College Learning Series

Haematology Revision

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RACP
Specialists. Together
EDUCATE ADVOCATE INNOVATE

Key learning points

1. Interpreting the Full Blood Count and Blood Film
2. Interpreting Coagulation Tests
3. EMQ Hot Topics/Pearls

Interpreting the Full Blood Count & Blood Film

Microcytic	Normocytic	Macrocytic
iron deficiency	**bleeding**	**vitamin B12 deficiency**
thalassaemia	**hemolysis**	**folate deficiency**
	chronic disease	**alcohol**
	metabolic problems	reticulocytosis
	endocrine dysfunction	hypothyroidism
	stem cell disorders	

Iron Deficiency Anaemia

Case Report

A female aged 35 years reports that she feels tired all the time.

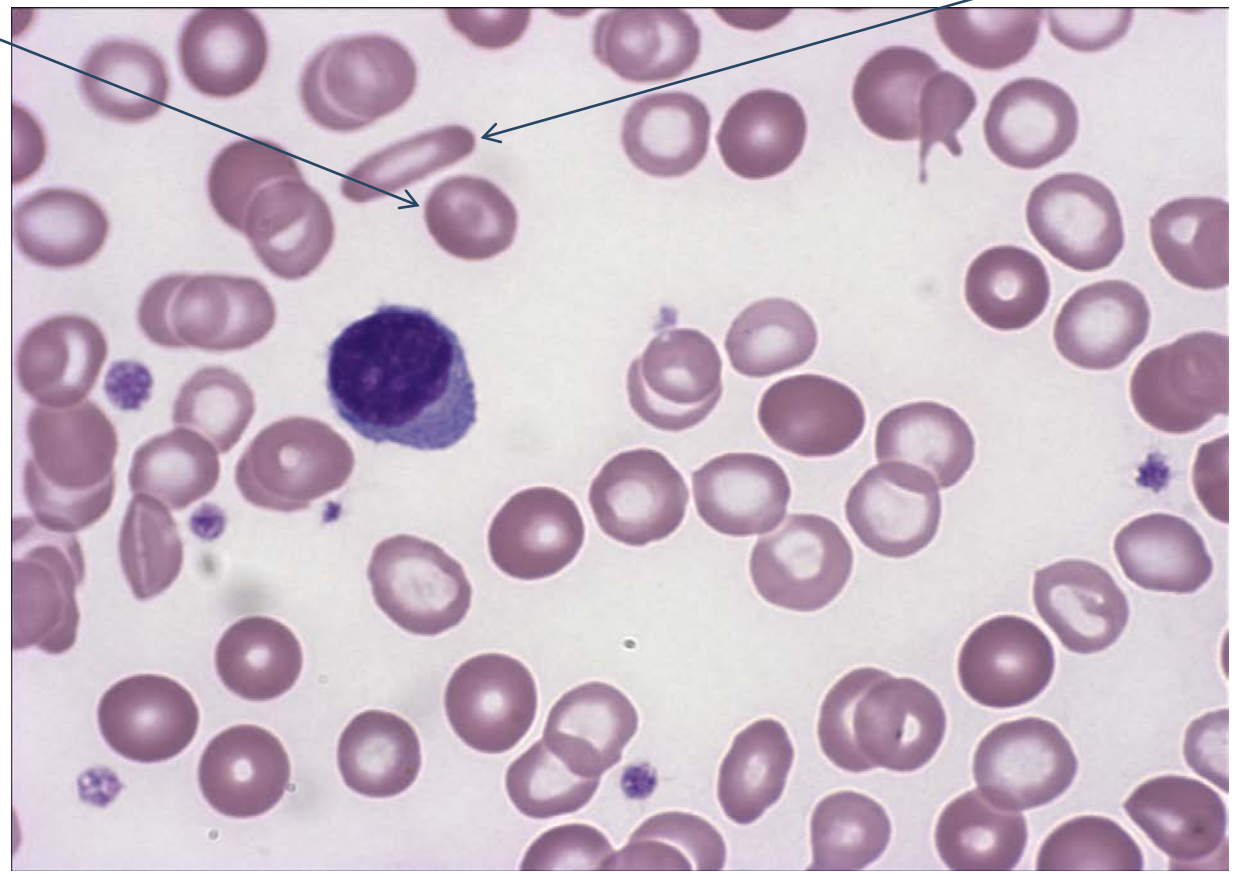
Over the last 2 years her periods have been much heavier in daily loss than previously, and last 6 to 7 days

Blood Results

Hgb	**115-165g/L**	**95**
RBC	**3.8-5.8 x 1012/L**	**3.80**
Hct	**0.37-0.47**	**0.285**
MCV	**79-98 fl**	**75.1**
MCH	**27.0-34.0 pg**	**25.0**
MCHC	**32.0-36.0 g/dl**	**32.0**
WBC	**4.0- 11.0 x 109/L**	**8.5**
Neut	**2.0- 7.5 x 109/L**	**6.0**
Lymph	**1.5- 0.4 x 109/L**	**1.9**
Mono	**0.2- 0.8 x 109/L**	**0.6**
Eos	**0.04- 0.40 x 109/L**	**…**
Baso	**0- 0.1 x 109/L**	**…**
Plt	**150- 450 x 109/L**	**280**
ESR	**4-15 mm/hr**	**10**

Iron Deficiency Anaemia – Blood Film

Red cells show hypochromia and anisocytosis, with an occasional pencil cell and target cell



Iron Deficiency Anaemia

Iron Studies

Serum iron	11-31 μ mol/l	6
Serum transferrin	1.7-2.9 g/l	3.2
Saturation	20-50%	9
Serum ferritin	14-186 μ g/l	9
Serum B12	185-815 pmol/l	245
Serum folate	7-39 nmol/l	12.2
Red cell folate	320-1370 nmol/l	450

Iron Deficiency Anaemia

Laboratory studies

- ✓Low Hb: men <130 g/l, and women <115 g/l
- ✓Transferrin saturation: <20%
- ✓Ferritin concentration:<30 ng/ml (with no signs of inflammation)

Red cell indices

Mean cell haemoglobin (hypochromasia)

most important red cell marker for detecting iron deficiency

Low mean cell volume (microcytosis)

Differential diagnosis - thalassaemia

Iron deficiency anaemia without microcytosis

- •Coexisting vitamin B12 or folate deficiency
- •Post-bleeding reticulocytosis
- •Oral iron treatment
- •Alcohol intake

Thalassaemia

Case Report

A 20 year old Italian man has a routine check-up. His spleen is just palpable at the end of inspiration

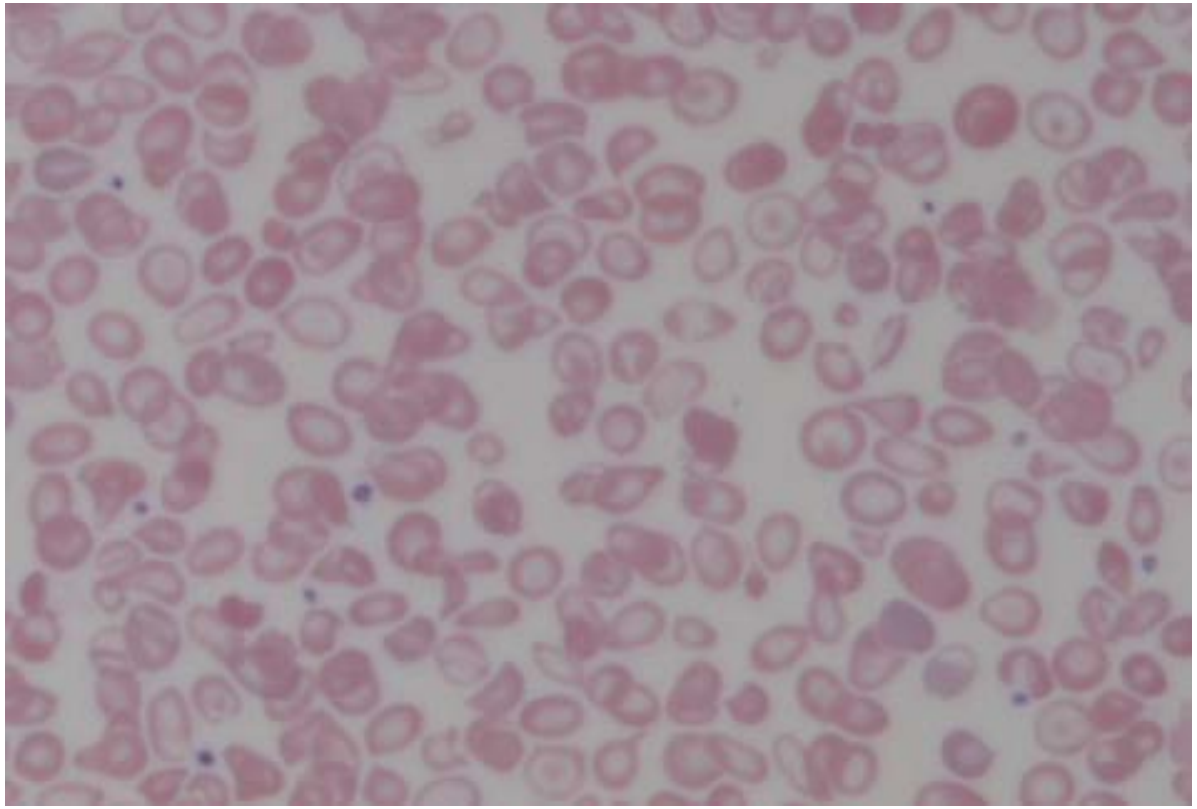
Blood Results

Hgb	130-180 g/L	125
RBC	4.50-6.50 x 1012/L	5.68
Hct	0.40-0.54	0.405
MCV	79-98 fl	70.0
MCH	27.0-34.0 pg	23.6
MCHC	32.0-36.0 g/dl	30.0
WBC	4.0- 11.0 x 109/L	10.5
Neut	2.0- 7.5 x 109/L	7.9
Lymph	1.5- 4.0 x 109/L	2.1
Mono	0.2- 0.8 x 109/L	0.5
Eos	0.04- 0.40 x 109/L	…
Baso	0-0.1 x 109/L	…
Plt	150-450 x 109/L	200
ESR	3-10 mm/hr	2

Thalassaemia

Blood Film

Red cells show moderate anisocytosis and hypochromia. There are numerous target cells.



Thalassaemia

Investigations

Other lab investigations:

Serum iron	11-31 μmol/l	20
Serum transferrin	1.7- 2.9 g/l	2.5
Saturation	20-50%	33
Serum ferritin	14-186 μg/l	150

Thalassaemia screen:

Haemoglobin electrophoresis : no abnormal band detected

HbA2	1.5-3.5%	4.5 %
HbF	0-1.0%	0.5%

Pathogenesis - Thalassaemia Syndromes

- **α / β globin chain imbalance: decreased production of one chain**

- **β thalassemias are due to mutations in the HBB gene on chromosome 11**
  - Heterogeneity in point mutations (some severe, some mild means clinical heterogeneity)

- **α thalassemias involve the genes HBA1 and HBA2**
  - Two gene loci and therefore four alleles exist

αα / αα	4	Normal
-α / αα	3	Normal
-α / -α	2*	MCV, MCH
-- / αα	2*	MCV, MCH
-α / --	1	HbH disease
-- / --	0	Hb Barts hydrops fetalis

Haemolytic anaemia

Case Report

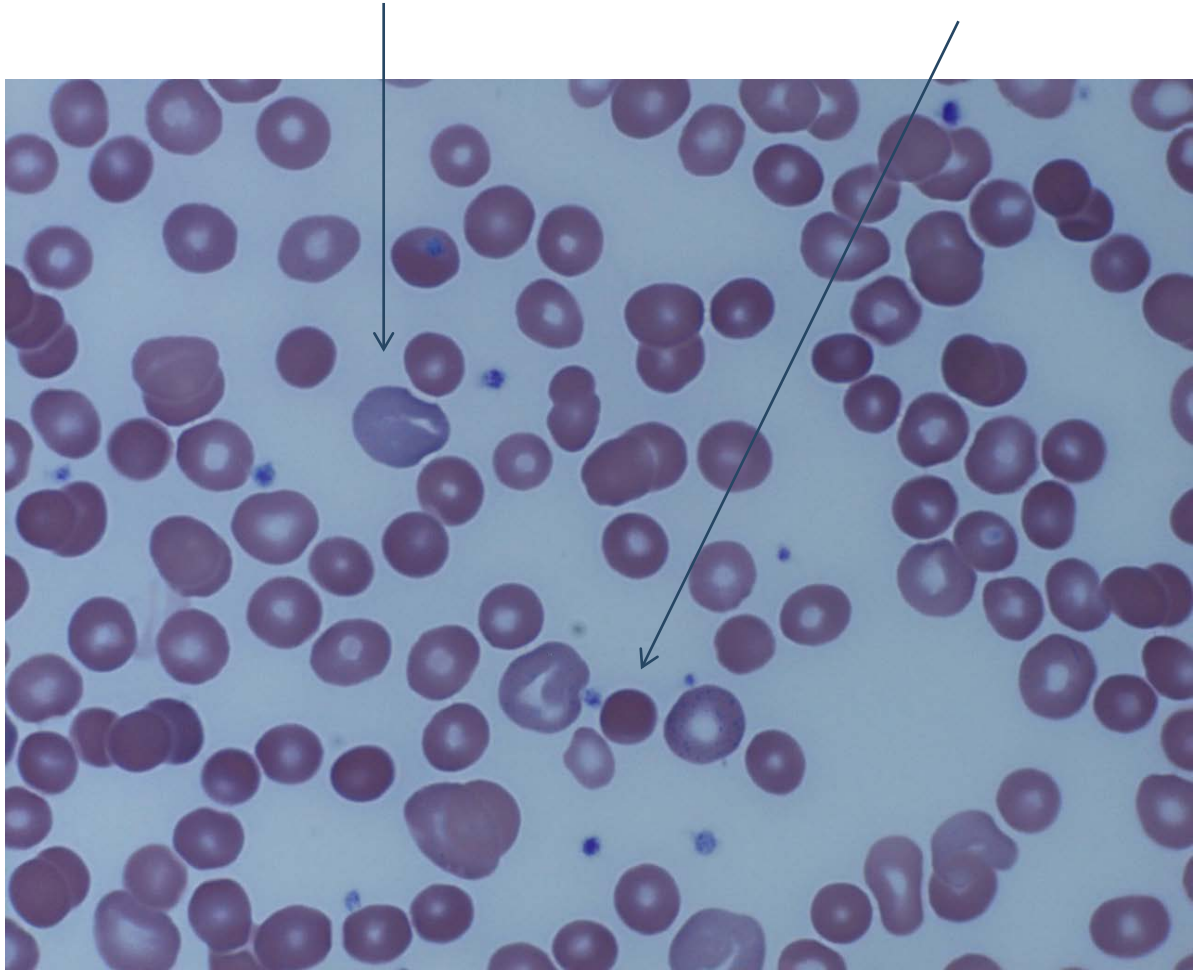
A previously well man of 60 develops profound lethargy, exertional dyspnoea and anorexia for 1 week

Blood Results

Hgb	**130-180 g/L**	**75**
RBC	**4.50-6.50 x 1012/L**	**2.35**
Hct	**0.40- 0.54**	**0.22**
MCV	**79-98 fl**	**92.0**
MCH	**27.0-34.0 pg**	**32.0**
MCHC	**32.0-36.0 g/dl**	**34.5**
WBC	**4.0-11.0 x 109/L**	**13.5**
Neut	**2.0-7.5 x 109/L**	**10.5**
Lymph	**1.5- 4.0 x 109/L**	**2.4**
Mono	**0.2- 0.8 x 109/L**	**0.6**
Eos	**0.04- 0.40 x 109/L**	**…**
Baso	**0-0.1 x 109/L**	**…**
NRC	**x 109/L**	**0.4**
Plt	**150-450 x 109/L**	**200**
ESR	**3-10 mm/hr**	**..**
Retics	**25-150 x 109/L**	**235**

Haemolytic anaemia

Marked anisocytosis and polychromasia. Numerous spherocytes seen.



Haemolytic anaemia

Other investigations

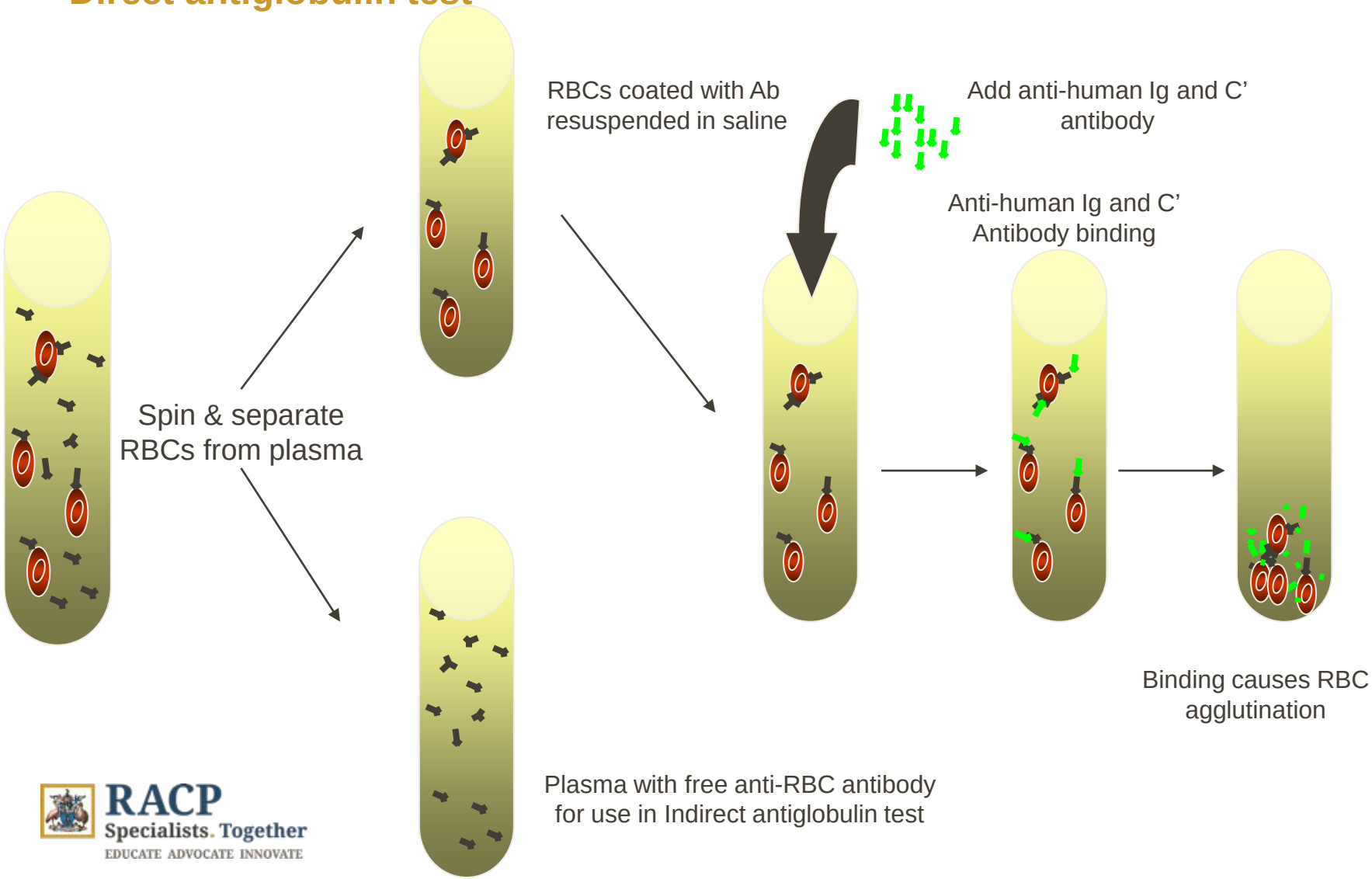
Serum bilirubin	0-20 μmol/l	32
Serum LDH	85-212 U/l	405
Serum haptoglobins		Reduced
Schumm's test		Negative

Direct antiglobulin test:

IgG	+++
C3b	+

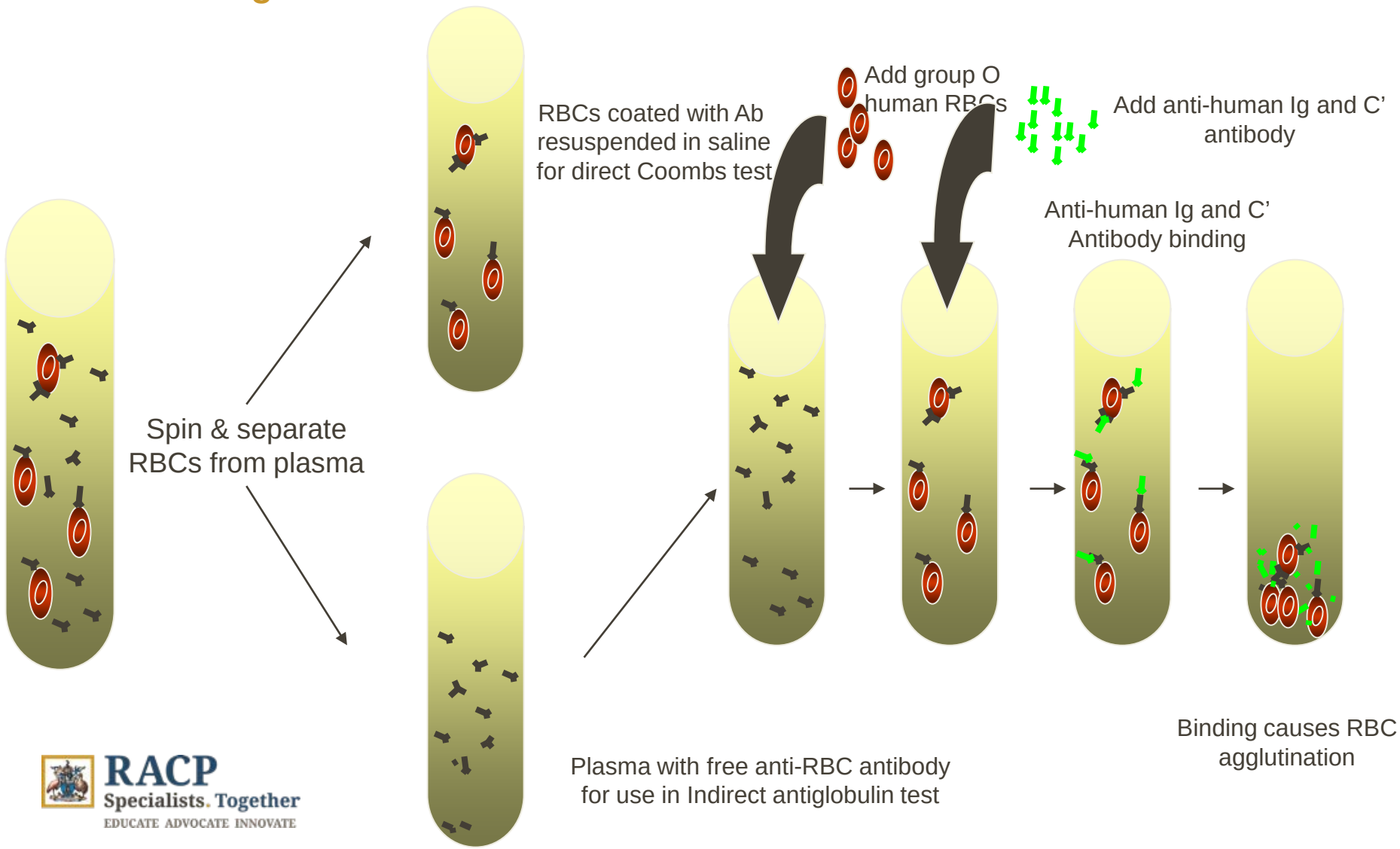
Haemolytic anaemia

Direct antiglobulin test

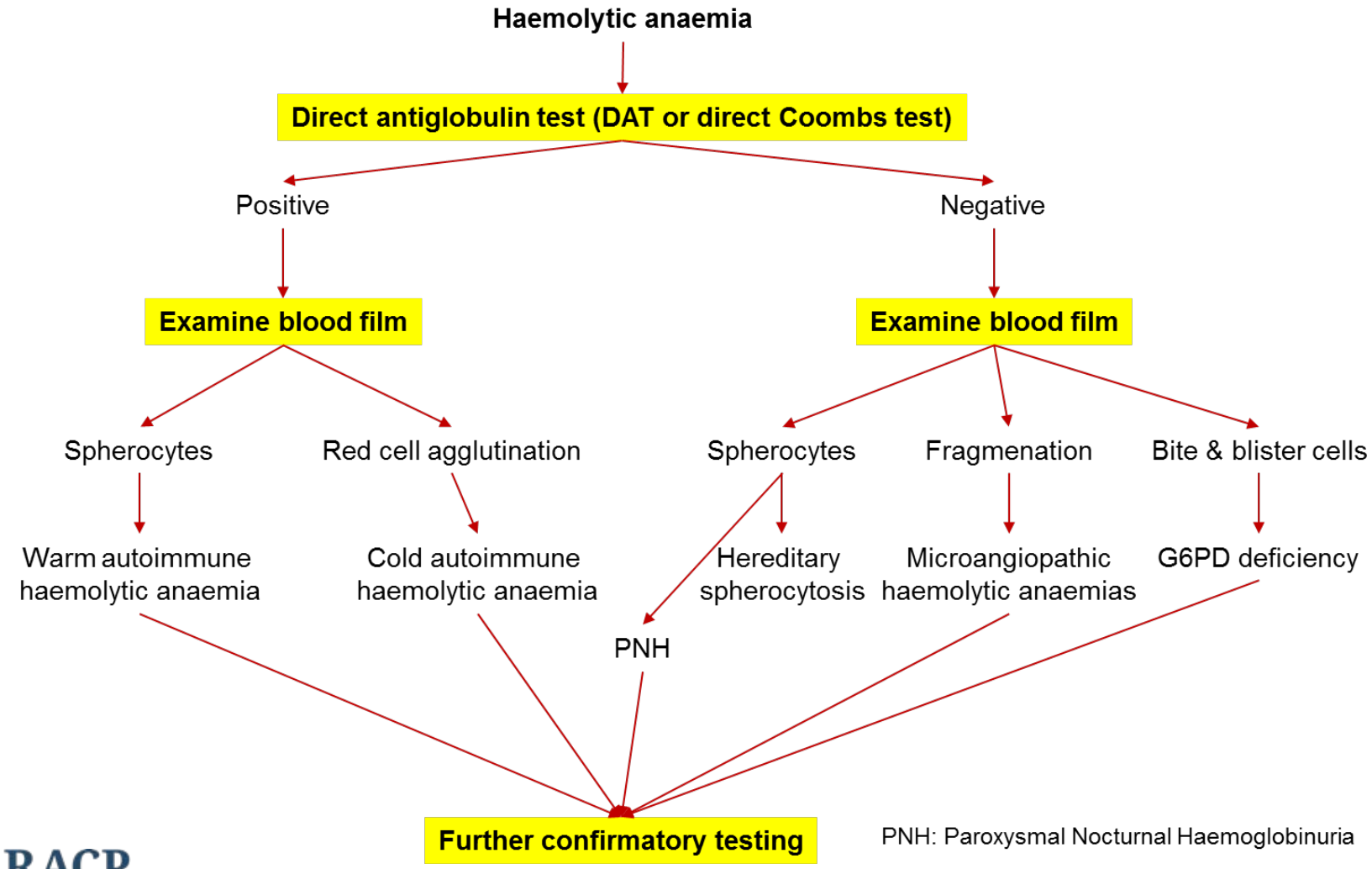


Haemolytic anaemia

Indirect antiglobulin test



Haemolytic anaemia



PNH: Paroxysmal Nocturnal Haemoglobinuria

Haemolysis Pearls

Atypical HUS

- Occurs as a familial form with mutations of complement regulatory proteins (factor H, factor I, MCP [membrane cofactor protein] and factor B), with consequent unrestricted complement activation and endothelial toxicity.
- In addition, some have mutations in molecules not directly linked to the complement system: diacylglycerol kinase, plasminogen, factor XII, and thrombomodulin.

Eculizumab

- Monoclonal antibody inhibits the production of terminal complement components and the membrane attack complex by binding to complement C5 is used to treat aHUS.
- Effective in treating acute hemolysis, thrombocytopenia, and stabilizing renal function.
- Severe aHUS can be maintained in remission using a long-term maintenance dose every 2 weeks.

Haemolysis Pearls

Hereditary spherocytosis

- Diagnosis is made by family history, blood film examination and;
- the eosin-5′-maleimide (EMA) binding test: a flow cytometric test.
- EMA binds to plasma membrane proteins, mainly to band 3 protein. In hereditary spherocytosis, the mean fluorescence of EMA-stained RBCs is lower when compared with control RBCs.

Vitamin B12 Deficiency

Case Report

A woman of 75 has been increasingly tired, short of breath on exertion, and off her food for 6 months

She has lost 7 kg in weight

Other than pallor and perhaps slight jaundice, there are no abnormal physical findings

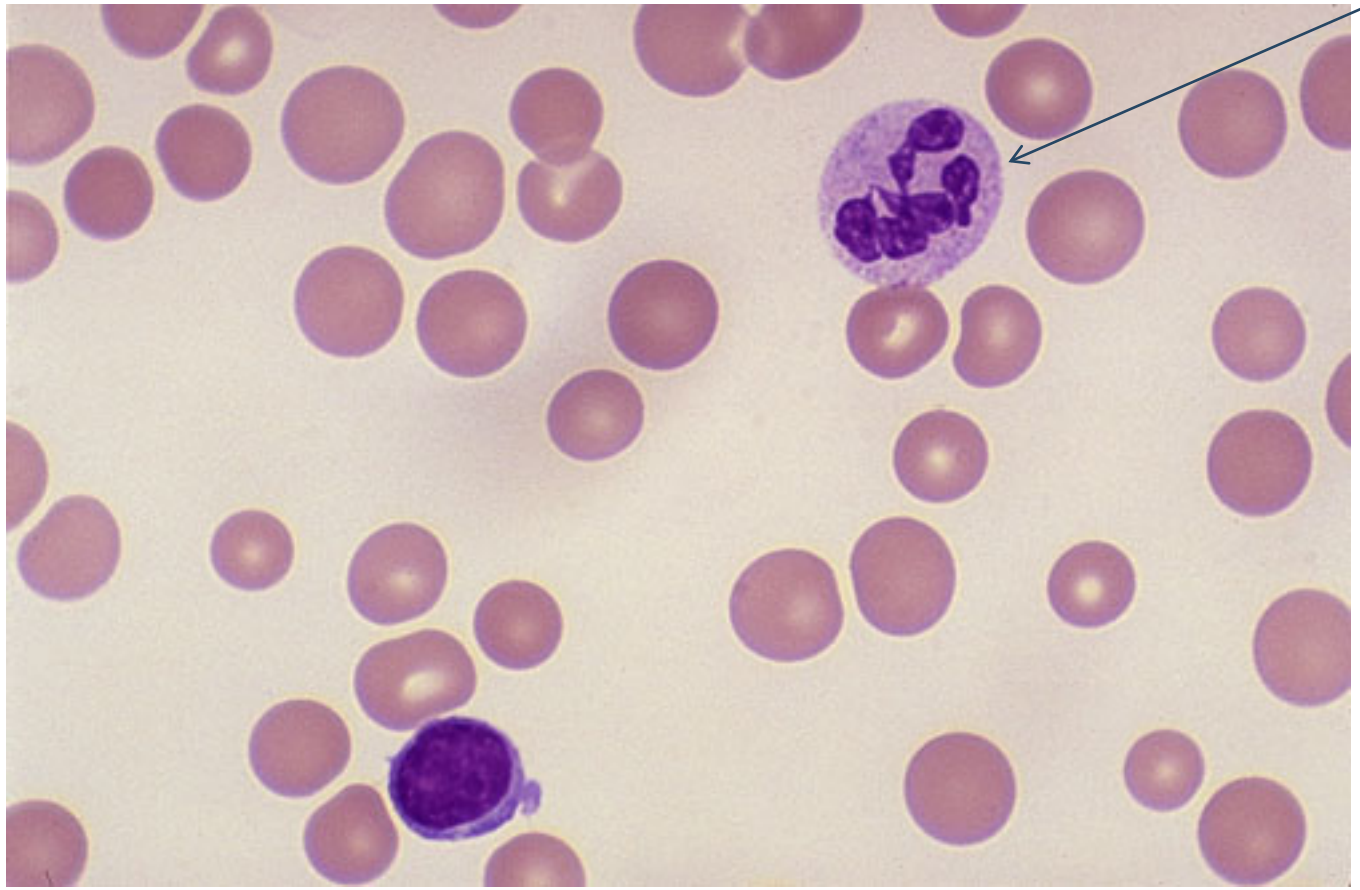
Blood Results

Hgb	115-166 g/dl	75
RBC	3.80-5.80 x 1012/L	1.98
Hct	0.37-0.47	0.23
MCV	79-98 fl	125.0
MCH	27.0-34.0 pg	37.9
MCHC	32.0-36.0 g/dl	33.0
WBC	4.0- 11.0 x 109/L	4.5
Neut	2.0- 7.5 x 109/L	2.5
Lymph	1.5- 4.0 x 109/L	1.6
Mono	0.2- 0.8 x 109/L	0.4
Eos	0.04- 0.40 x 109/L	…
Baso	0-0.1 x 109/L	…
Plt	150-450 x 109/L	200
ESR	4-15 mm/hr	12
Retics	25-150 x 109/L	20

Vitamin B12 Deficiency

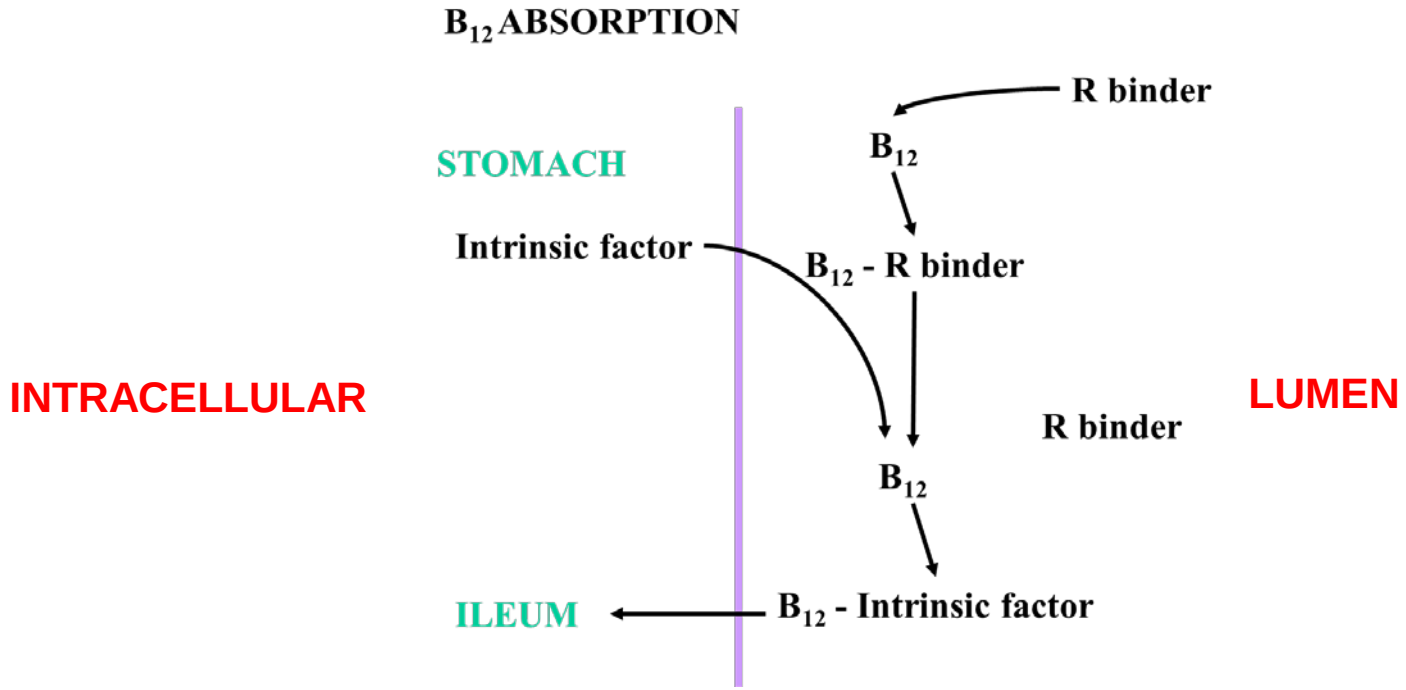
Blood film

There is marked anisocytosis and moderate macrocytosis. Neutrophils show hypersegmentation.



Vitamin B12 Deficiency

Pernicious anaemia



Presence of antibodies to parietal cells and intrinsic factor

- dUMP not converted to dTMP
- Cells try to replace uridine for thymidine but fail
- DNA fragmentation and death

Chronic lymphocytic leukaemia

Case Report

A previously well man aged 65 is admitted with an acute lower respiratory infection.

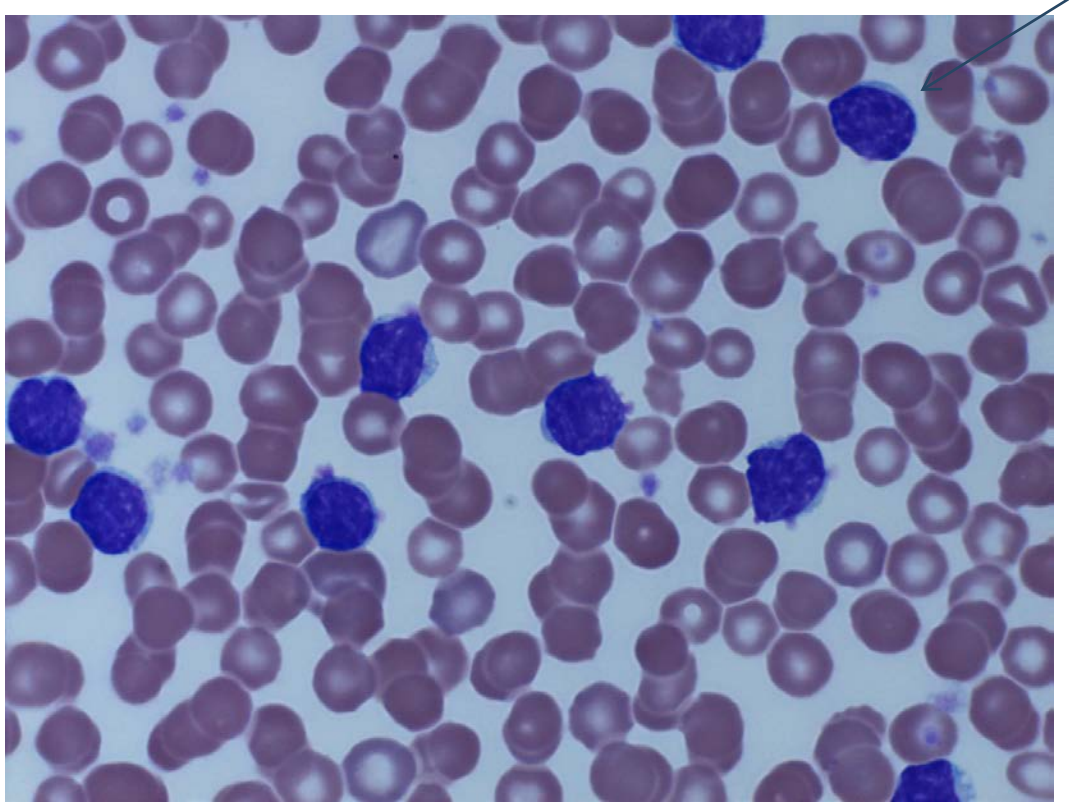
Blood Results

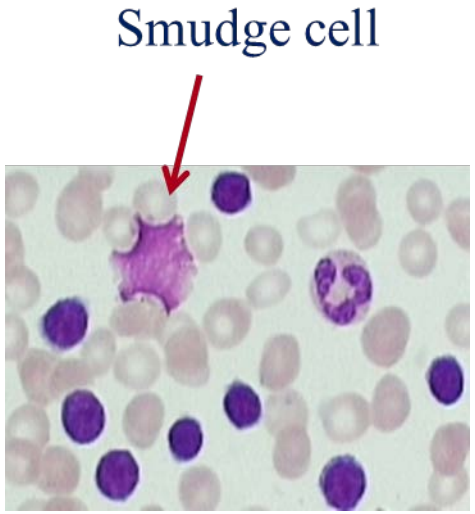
Hgb	130-180 g/L	102
RBC	4.50 -6.50 x 109/L	3.39
Hct	0.40-0.54	0.322
MCV	79-98 fl	95.0
MCH	27.0-34.0 pg	30.1
MCHC	32.0-0.36 g/dl	33.5
WBC	4.0-11.0 x 109/L	51.0
Neut	2.0- 7.5 x 109/L	4.2
Lymph	1.5- 4.0 x 109/L	46.4
Mono	0.2- 0.8 x 109/L	0.4
Eos	0.04- 0.40 x 109/L	…
Baso	0-0.1 x 109/L	…
Plt	150 - 450 x 109/L	200
ESR	3-10 mm/hr	58
Retics	25-158 x 109/L	46

Chronic lymphocytic leukaemia

Blood film

Red cells show slight anisocytosis. There is a marked lymphocytosis, and numerous smudge cells are seen





Chronic lymphocytic leukaemia

- Over 50% of patients present with an asymptomatic peripheral blood lymphocytosis detected on a full blood count performed as part of a “routine check-up”
- With more advanced disease, patients may present with lymphadenopathy or symptoms of bone marrow infiltration and failure
- Treatment may be started only after the development of anaemia or thrombocytopenia, and for disease-related symptoms such as fatigue, night sweats, weight loss and fever

Chronic lymphocytic leukaemia Pearls

Relapsed/refractory patients

- Ibrutinib, a Bruton's tyrosine kinase inhibitor is used. Has activity in p53-deleted CLL cases and may in future be used as first-line therapy.
- Venetoclax a BCL-2 inhibitor is used in combination with rituximab, and in heavily pre-treated patients and those with p53 deletion, > 75% of patients respond, including > 20% complete responders.

In patients <65

- Fludarabine, cyclophosphamide and rituximab ‘FCR’ considered as a first-line treatment
- Overall response rates > 90%, complete remission 50%, and 3-year survival > 80%.

Lymphoma Pearls

'Cell of origin' classification of diffuse large B cell lymphoma

- Immunohistochemistry classify DLBCL into germinal center B-cell (GCB)-like subtype and the activated B-cell (ABC)-like subtype.
- ABC disease subtype have significantly poorer outcomes compared to GCB disease
- Triple-hit lymphomas have genetic rearrangements of MYC, BCL2 and BCL6. Prognosis is generally poor, with a median overall survival of only 0.2–1.5 years

Relapsed/refractory Hodgkin lymphoma

- Options for relapsed/refractory disease following autologous stem cell transplantation include the anti-CD30 antibody, brentuximab vedotin, and the anti-PD1 antibody pembrolizumab.

Myeloma Pearls

Options for initial therapy in patients not fit for autologous transplantation

- Thalidomide, bortezomib, combined with cyclophosphamide and dexamethasone, carfilzomib combined with dexamethasone, and lenalidomide combined with dexamethasone

Relapsed myeloma

- Pomalidomide, and the anti-CD38 antibody, daratumumab.

Acute Myeloid Leukaemia

Case Report

A 16 year old boy is brought to the GP by his mother.

He has become listless, fatigued and complains of mouth ulceration

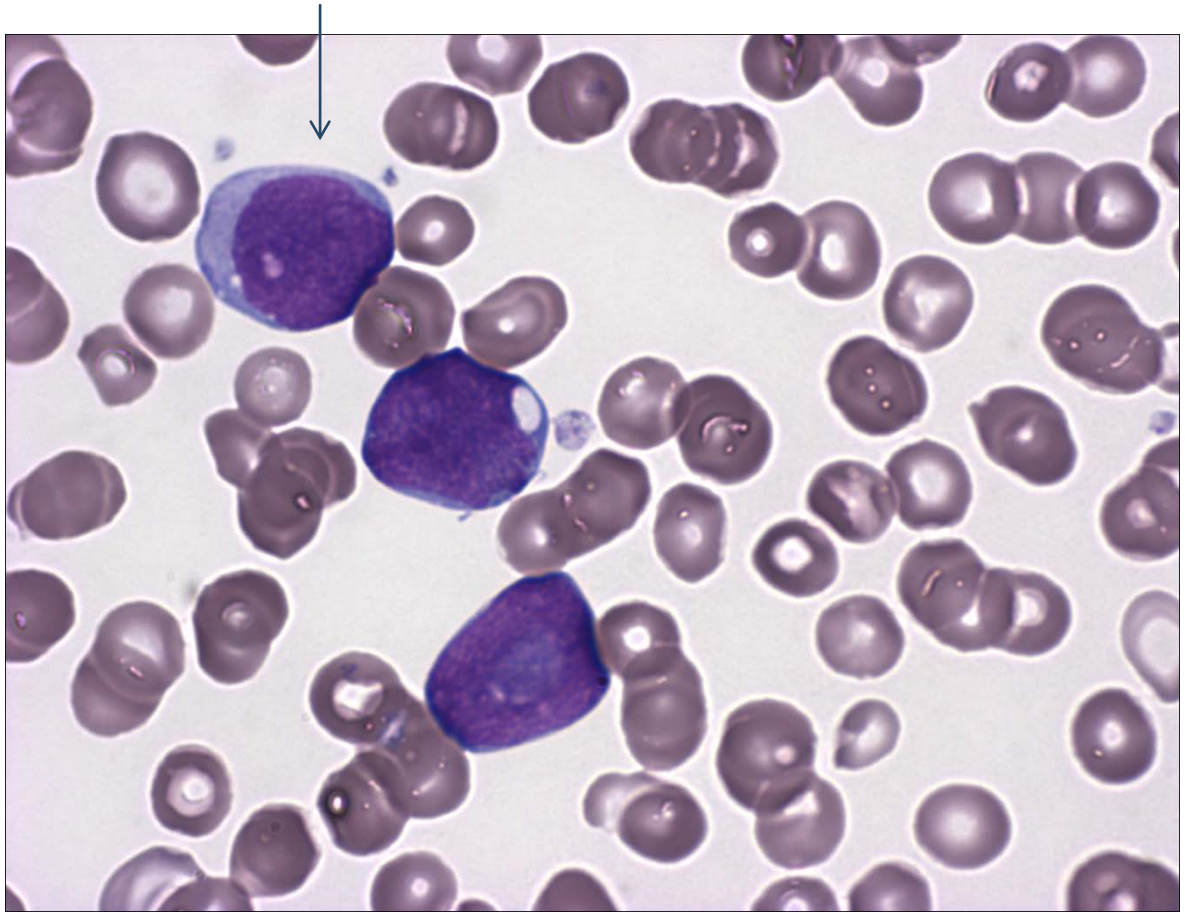
Recently he noticed that was unable to keep up with the team at football training

Blood Results

Hgb	130-180 g/L	109
RBC	4.5-6.5 x 1012/L	4.02
Hct	0.40-0.54	0.318
MCV	79-98 fl	79.3
MCH	27.0-34.0 pg	27.2
MCHC	32.0-36.0 g/dl	34.2
WBC	4.0-11.0 x 109/L	1.6
Neut	2.0-7.5 x 109/L	0.3
Lymph	1.5-4.0 x 109/L	0.6
Mono	0.2-0.8 x 109/L	0.2
Blast cells		0.4
Eos	0.04-0.40 x 109/L	…
Baso	0-0.1 x 109/L	…
NRC		Occ
Plt	150-450 x 109/L	14
ESR	3-10 mm/hr	48

Acute Myeloid Leukaemia

Pancytopenia with large blast cells with scanty cytoplasm.



Acute Myeloid Leukaemia

Prognosis

Risk Category	Cytogenetics	5 year survival %	Relapse Rate %
Good	t(8;21), t(15;17), inv(16)	70	33
Intermediate	Normal	48	50
Poor	-5, -7, del(5q), abnormal 3q, complex	15	78

Acute Lymphoblastic Leukaemia

Case Report

A 39 year old man presents with swelling in the neck for around 1 week.

He has lost around 3 kg in weight in the last 6 months (normal weight 74 kg).

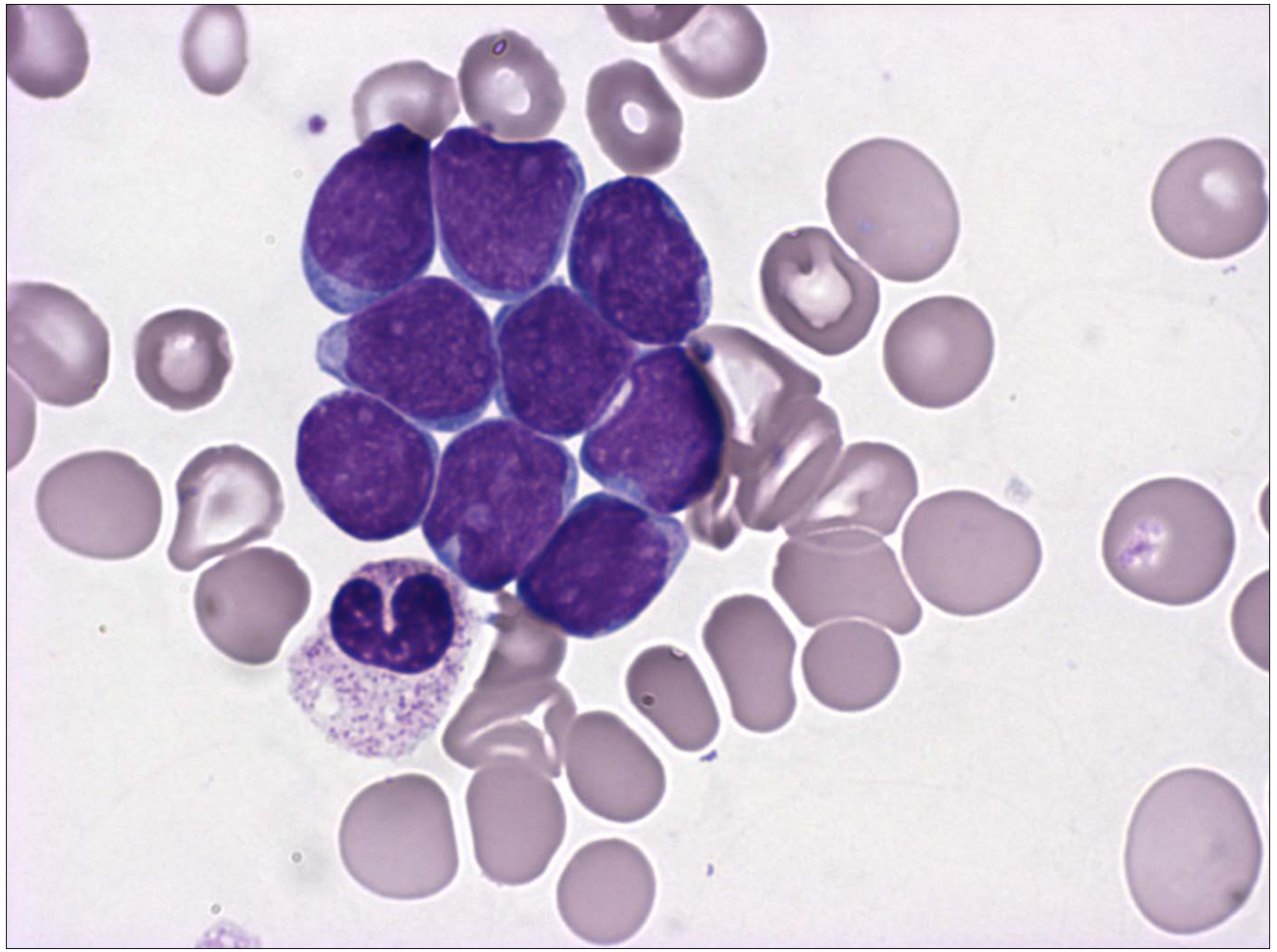
A CXR shows a large mediastinal mass

Blood Results

Hgb	130-180 g/L	114
RBC	4.5-6.5 x 1012/L	3.92
Hct	0.40-0.54	0.36
MCV	79-98 fl	81
MCH	27.0-34.0 pg	30.6
MCHC	32.0-36.0 g/dl	35.7
WBC	4.0-11.0 x 109/L	26.7
Neut	2.0-7.5 x 109/L	3.4
Lymph	1.5-4.0 x 109/L	1.6
Mono	0.2-0.8 x 109/L	0.6
Eos	0.04-0.40 x 109/L	0.5
Baso	0-0.1 x 109/L	0.1
Blast cells		+++
Plt	150-450 x 109/L	35

Acute Lymphoblastic Leukaemia

Blood film



Acute Leukaemia Pearls

AML - FMS tyrosine kinase 3 (FLT3) mutation positive cases

Midostaurin: multi-targeted protein kinase inhibitor, used for FLT3 internal tandem duplication (ITD) or tyrosine kinase domain (TKD) cases. Given orally following induction and consolidation chemotherapy.

ALL - minimal residual disease

Detection by sensitive techniques (PCR, FISH, immunophenotype) is associated with poorer outcomes

identifies patients who need treatment intensification, allogeneic transplantation or use of novel agents

ALL - novel agents

CAR T-cell therapy for relapsed/refractory ALL and diffuse large cell lymphoma, and bi-specific T-cell engager therapy (blinatumomab) directed against CD19

Philadelphia-positive ALL: poor prognostic group. Incorporation of tyrosine kinase inhibitors (imatinib and ponatinib if expressing the T315I mutation) has improved prognosis.

Chronic Myeloid Leukaemia

Case Report

A 49 year old man presents with a 4 week history of fatigue.

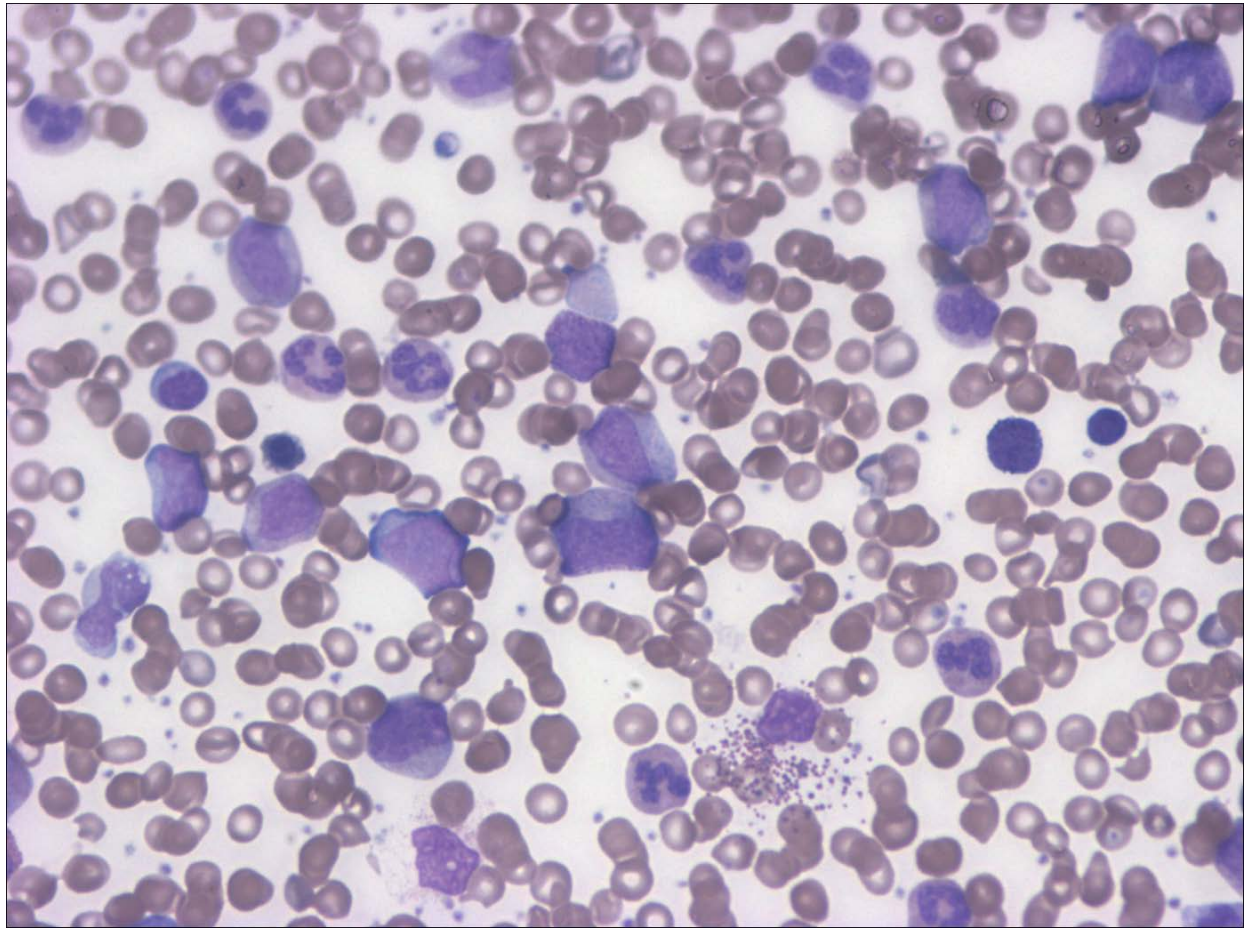
Examination reveals splenomegaly measuring 4 cm below the left costal margin

Blood Results

Hgb	130-180 g/L	114
RBC	4.5-6.5 x 1012/L	3.92
Hct	0.40-0.54	0.36
MCV	79-98 fl	84
MCH	27.0-34.0 pg	30.6
MCHC	32.0-36.0 g/dl	35.7
WBC	4.0-11.0 x 109/L	268.7
Neut	2.0-7.5 x 109/L	32.1
Lymph	1.5-4.0 x 109/L	3.6
Mono	0.2-0.8 x 109/L	1.6
Eos	0.04-0.40 x 109/L	0.5
Baso	0-0.1 x 109/L	0.1
Metamyelocytes		73.7
Myelocytes		83.1
Promyelocytes		40.8
Blast cells		4.1
Plt	150-450 x 109/L	201

Chronic Myeloid Leukaemia

Accumulation of immature and mature myeloid cells in blood



Chronic Myeloid Leukaemia

- **Findings on full blood count, blood film and special tests**
  - neutrophil leucocytosis
  - immature cells mainly myelocytes circulating in the peripheral blood
  - increase in circulating basophils
  - anaemia
- **Findings on bone marrow biopsy**
  - hypercellular
  - increase in myeloid series (blood and bone marrow appear similar)
  - cytogenetic analysis and molecular analysis to detect t(9;22)

    & BCR-ABL

Myeloproliferative Neoplasms Pearls

Essential Thrombocythemia

- Mutations in the thrombopoietin receptor gene MPL - 4–8% of patients with ET, 15–30% have a CALR mutation, 10–20% of the patients are triple-negative.

Management of ET

High-risk patients

- >60 years of age with JAK2 or MPL mutation, or a history of venous or arterial thrombosis
- Treated with hydroxyurea and aspirin
- Venous thrombosis treated with hydroxyurea and systemic anticoagulation, and if JAK2 or MPL positive, aspirin added.
- Platelet count >1000 x 10^9/L are at risk of bleeding and should be treated with hydroxyurea

Myeloproliferative Pearls

Myelofibrosis

Ruxolitinib: JAK inhibitor with selectivity for subtypes JAK1 and JAK2, improves hypermetabolic symptoms and splenomegaly.

Activity is independent of JAK2 mutational status.

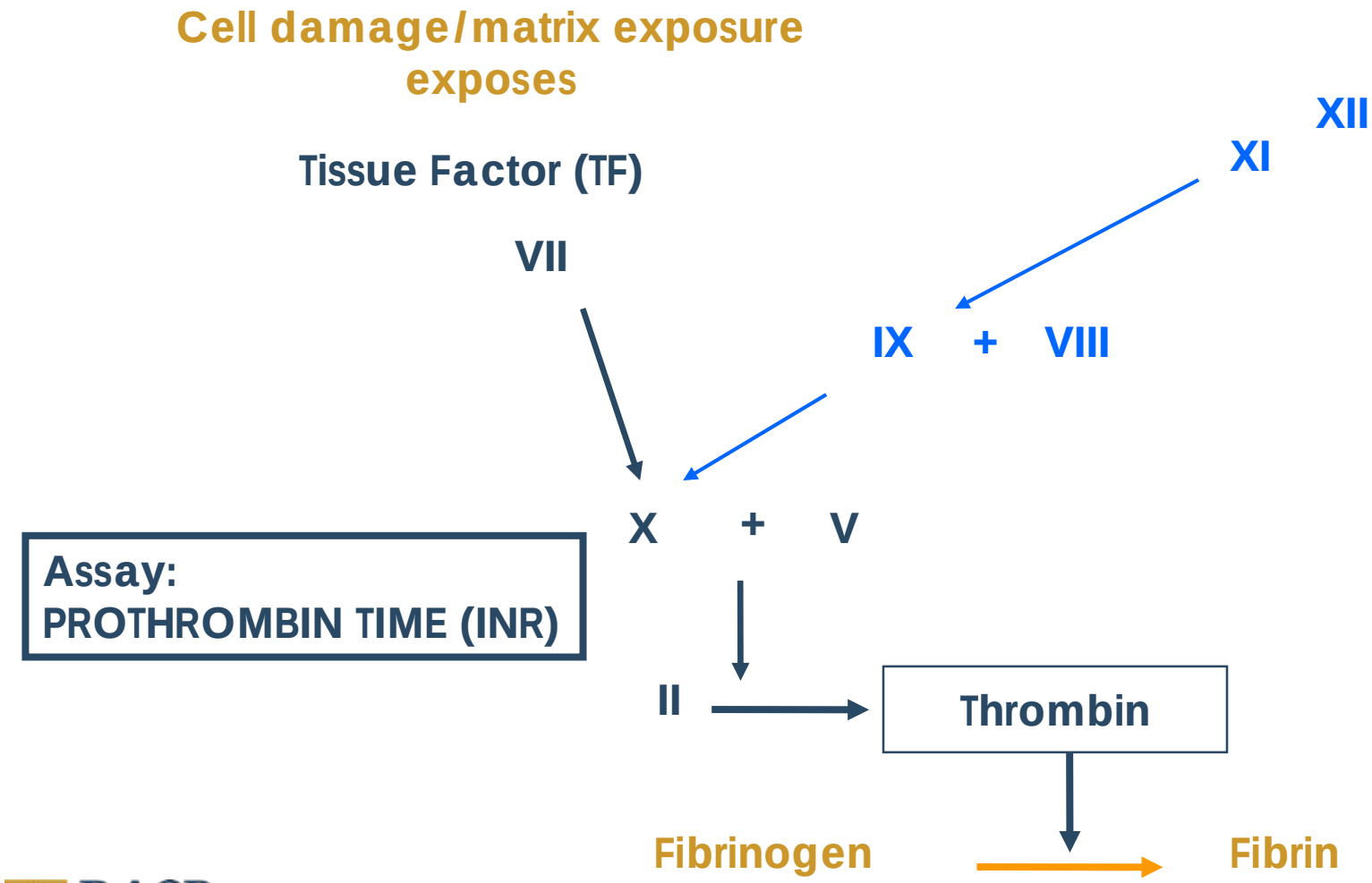
Does not prevent transformation to acute myeloid leukemia

CML with T315I mutation

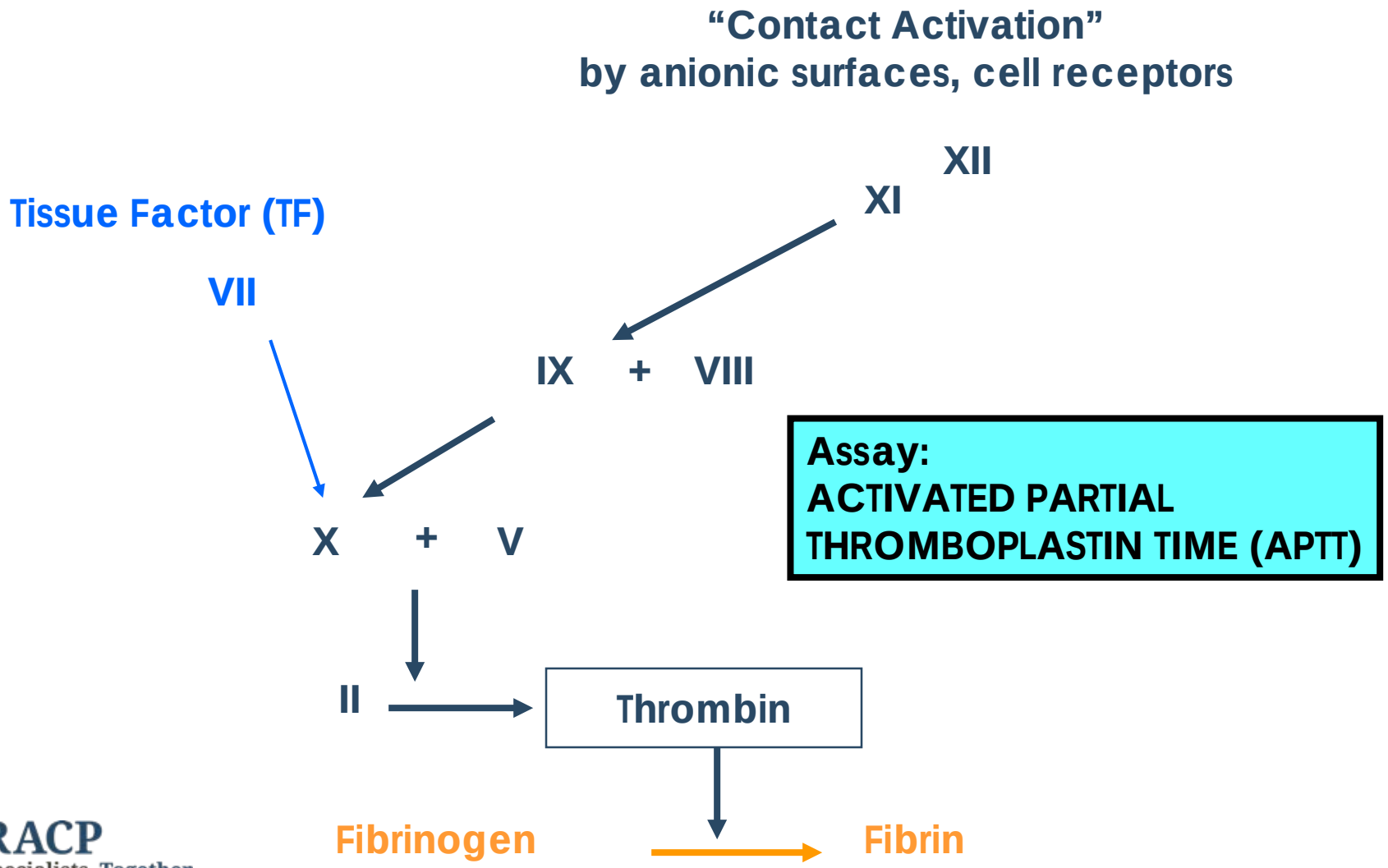
1st-and 2nd-generation TKIs are not effective against this mutation.

A 3rd-generation inhibitor, ponatinib, is approved for use in the T315I mutation.

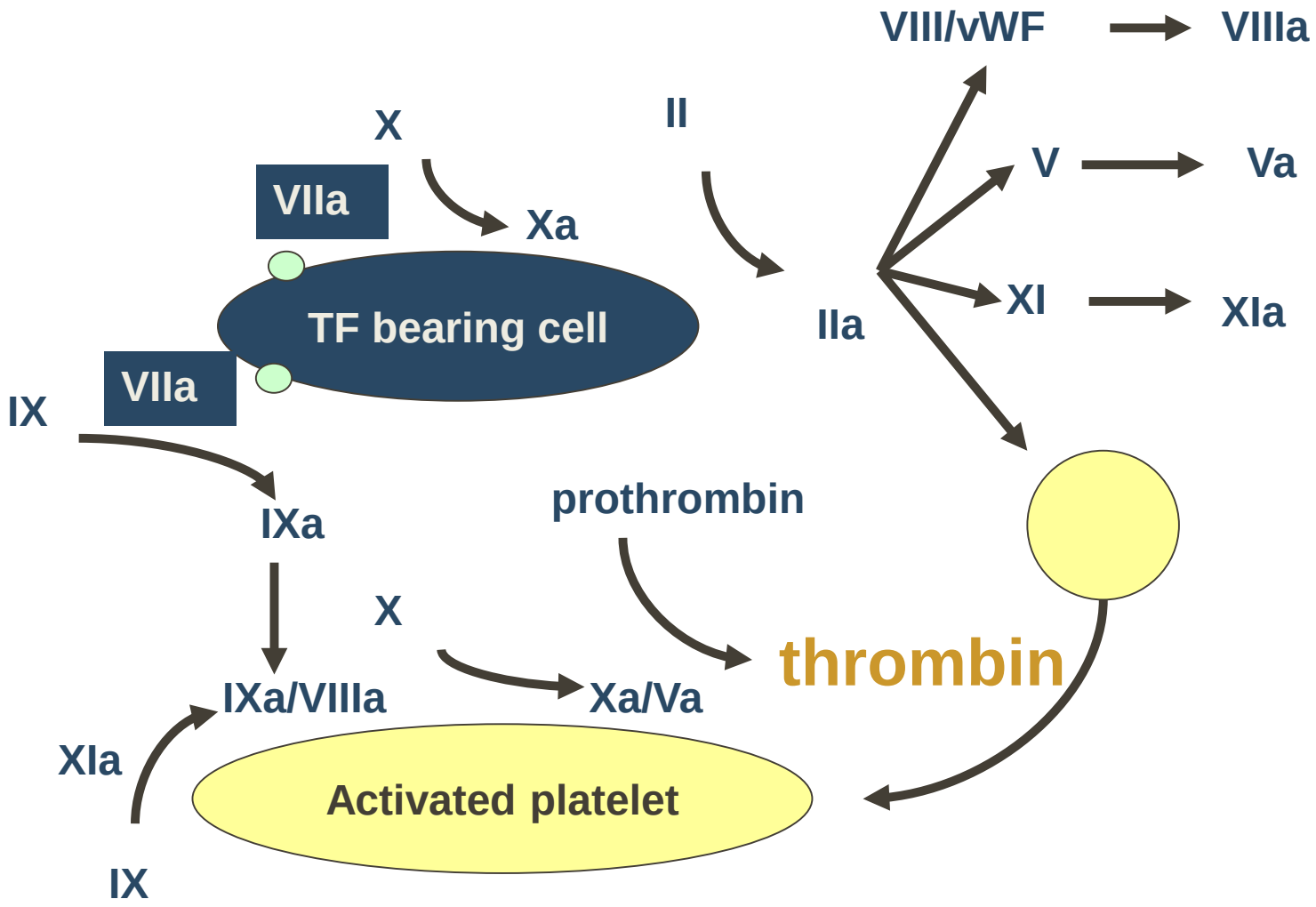
Coagulation cascade – “Extrinsic Pathway”



“Intrinsic Pathway”



Cell based coagulation model



Immune thrombocytopenic purpura (ITP)

Case Report

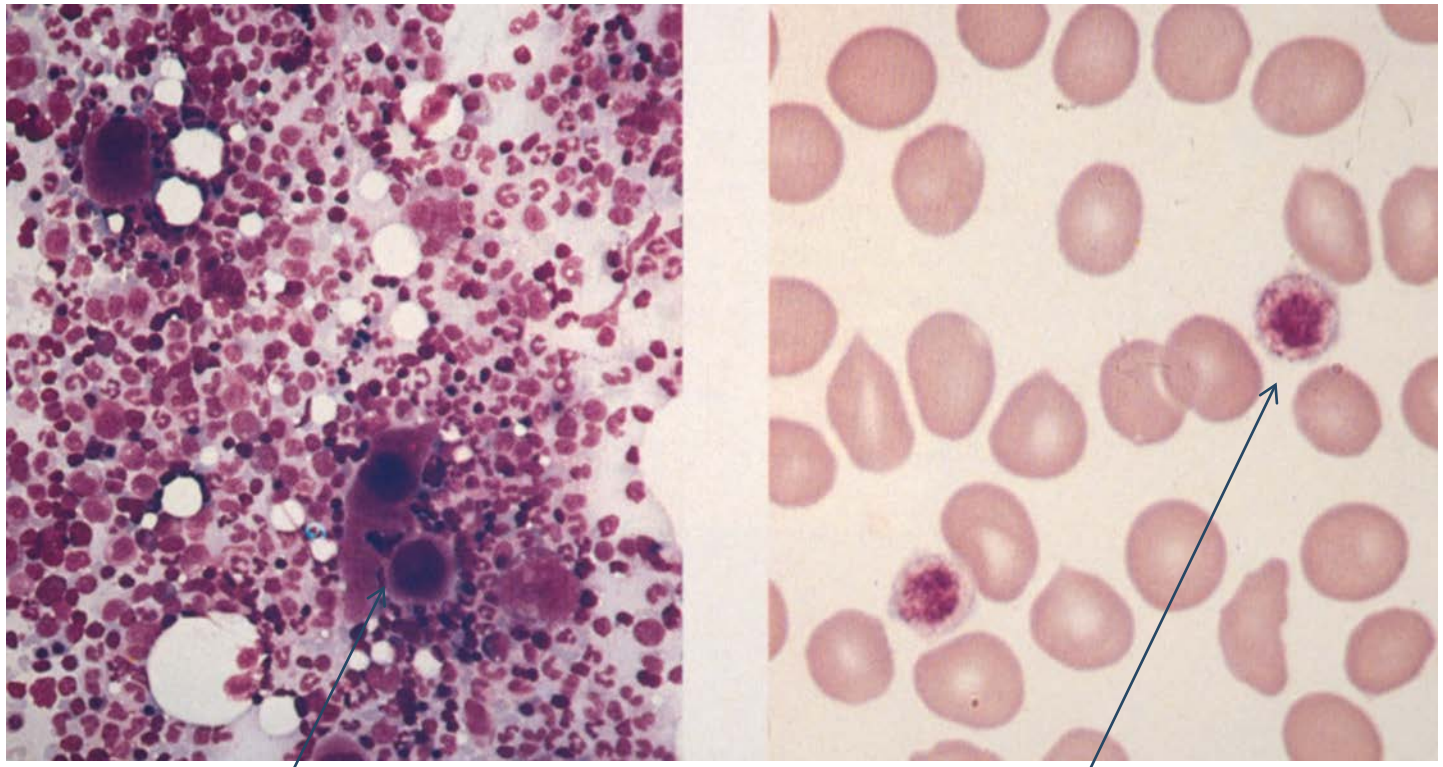
A 17 year old female presents with a history of a sudden onset rash on the lower limbs and epistaxis.

On examination she has a red spotty rash on both shins

Blood Results

Hb	104 g/L
WCC	6.3 x 109/L
Platelet count	2 x 109/L
MCV	80 fl
Blood film	normal
PT	15 seconds (<15s)
APTT	37 seconds (<38s)
Biochemistry	normal
Liver function tests	normal

Blood film and bone marrow



Increased megakaryocytes

Large platelets

Immune thrombocytopenic purpura

Autoimmune idiopathic thrombocytopenia

- **Blood film**
  - Large platelets
  - thrombocytopenia
  - Blood film

- **Associated with**
  - Systemic lupus erythematosis
  - HIV
  - Chronic lymphocytic leukaemia
  - Hodgkin lymphoma
  - Autoimmune haemolytic anaemia

Artefact

Case Report

A previously well 65 year old man was referred because of an abnormality on coagulation tests performed prior to major surgery

Blood Results

- APTT was 56 seconds (<38 secs),
- PT was 27 secs (<15 secs)
- platelet count was 198 x 109/L.

Repeat coagulation tests are requested

Pre-analytical variables

Anticoagulant contamination -blood collection from a venous/arterial line

Haemolyzed samples interfering with photo-optical clot detection methods

Prolonged time lapse between specimen collection and performance of aPTT (>4 hours) and PT (>24 hours) assays

Under-filled collection tubes may produce erroneously prolonged PT and aPTT

Haemophilia

An 18 year old man presents to the Emergency Dept. with a large swelling over the lower back which developed shortly after a game of football

His mother's brother was reported to have had "easy bruising and bleeding"

Blood Results

FBC

Hb	147 g/L
WCC	10.3 x 109/L
Platelet count	299 x 109/L
Blood film	normal

Coagulation studies

PT	14 seconds (<15s)
APTT	42 seconds (<38s)

Haemophilia

Mixing studies:

APTT corrects to normal with a 50:50 mix with normal plasma

Factor assays

FVIIIC	**16%**	**(50-200%)**
FIX	**146%**	**(50-200%)**
FXII	**102%**	**(50-200%)**
FXI	**85%**	**(50-200%)**

Haemophilia

Haemophilia A (FVIII) and B (FIX) are X-linked recessive disorders

Haemophilia is typically expressed in males and carried by females

Degrees of Severity of Haemophilia

- Normal factor VIII or IX level = 50-150%
- Mild hemophilia
  - factor VIII or IX level = 6-50%
- Moderate hemophilia
  - factor VIII or IX level = 1-5%
- Severe hemophilia
  - factor VIII or IX level = <1%

Von Willebrands Disease

35 year old woman presents with excess bleeding following a tooth extraction

She says her father bled significantly following two teeth extractions and required a transfusion because of excessive bleeding after a cholecystectomy

Her aunt also bled significantly following the birth of her only child and was transfused as a result

Blood Results

PT	12 seconds	(<15 secs)
APTT	47 seconds	(<35 secs)
Platelet	188 x 109/L	

Von Willebrands Disease

Factor assays

Factor VIIIC level	11%	(50-200%)
vWF antigen	10%	(40-200%)
Ristocetin cofactor	8%	(45-200%)
Collagen binding	5%	(50-400%)

A prolonged bleeding time and APTT in screening tests is suggestive, however these are normal in many patients with VWD and specific assays must be performed

Many with levels down to 30% of normal do not have any significant bleeding tendency - caution in diagnosing VWD on the basis of moderately low VWF levels alone (blood O group subjects have lower VWF values)

Liver disease

Case Report

A 57 year old male presents with abdominal distension, melaena, bruising on the limbs and ankle oedema

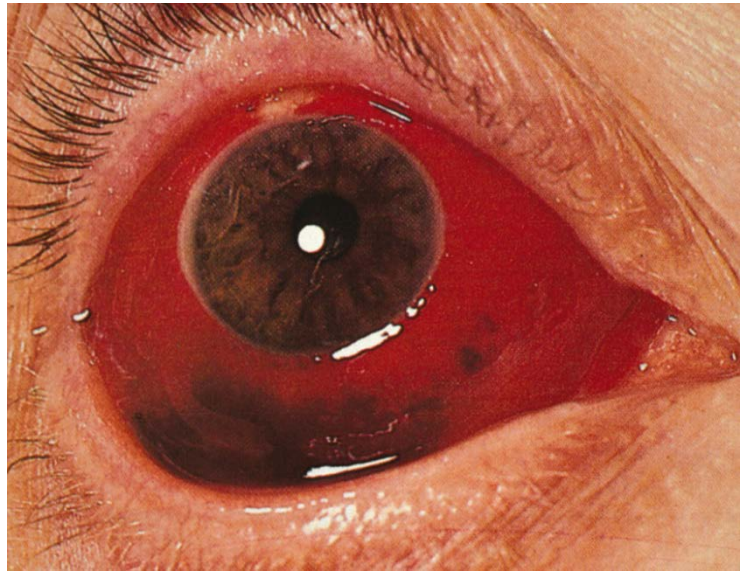
There is a history of chronic alcohol abuse

His spleen can be felt in the left upper quadrant of his abdomen

Blood Results

Hb	104 g/l	
WCC	3.5 x 109/L	
Platelets	63 x 109/L	
PT	43 seconds	(<15 secs)
APTT	41 seconds	(<38 secs)

Bleeding in Liver Disease



Impaired synthesis clotting factors

- II, VII, IX, X, Fibrinogen

Thrombocytopenia

Marrow suppression

Hypersplenism

Increased fibrinolysis

- Decreased clearance of plasminogen activators
- Decreased synthesis anti-plasmin

Platelet dysfunction

Dysfibrinogenaemia

Direct Oral Anticoagulants

Direct FXa inhibition

- Rivaroxaban and apixaban: Andexanet for reversal currently not available

Direct thrombin inhibition

- Dabigatran: Idarucizumab for reversal

	Dabigatran	Rivaroxaban	Apixaban
Significant anticoagulant effect unlikely	APTT & TT normal	PT normal (using a sensitive thromboplastin	PT normal (using a sensitive thromboplastin)
Anticoagulant effect present (Screening tests)	TT prolonged or no clot obtained; APTT prolonged	PT prolonged	PT prolonged – apixaban likely present in excess
Drug effect likely (confirmatory tests	Dilute thrombin clotting time assay (HEMOCLOT) prolonged	Modified anti-Xa positive (rivaroxaban level	Use modified anti-Xa apixaban assay when available

Coagulation Pearls

Testing for thrombophilia

- Should not be performed in most patients.
- Only if a positive family history, thrombosis at unusual sites, recurrent idiopathic thromboses, patients < 45 years with unprovoked thrombosis, and patients with warfarin-induced skin necrosis (PC deficiency)

VTE

A negative D-dimer assay

- >90% negative predictive value in patients with a low clinical pre-test probability using validated prediction rules such as the Wells criteria for DVT

DOACs and warfarin

- Equally effective for treatment
- DOACs have not been validated for use in patients with cancer-associated thrombosis, prothrombotic disorders and prosthetic valves, and are contraindicated in pregnancy and severe renal or hepatic failure
- Patients with active cancer are better treated with LMWH.

Coagulation Pearls

First unprovoked or non-surgically provoked VT

- Extended low intensity anticoagulation (rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily) beyond 3-6 months should be considered

Cerebral vein thrombosis

- No/small haemorrhagic infarction, LMWH followed by oral anticoagulation therapy of the same duration as for lower limb DVT (3 months if provoked, 6 months if unprovoked and consideration of extended low-intensity anticoagulation, or lifelong in the presence of recurrence or markers of severe thrombophilia).
- Large haemorrhagic infarction, anticoagulation is delayed until a stabilization or reduction of haemorrhage is documented.

vWD

- DDAVP ineffective in type 3 vWD and should not be given in type 2B because it induces platelet aggregation
- Recombinant FVIII (rFVIII) concentrates are the treatment of choice for haemophilia A. Donor-derived products should only be used for urgent treatment in cases where recombinant products are not available.

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