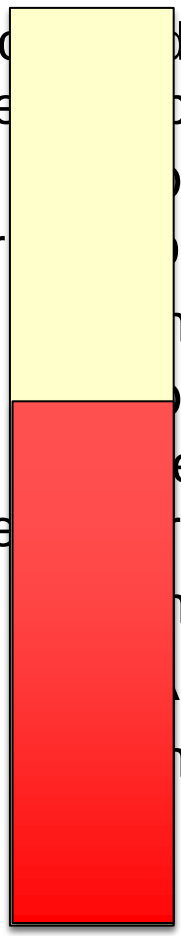


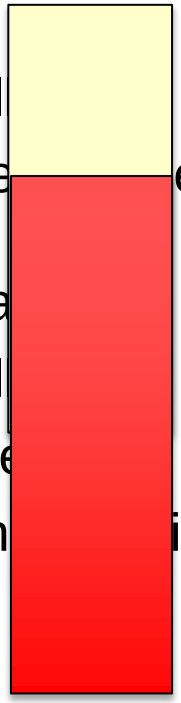


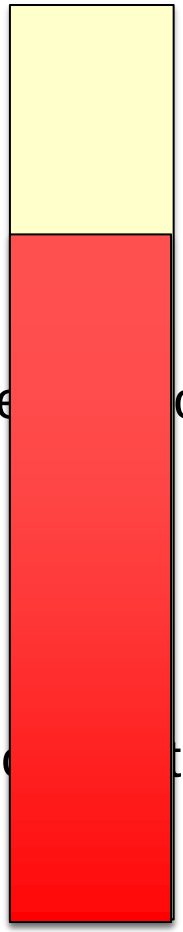


Pathophysiology

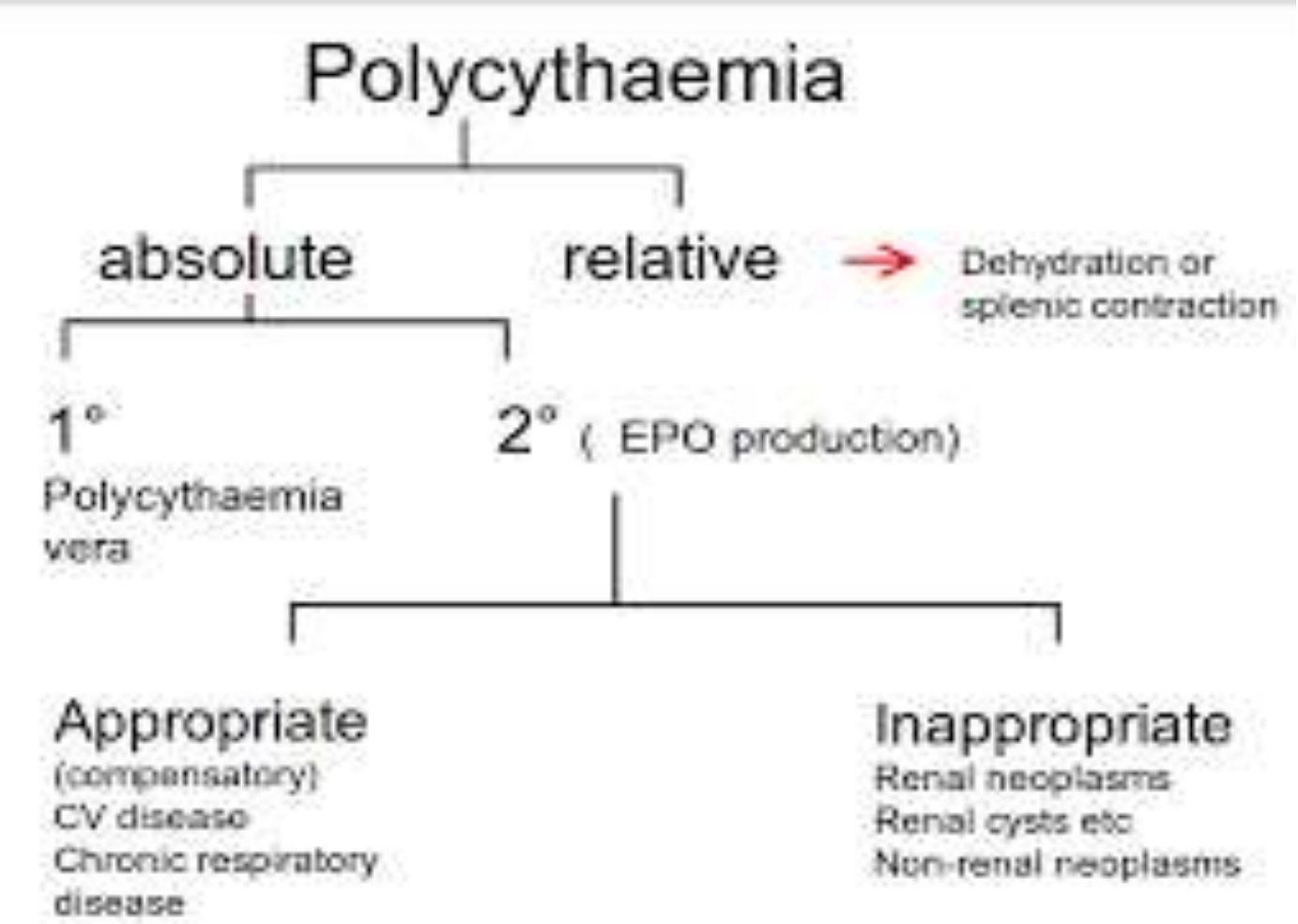
- Inc d haemoglobin and haematocrit values
- Re olycythaemia
  - ecreased plasma volume
- Pr olycythaemia
  - ncreased red cel
  - ue to mutation e ed within the hae oietic stem ell
- Se y polycythaemia
  - ncreased red cel
  - cquired or conge
  - ndependent of th ion of haematope tem cells







Causes


Polycythaemia
absolute
relative
Dehydration or splenic contraction
1°
Polycythaemia vera
2° (EPO production)
Appropriate
(compensatory)
CV disease
Chronic respiratory disease
Inappropriate
Renal neoplasms
Renal cysts etc
Non-renal neoplasms

Mechanism	Found in
Reduction of plasma volume (relative erythrocytosis)	• Acute (protracted vomiting or diarrhea, severe burns, protracted fever, diabetic ketoacidosis) • Chronic (prolonged and inappropriate use of diuretics, Gaisböck syndrome)
Appropriately increased sEPO levels	• Chronic obstructive pulmonary disease • cyanotic heart disease • Smokers • people living at high altitudes • sleep apnea • obesity, eventually associated with sleep apnea, • drugs (androgens and corticosteroids) • doping with recombinant preparation of human EPO
Inappropriately increased sEPO levels	• Renal cell carcinoma • non-neoplastic renal lesions (cysts, hydronephrosis, and severe stenosis of the renal artery) • hepatocellular carcinoma • uterine fibroma • Meningioma • cerebellar hemangioblastoma • other tumors (Wilms' tumor, ovarian, carcinoid, and pituitary adenoma), • following renal transplantation

Workup

- Repeat FBC in 4-12 weeks

- *JAK2* V617F mutation
- Erythropoietin (EPO) level
- Other mutations in exon 12 and 13 of *JAK2*
- Measure red blood cell mass and plasma volume
- Measuring arterial oxygen saturation
- Carboxyhemoglobin levels of greater than 8% in individuals who smoke or those who may have an occupational exposure to carbon monoxide may be associated with the development of polycythemia.

- Sleep studies

- CXR
- CT /US abdomen

Risk stratification

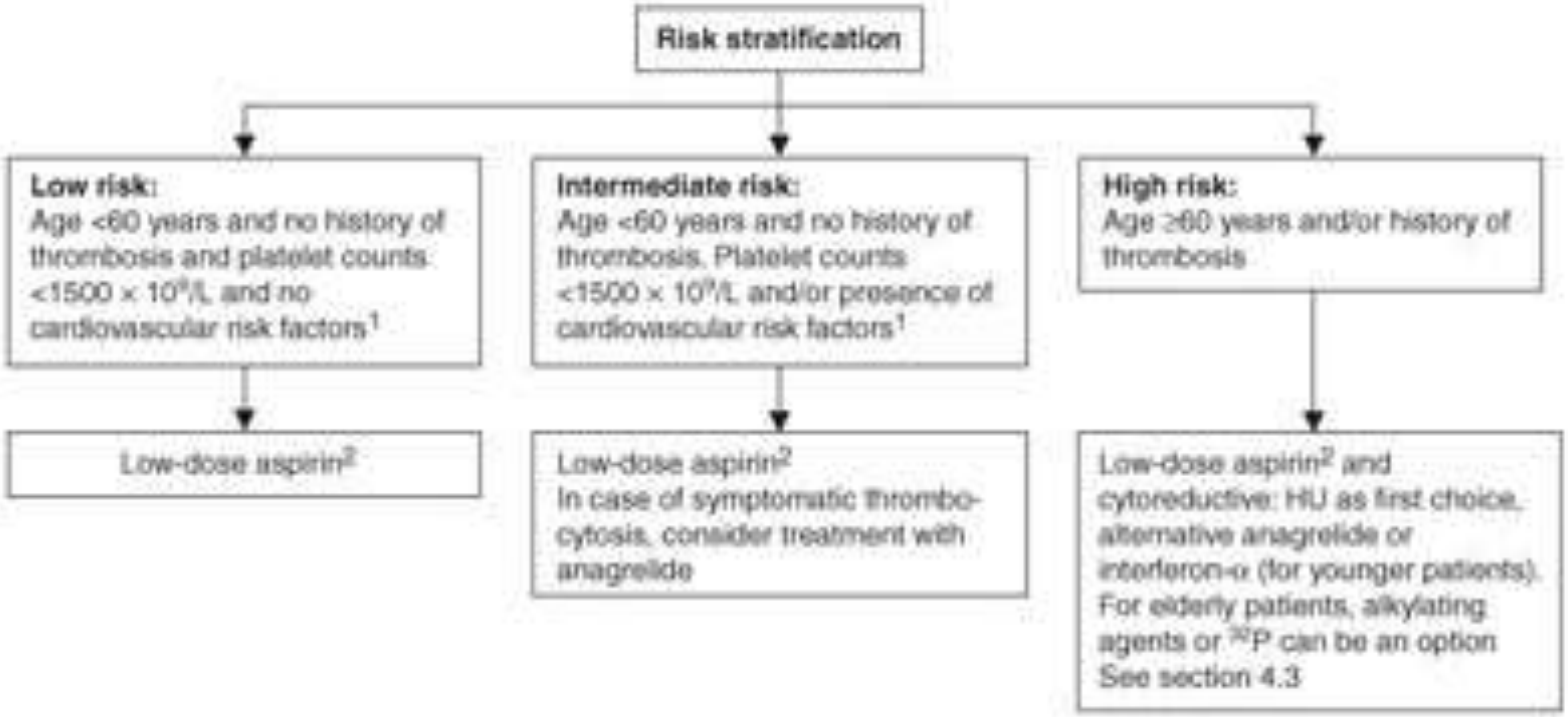


Fig. 2. Treatment algorithm for patients with essential thrombocythaemia. **HU** = hydroxycarbamate (hydroxyurea). **1.** Cardiovascular risk factors include diabetes mellitus, obesity, smoking, hypertension, hyperlipidemia, hypercholesterolaemia. **2.** Contraindications to aspirin: prior haemorrhagic events and/or platelet counts >1000–1500 × 10^9/L and acquired von Willenbrand's disease.

When to refer to SOC

- Persistent increase in Haematocrit without good reason
- Very high first Haematocrit >60%
- Thrombosis
- Constitutional symptoms

Case 1

47-year-old dentist who presented in early 2012 with a routine blood test showing the following:

- Hb 23.3 g/dL; hematocrit (Hct), 68.9%; MCV 81 fL; WCC, 4.4 × 10^9/L; platelets, 145 × 10^9/L;
- hyperuricemia, and low ferritin levels.
- He said he felt “perfectly well”
- Physical examination was unremarkable except for mild hypertension.
- No previous blood results and no past history or family history of note
- Repeat FBC done by GP over the next 3, 6 months showed a persistant haematocrit of 68%
- Referred to SOC

Case 1

- sEPO levels undetectable
- *JAK2*V617F mutation positive

Treatment

- Phelobotomise to haematocrit <45% and low dose aspirin.

Case 2

68-year-old retired man, who was a heavy smoker and obese

- Hb, 178 g/L; Hct, 53.7%; MCV, 74 fL; WCC, 13.6 × 10^9/L; platelets, 535 × 10^9/L.
- One year before, he had an acute myocardial infarction; an Hb and Hct of 165 g/L and 52.6%, respectively, were not further investigated.
- He was on antihypertensive medications and antidiabetics and was taking aspirin.
- He complained of tiredness.
- The abdominal exam was normal.

Case 2

- His sleep studies were consistent with sleep apnoea

Treatment

- Stop smoking
- Loose weight
- CPAP machine at night

Too little red cells

What is Anaemia?

The word “anemia” is composed of two Greek roots that together mean “without blood”

Anemia is any condition characterized by an abnormal decrease in the body's total red blood cell mass

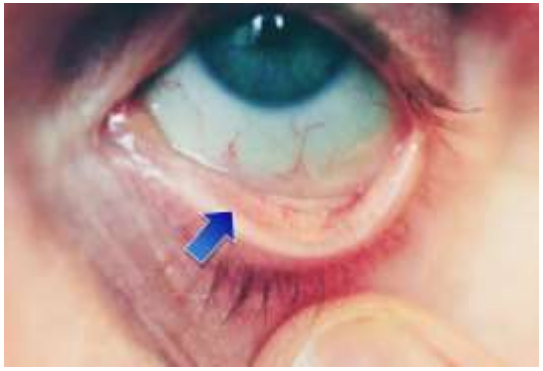
History taking

- Rapidity of onset: gradual onset is suggestive of bone marrow failure or chronic blood loss, whereas sudden onset of symptoms suggests hemolysis or acute haemorrhage
- History of infection (sepsis, acquired immunodeficiency syndrome, malaria)
- External blood loss: gastrointestinal, genitourinary (enquire about melaena, hematochezia, gross hematuria), frequent phlebotomy
- History of cancer, renal disease, or endocrine disease
- Family and ethnic history: enquire about thalassemia, sickle cell anaemia, splenectomy, cholelithiasis at an early age
- Drug and toxic exposures (e.g., chloramphenicol, methyldopa, quinidine, benzene, alkylating agents)
- Obstetric and menstrual history: “excessive” menstrual bleeding is a frequent cause of iron deficiency anaemia in menstruating women.
- Dietary habits: poor dietary habits and alcohol intake may result in folic acid deficiency

Physical Examination

General appearance: Evaluate nutritional status.
Vital signs: hypotension, tachycardia (acute blood loss)
Skin: pallor of the conjunctiva, lips, oral mucosa, nail beds, and palmar creases; jaundice (haemolysis); petechiae; purpura (thrombocytopenia)
Mouth: glossitis (pernicious anaemia, iron deficiency anemia)
Heart: listen for flow murmurs, prosthetic valves (increased RBC destruction).
Abdomen: splenomegaly (haemolysis, neoplasms, infiltrative disorders)
Rectum: examine stool for occult (or gross) blood.
Lymph nodes: infiltrative lesions, infections

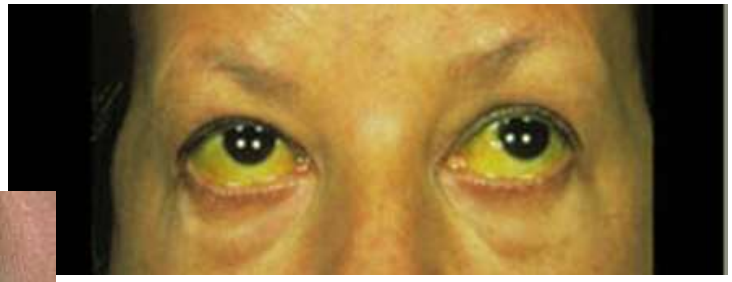
Clinical signs of anemia

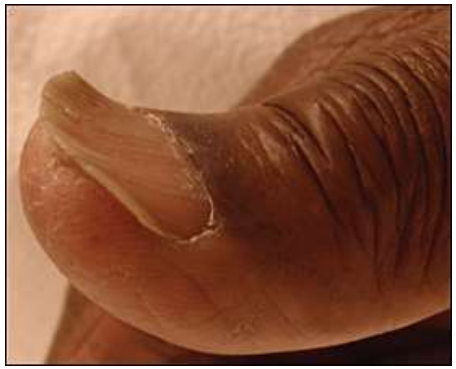


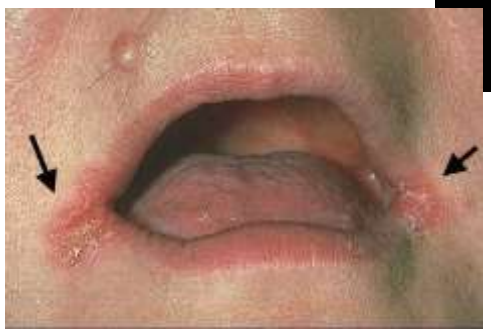
Pallor due to anemia

Other symptoms and signs with anemia are due to underlying cause of anemia

JAUNDICE → HAEMOLYSIS

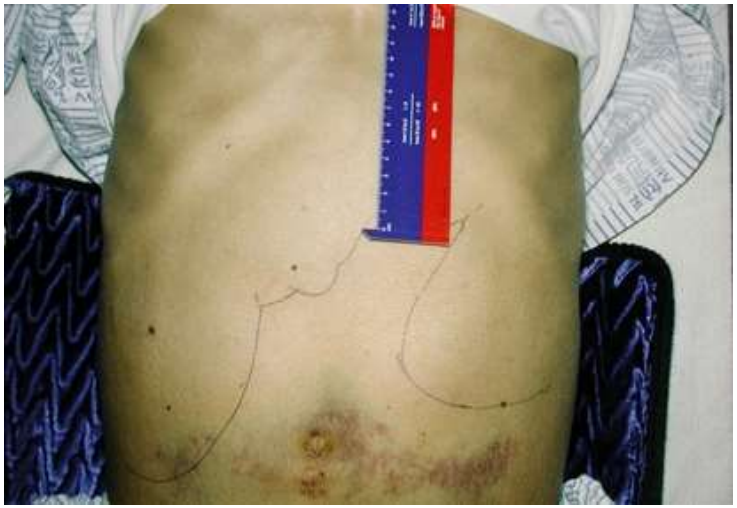


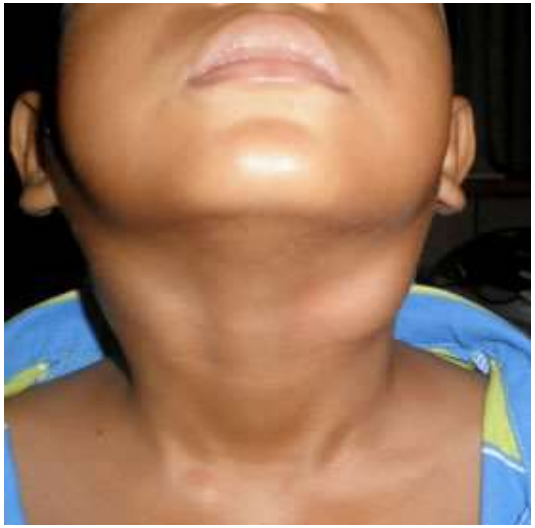




SIGNS OF IRON DEFICIENCY

Other important signs to look out for …..

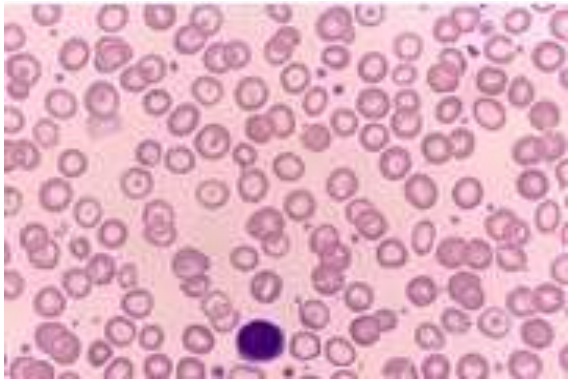




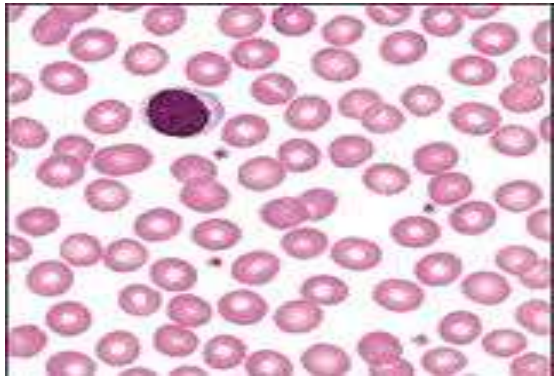
Classification of anemia by morphology : mean cell volume

MCV

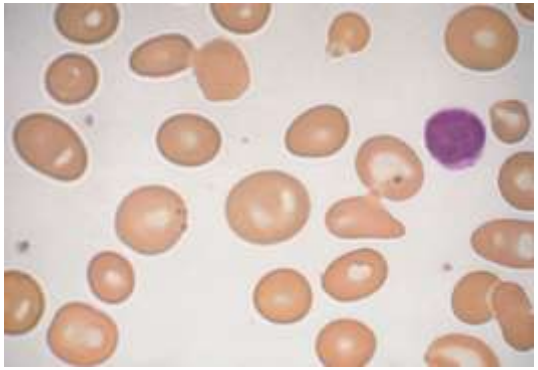
Microcytic



Normocytic



Macrocytic



Classification of anaemia by morphology: mean cell volume

MCV

Microcytic

Iron Deficiency anemia

Thalassemias

Sideroblastic Anemia

Normocytic

Chronic diseaseNormal WBC/Platelets:

- AOCD
- Early IDA
- Renal failure
- Pure red cell aplasia

Pancytopenia

- Primary failure: AA
- Secondary failure: chemo/RT, MDS, marrow infiltration

Macrocytic

Megaloblastic anemias

Liver disease

Alcohol

Hypothyroidism

Drugs eg AZT

MDS

Reticulocytosis

Patient C

Date of Birth	3/22/69
Sex	F
Consultant	Chee Yen Lin
Accession No.	1082512918
Location	NCKCNX
Receipt Date	23/08/2011 13:44

Procedure	Results		Unit	Expected Ranges
Full Blood Count				
White Blood Cell	5.08		x10 9/L	3.40 - 9.20
Red Blood Cells	5.02		x10 12/L	3.74 - 4.90
Haemoglobin	7.8	<	g/dL	10.7 - 14.3
MCV	63.1	<	fL	80.0 - 95.0
MCH	18.2	<	pg	26.0 - 32.0
MCHC	28.9	<	g/dL	31.0 - 35.0
Haematocrit	27.0	<	%	32.0 - 44.0
Platelets	200		x10 9/L	155 - 393
RDW	26.1	>	%	11.7 - 14.5
Differential Counts	.			
Neutrophils %	57.1		%	
Neutrophils	2.90		x10 9/L	1.50 - 6.00
Lymphocytes %	37.8		%	
Lymphocytes	1.92		x10 9/L	1.04 - 2.86
Monocytes %	3.9		%	
Monocytes	0.20		x10 9/L	0.14 - 0.68
Eosinophils %	1.0		%	
Eosinophils	0.05		x10 9/L	0.00 - 0.41
Basophils %	0.2		%	
Basophils	0.01		x10 9/L	0.00 - 0.07
Fragmentation	1+			
Poikilocytosis	2+			
Anisocytosis	2+			
Elliptocytes	2+			
Hypochromasia	2+			
Reticulocytes (Abs)				
Reticulocytes (Abs)	100		x10 9/L	15.00 - 86.70

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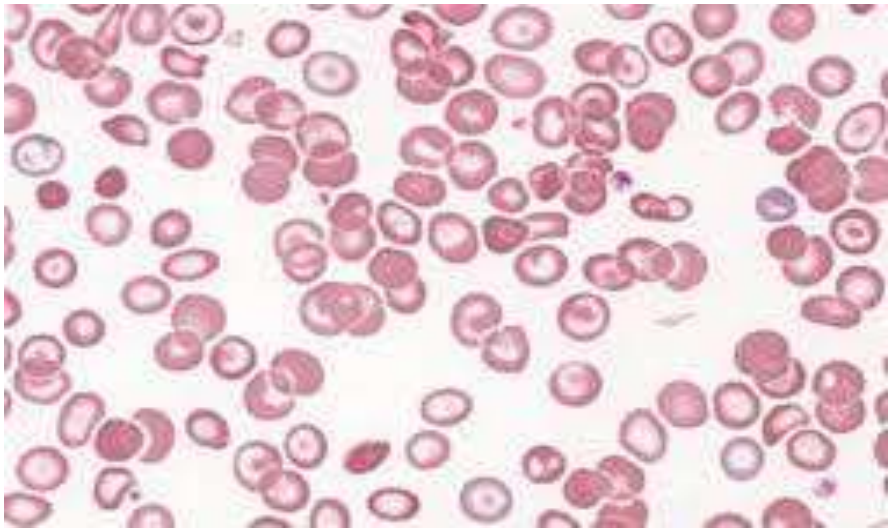
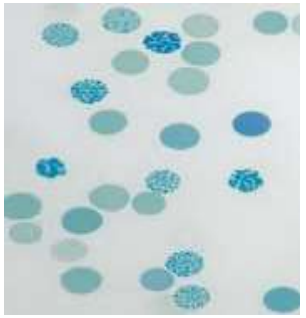
Classification of anaemia by morphology: mean cell volume

MCV

Microcytic	Normocytic	Macrocytic
Iron Deficiency anemia Thalassemias Sideroblastic Anemia		



Thalassaemia No	2011-3083			
Hb A2	1.0	<	%	1.7 - 3.2
HB F	< 0.5		%	0.0 - 1.0
HBH Inclusion Bodies	3+			
Hb Electrophoresis	HbA and HbA2 band detected			
Hb Report	Hb H Disease			



Iron Panel

Iron	11.4		umol/L	8.8 - 27.0
Ferritin	436	>	ug/L	10 - 120
Transferrin	161	<	mg/dL	200 - 300
TIBC	42		umol/L	38 - 67
Iron Saturation	27		%	15 - 50

Thalassaemia

- Heterozygotes very common (alpha, beta)
- Borderline asymptomatic anemia
  - hypochromic microcytic indices
  - raised RBC, normal RDW
  - peripheral film – hypochromic, microcytic with target cells
- Exclude co-existing iron deficiency
- Implications for family planning

Iron deficiency anemia

- Find a cause for the iron deficiency
- Replace iron stores – AVOID transfusion
- Regimen
  - Oral iron – elemental iron 100 – 200 mg/day (ferrous fumarate 65 mg iron per 200 mg tablet)
  - Sangobion has a lot of unnecessary minerals- cu sulfate 200 mcg, Fe gluconate 250 mg (elemental iron 30 mg), folic acid 1 mg, mn sulfate 200 mcg, sorbitol 25 mg, vit B12 7.5 mcg, vit C 50 mg
- Warn patients of iron replacement side effects – nausea and epigastric pain (dose related), constipation/diarrhoea – reduce dose or change prep
- Therapeutic response
  - 0.1-0.2 g/dL per day or 2 g/dL over 3-4 weeks
  - Treat till Hb is in reference range
  - Then for further 3 months to replenish stores

Patient D

HRN	S2203906G	**Sex**	F	**Date of Birth**	02/01/1970
Printed By	CHEE YEN LIN			**Printed Date**	11/01/2011 14:08:34

Receive Date	Test	Result		Units	Reference Interval
28 Dec 2009 07:28					
	Potassium	**3.9**	**N**	**mmol/L**	**3.5 - 5.0**
	Full Blood Count				
	White Blood Cell	3.00	L	x10 9/L	3.26 - 9.28
	Red Blood Cells	1.55	L	x10 12/L	3.77 - 4.92
	Haemoglobin	6.2	L	g/dL	11.7 - 14.7
	MCV	120.6	H	fL	80.1 - 96.7
	MCH	39.9	H	pg	24.5 - 34.3
	MCHC	33.1	N	g/dL	30.8 - 38.4
	Haematocrit	18.7	L	%	33.5 - 43.8
	Platelets	125	L	x10 9/L	160 - 398
	MPV	9.0	N	fL	6.6 - 9.9
	RDW	24.2	H	%	10.5 - 15.9
	Differential Counts	.			
	Neutrophils %	49.8		%	
	Neutrophils	1.49	N	x10 9/L	1.41 - 6.83
	Lymphocytes %	38.2		%	
	Lymphocytes	1.14	N	x10 9/L	0.53 - 3.98
	Monocytes %	6.8		%	
	Monocytes	0.20	N	x10 9/L	0.10 - 0.80
	Eosinophils %	3.6		%	
	Eosinophils	0.11	N	x10 9/L	0.00 - 0.72
	Basophils %	0.1		%	
	Basophils	0.00	N	x10 9/L	0.00 - 0.11
	LUC %	1.5		%	
	LUC	0.06	N	x10 9/L	0.02 - 0.29
	Polychromasia	2+			
	Tear-Drop Cells	1+			
	Fragmentation	1+			
	Anisocytosis	3+			
	Macrocytosis	3+			
	Slide	Reviewed			
Reticulocytes (Abs)		**91.40**	**N**	**x10 9/L**	**29.13 - 112.60**

Morphology classification of anemia – mean cell volume

MCV

Microcytic

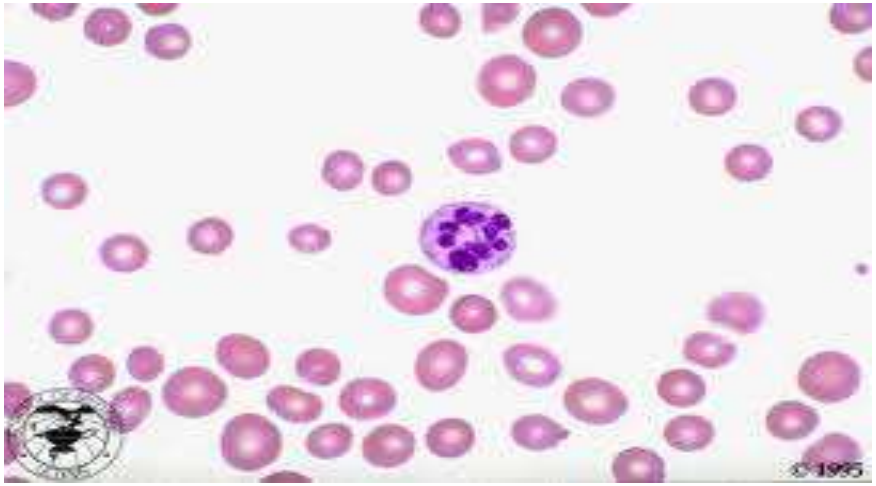
Normocytic

Macrocytic

Megaloblastic anemias

Non-megaloblastic:

- Liver disease
- Alcohol
- Hypothyroidism
- Drugs eg AZT
- MDS



Folate / Vitamin B12

Folate	5.9	L	nmol/L	7.0 - 39.7
	Normal 7.0 - 39.7 Borderline deficient 5.0 - 6.9 Deficient < 5.0 Excessive > 39.7			
Vitamin B12	53	L	pmol/L	179 - 660

Anti-Intrinsic Fact **Negative**

Test referred to
TTSH Immunology Lab,
Tel 63578464

Parietal Cell Ab **< 20** **U/mL**

Interpretation:
No antibody detected <20
Antibody positive >=20

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Megaloblastic anemia

- PANCYTOPENIA
  - B12/folate needed for DNA synthesis
  - Peripheral film – macrocytosis, oval macrocytes, hypersegmented neutrophils
  - Intramedullary hemolysis (bili, LDH raised)
- Find a CAUSE for the megaloblastic anemia
  - No B12 in vegetables (unless bacterial contamination) - vegans
- B12 replacement
  - No neurological involvement - hydroxycobalamine im 1 mg x3 per week for 2 weeks then 1 mg every month
  - Neurological involvement 1 mg alternate days till no improvement, then 1 mg every month
- Folate replacement
  - 5 mg daily

Patient G

G8091416X **Sex** F **Date of Birth** 09/02/1968
CHEE YEN LIN **Printed Date** 11/01/2011 18:33:34

Test	Result			Units	Reference Interval
:00					
Full Blood Count					
White Blood Cell	8.15		N	x10 9/L	3.26 - 9.28
Red Blood Cells	1.62		L	x10 12/L	3.77 - 4.92
Haemoglobin	4.9		LL	g/dL	11.7 - 14.7
MCV	88.2		N	fL	80.1 - 96.7
MCH	30.1		N	pg	24.5 - 34.3
MCHC	34.1		N	g/dL	30.8 - 38.4
Haematocrit	14.3		L	%	33.5 - 43.8
Platelets	15		LL	x10 9/L	160 - 398
MPV	6.5		L	fL	6.6 - 9.9
RDW	21.7		H	%	10.5 - 15.9
Differential Counts	.				
Neutrophils %	72.6			%	
Neutrophils	5.92		N	x10 9/L	1.41 - 6.83
Reticulocytes (Abs)					
Reticulocytes (Abs)	450.90	>	x10 9/L		29.13 - 112.60

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Patient G

G8091416X **Sex** F **Date of Birth** 09/02/1968
CHEE YEN LIN **Printed Date** 11/01/2011 18:33:34

Test	Result		Units	Reference Interval
:00				
Full Blood Count				
White Blood Cell	8.15	N	x10 9/L	3.26 - 9.28
Red Blood Cells	1.62	L	x10 12/L	3.77 - 4.92
Haemoglobin	4.9	LL	g/dL	11.7 - 14.7
MCV	88.2	N	fL	80.1 - 96.7
MCH	30.1	N	pg	24.5 - 34.3
MCHC	34.1	N	g/dL	30.8 - 38.4
Haematocrit	14.3	L	%	33.5 - 43.8
Platelets	15	LL	x10 9/L	160 - 398
MPV	6.5	L	fL	6.6 - 9.9
RDW	21.7	H	%	10.5 - 15.9
Differential Counts	.			
Neutrophils %	72.6		%	
Neutrophils	5.92	N	x10 9/L	1.41 - 6.83
Reticulocytes (Abs)				
Reticulocytes (Abs)	450.90	>	x10 9/L	29.13 - 112.60

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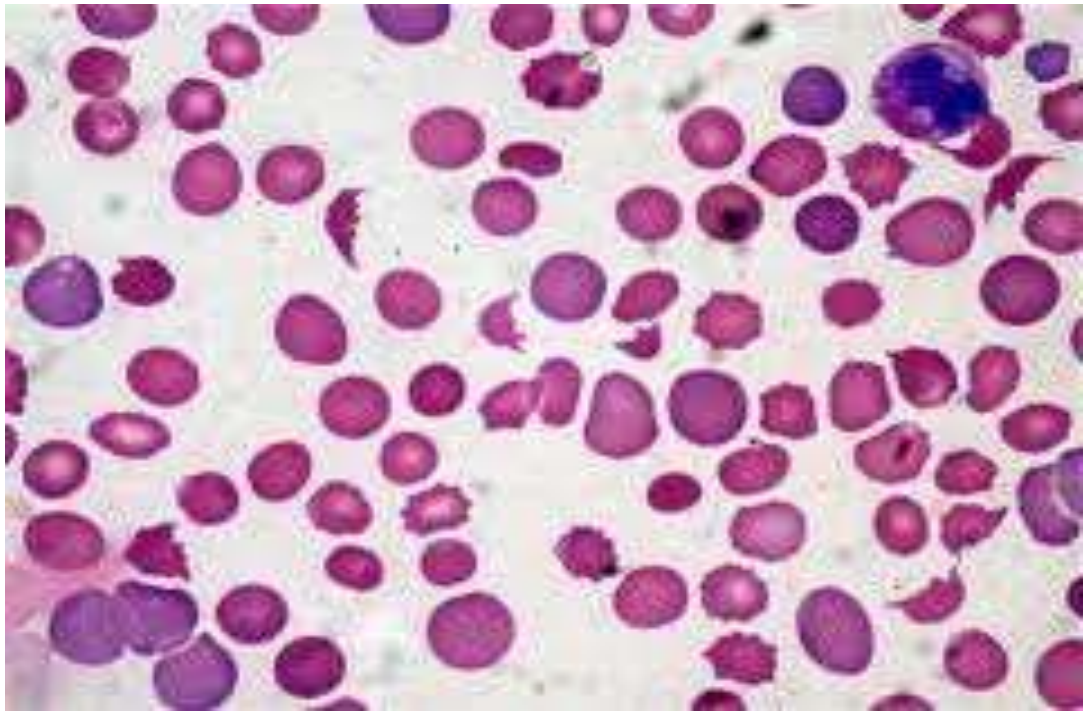
Iron Panel				
Iron	6.0	L	umol/L	8.8 - 27.0
Ferritin	123	H	ug/L	10 - 120
Transferrin	198	L	mg/dL	200 - 300
TIBC	51	N	umol/L	38 - 67
Iron Saturation	12	L	%	15 - 50
Renal Panel 1				
Sodium	137	N	mmol/L	135 - 150
Potassium	4.3	N	mmol/L	3.5 - 5.0
Urea	14.6	H	mmol/L	2.0 - 6.5
Creatinine	395	H	umol/L	50 - 90

Patient G



Peripheral Bld Film

RBC: Significant schistocytes and polychromasia.
WBC: Unremarkable.
PLT: Markedly reduced.
Impression: MAHA

Classification of anaemia by morphology: mean cell volume

MCV

Microcytic

Normocytic

Chronic diseaseNormal WBC/Platelets:

- AOCD
- Early IDA
- Renal failure
- Pure red cell aplasia

Pancytopenia

- Primary failure: AA
- Secondary failure: chemo/RT, MDS, marrow infiltration

Macrocytic

TTP-HUS

- Presents with MAHA and thrombocytopenia
- Causes include:
  - Primary TTP-HUS
    - Primary autoimmune TTP
    - Childhood diarrhoea-positive HUS
  - Secondary
    - DIC
    - Malignant hypertension
    - Cancer
    - Autoimmune
    - Pregnancy, drugs, infection, HSCT

Summary

- Anaemia unless causing haemodynamic compromise can be managed as outpatient.
- Anaemia is a sign of disease. An underlying cause needs to be found
- Approach to diagnosing cause – morphology
- 3 simple initial tests: reticulocyte, MCV, and peripheral blood film
- Other clues: WBC/Platelet, bilirubin, LDH and specific causes (ferritin, B12/folate, renal)
- Do not to transfuse patients without symptoms

Risks of RBC Transfusion

Febrile non-hemolytic RXN: 1/100 tx
Minor allergic reactions: 1/100-1000 tx
Bacterial contamination: 1/ 2,500,000
Viral Hepatitis 1/45,000
Hemolytic transfusion rxn Fatal: 1/500,000
Immunosuppression: Unknown
HIV infection 1/500,000

National University Cancer Institute, Singapore

Thank you for your attention

NCIS Cancer Appointment Line: 6773 7888

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