Pediatrics TeamWork

437

Common Hematological Diseases

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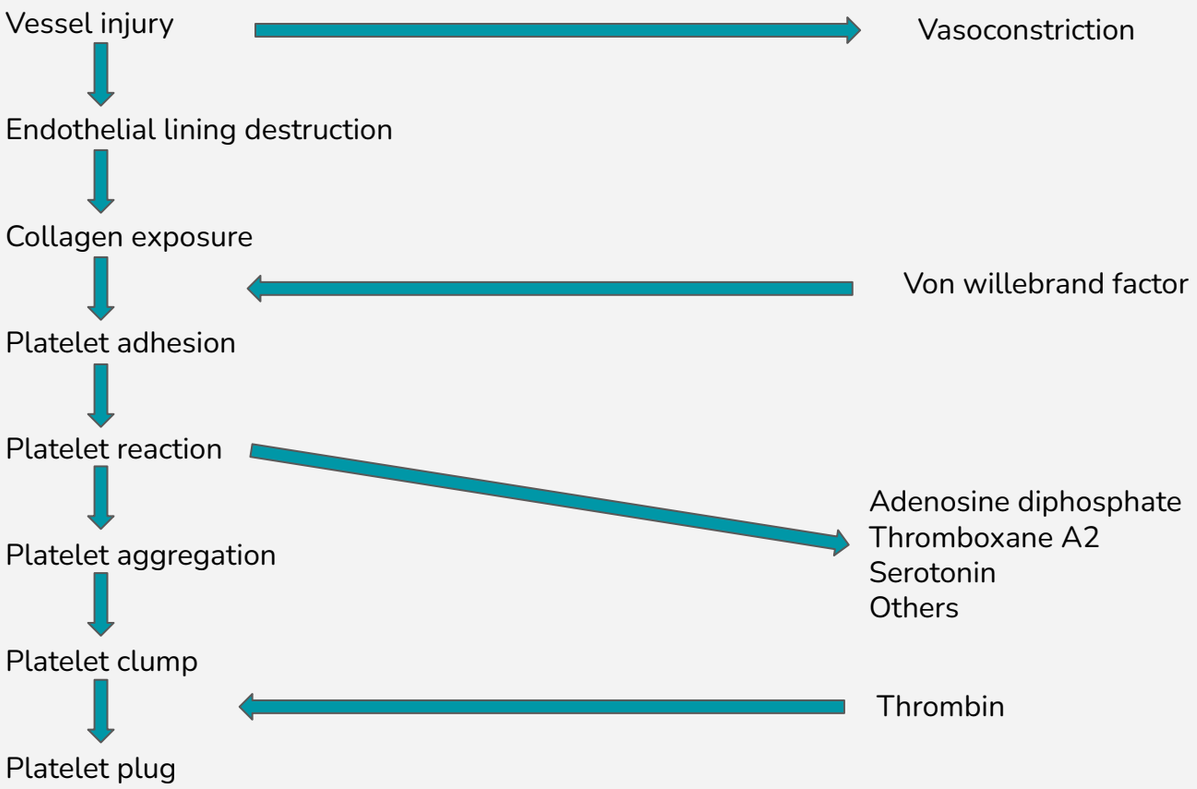
We added some important details about anemia! Please make sure to go through it but it is a summary and you have to refer to your textbook

Notes Previous Notes Book Important!

Bleeding



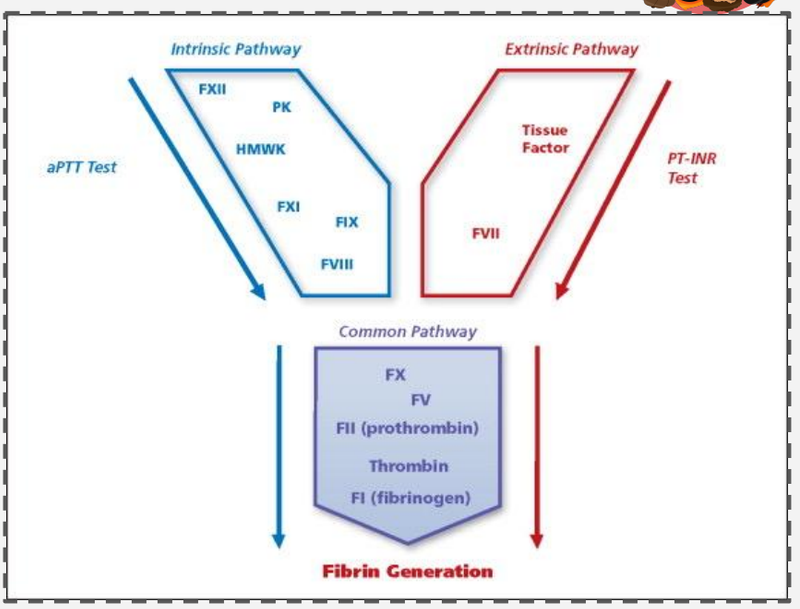
- Normal bleeding takes 6-8 min to stop bleeding, max time to stop bleeding normally is 8 min .
- **How children stop bleeding mechanism (normal child)?**

1. normal vessels and normal capillaries
2. normal platelets count and function
3. protein (coagulation factors) normal in amount and function

- **Physiology**: Children have clear smooth arteries Not like adults (ugly with lipids)

1. Injury in endothelial lining will get collagen to be exposed.
2. Vasoconstriction (vessels will have immediately constriction) “first Event That Help To Stop Bleeding”.
3. platelet will adhere to the collagen(platelets need von willebrand to adhere)
4. start to release substance **(ADP & Thromboxane A2) are the most imp*** , they release these substance in order to aggregate
5. forming adhesive clout (platelet plug)
6. Bleeding will be stopped If any step of these has disease (adhesion or aggregation affected) ,If the child continues oozing there is problem with the child within blood vessel , platelet or coagulation factor

Coagulation pathway



- **Coagulating cascade: (3 areas =intrinsic, extrinsic, common pathway)**

1. **Tissue thromboplastin pathway** (factor 3) : it will combine and activate factor 7 - we test this pathway by (PT and PTT) : PTT40s If PT is abnormal(prolonged) and PTT is normal —- factor 7 deficiency
2. Why not factor (3)? it's has never ever been inherited as deficient in animal or human.

3. **contact pathway:**
    - If PTT is abnormal (prolonged) and PT is normal —- factor 12,11,8,9 def
    - We approve the dx by hx if the child was a boy then — must be 8,9 def , If the child is a girl —something else.
    - Factor (12) called Hageman factor — if def it makes a prolonged PTT without prolonged bleeding.
    - Factor (11) causes bleeding only in jewish ashkenazi don't have it in another nation ,so for the lab do (11.12).
    - when you have a prolonged PTT alone then you are dealing with either factor (8,9).
    - Both factor (8) (9) are x-linked but factor (8) is 100 times more common than (9).
    - Factor (8) def called -hemophilia A.
    - Factor (9) def called -hemophilia B.
    - 8,9 are the only x-linked the others are autosomal dominant or autosomal recessive
    - The acquired causes of prolong PTT are more common than the inherited causes **so the lab will do mixing study**— they add all the defect factors to the blood to see if it's corrected or not to rule out antiphospholipid antibodies' syndrome.
    - If child has prolonged PTT with no bleeding at all — ask for mixing study.
    - If child has real bleeding with family hx with epistaxis and ecchymosis —factor 8,9 if is a boy , if it's a girl she must have von willbrand factor.
    - PTT is prolonged there is no bleeding what is the cause ? Don't say factor 12 it is very rare , but viral and bacterial infection are common, you do mixing study

They test IgG antibodies against any inflammatory processes " thus cause prolonged PTT due to antibodies against one of the factors"

4. **common pathway** (factor1 = fibrinogen) (factor 2= prothrombin).
    - Contain only 4 proteins = Factor 10,5,2,1.
    - Factor (7) from the extrinsic pathway comes to activate factor (10).
    - Also factor 8,9 from the intrinsic pathway will activate factor 10 —- will activate 5 —and form factor 5,10 complex — then activated prothrombin to form thrombin —- then thrombin will cleave a huge molecule which is fibrinogen to form the fibrin (clot).

Then how to know if its factor 10,5,2,1?

- You have to ask for PT and PTT and fibrinogen.
- So when we have PT abnormal and PTT abnormal— it has to be either factor 10 or 5 or 2 or 1.
- If the fibrinogen is not deficient it is HIGH and there is a bleeding problem in a child —- the child may have dysfibrinogenemia (very rare) the amount is high and super normal , BUT is NOT FUNCTIONING

Q: Child has bleeding, and he is normal with normal platelets in function and count, and normal PT and PTT = factor 13 def.

- **factor 13 does not belong to the cascade, it is formed to solidified the fibrin – it is called clot stabilizing factor A**
- Its function: it facilitate the crossing of fibrin on each other, so the clot will be solid and stable.
- A clot Without factor 13 will not be solid and will lysed and turns to blood again.

- Clot dissolving test (screening test) for factor 13 done using : acetoacetic acid or 5 mol of urea , all other teats are normal.
- In the hx there is leading Q for suspecting and diagnosing factor 13 def : Ask the mother about the umbilical cord stump when child was born when if fall off ? (it should fall off within week or 10 days).
- if it took time more than that and it was wet not dry .= factor 13 def.
- Ask that Q even if the child is 4 y.o. And you suspecting factor 13 def.

- Child who doesn't have any bleeding he was tested routinely for surgery, family hx is negative platelet count is normal everything was fine, but now he has a prolonged PTT (so child is not bleeding but he has a prolong PTT) —- the lab did mixing study (to see if its APLS) nothing was found what is the diagnosis? it must be factor 12 def —- so they screen for factor 12 and high molecular weight kininogen (this molecule also gives a prolonged PTT with no bleeding.

Relationship of factor level to severity of clinical manifestation of hemophilia A and B		
Type	**Percentage factor VIll/VIX**	**Type of hemorrhage**
Severe	**<1**	**Spontaneous; hemorrhage and deep tissue hemorrhage.**
Moderate	**1-5**	**Gross bleeding following mild to moderate trauma; some hemarthrosis; seldom spontaneous hemorrhage.**
Mild	**2-25**	**Severe hemorrhage only following moderate to severe trauma or surgery.**
High risk carriers female	**30-50**	**Gynecologic and obstetric hemorrhage**

- Ecchymosis: coagulation function
- Petechiae : platelet problem

hemophilia :

- X linked disease and the mother is the carrier.
- **Severity of disease:**
  - ❏ we have 100% of factor 8 and 9 and that means normally you have 1 unit of factor 8 in each ml of plasma.
  - ❏ if factor 8 or 9 is less than 1%= almost 0 —they will have massive GI or brain bleeding, and spontaneous bleeding with no documented trauma and they usually bleed deep into tissue, muscles and joint (hemarthrosis).
  - ❏ if factor 8 between 1-5% - they still bleed deep into tissue but upon trauma (ecchymoses) , and bleed heavily upon surgery, and might develop hemarthrosis because 1-5% is not enough.
  - ❏ More than 5% in mild.
  - ❏ The mother will not have ecchymosis because she has between 60-40% factors the only compline will be menorrhagia.
  - ❏ family Hx is very important in Hemophilia.
  - ❏ not only the mother is responsible for hemophilia, 20% of hemophiliac boys they have a spontaneous mutation of gene in utero.
  - ❏ Genetic study is the definitive way to know if the mother is a carrier or not.

Difference between von willebrand disease and hemorrhage		
	Von willebrand disease	Hemophilia A
Symptoms	Bruising epistaxis Menorrhagia or mucosal bleeding	Joint bleengig Muscle bleeding
Sexual distribution	Male = female	Males
Frequency	1:200 to 1:500	1:6000 males
Abnormal protein	vWF	Factor Vlll
Molecular weight	0.6-20x10 Da	280 kDa
Function	Platelet adhesion	Clotting cofactor
Site of synthesis	Endothelial cell or megakaryocytes	??
Chromosome	Chromosome 12	X chromosome
Inhibitors frequency	Rare	14-25% of patients
History	Abnormal	Abnormal
aPTT	Normal or prolonged	Prolonged
Factor Vlll activity	Borderline or decreased	Decreased or absent
vWF Ag	Decreased or absent	Normal or increased
Bleeding time	Prolonged	

The Schedule of VWD vs Hemophilia :

- Type 1 von willebrand— the commonest 95% of all VWB deficiency cases , easy to diagnose autosomal dominant that means one of the parents should have it, hematuria . Gi bleeding . epistaxisis bilateral.
- Type 3 von willebrand is the severe type -autosomal recessive - the parents are cousins—have epistaxis all the time -Similar to hemophilia they have joint bleeding, deep tissue bleeding.
- If the child is girl with a manifestation that resembles severe hemophilia = type 3 vwd until proven Otherwise.
- Girls can have Hemophilia but only if the father is affected and the mother is carrier(2 x gens must be affected).
- In von willebrand disease the amount and the function(aggregation & adhesion) of the platelets are all affected
- Von willebrand is responsible for factor 8 if its def, then factor 8 will also be defect, so if you have aggregation problem in that girl – that means she does not have hemophilia at all – and platelet function will come to be abnormal because VWF is deficient .
- If there is a problem with the factors it is either in amount or function, for instance; in hemophilia the amount in normal , but the function is affected . on the other hand , in vWd both are low amount and function(but the ratio between amount and function is 1:1)while in hemophilia the ratio is very bad 1:100

Type 1	Type 3
The commenset 95% of all VWB deficiency caese	Rarest
Autosomal dominant, one of the parent have it	Autosomal recessive, parent are normal
Mucosal bleeding such as hematuria. Gi bleeding epistaxis bilateral.	Joint bleeding, deep tissue bleeding, very bad ecchymoses, and bleeding usually require blood transfusion
Very mild, factor 8 is almost normal	Factor 8 is only 2-3%
Tx: desmorpression	Tx: factor 8

Thrombocytopenia

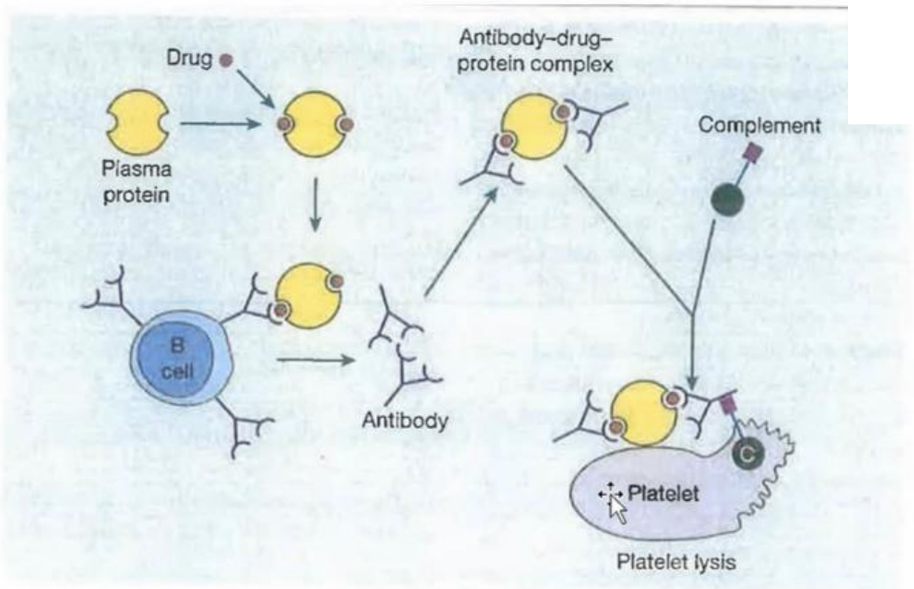


Figure 25.6 Usual type of platelet damage caused by drugs in which an antibody–drug–protein complex is deposited on the platelet surface. If complement is attached and the sequence goes to completion, the platelet may be lysed directly. Otherwise it is removed by reticuloendothelial cells because of opsonization with immunoglobulin and/or the C3 component of complement.

Thrombocytopenia:

- platelet problems : thrombocytopenia = in 92% of cases patient have ITP.
- mechanism : post viral infection or taking a drug , the immune system develop immunoglobulin, but they were not specific to that virus , and those immunoglobulin has coat the platelet after that monocyte will take the platelet right away and carry them to spleen where they will be degraded by macrophages as a result platelet will be low in circulation .
- **immune thrombocytopenia purpura :** common MCQ topic

➢ child has viral infection 2-3 weeks ago with no history of autoimmune disease, and now complain of petechial hemorrhage (DDX: thrombocytopenia or vasculitis) , Systematic review should be negative for any active problem at that stage, the complaint is only pinpoint bleeding into skin or mucous membrane 1st criteria no active problem at all specially fever , common cold or sore throat or minor disease.+ no history of bleeding disorder in family

➢ physical exam : child is completely normal (no palpable spleen) (petechial hemorrhage with palpable spleen = leukemia),

➢ CBC: all normal except low platelet

- To summarize ITP :History of viral infection +negative history for autoimmune disease + normal physical examination + normal CBC except for low platelet = ITP until proven otherwise .

1. Q: 10 y old girl with similar presentation what DDX? could be autoimmune diseases + most common autoimmune disease associated with petechiae is thyroiditis, SLE .
2. Viral infection = very good prognosis, if platelet less than 20,000 we admit and treat with immunoglobulin, complication: spontaneous bleeding in brain , immunoglobulin are only used to raise platelet count.
3. If there is no improvement steroid is the drug of choice.
4. Can be used in combination: immunoglobulin to saturate the macrophages, steroid to kill B lymphocyte.
5. If chronic more than 1 year we use RITUXIMAB . Either to cure , remission for 1 y or 6 m + steroid must be stopped at 6 months in order to allow child to grow

in female more than 6 years with no complain and physical exam is Normal Just Petechiae and thrombocytopenia think of SLE Send for dsDNA and ANA test and follow up for ANA test make sure No sle , Also Send for T4 and TSH and antithyroid antibodies because thyroiditis is very common then SLE

If a child with petechial hemorrhage and in good health, platelet is 40,000 what would you do ? Send home and follow up after 10 days to see the platelet is it going down or up

you admit the pt if platelets less than 20,000 to give Immunoglobulins.

Pt with platelets less than 20,000 here the risk to bleeding the brain that is why we admit

1g/kg of immunoglobulin b.c we want the macrophages to take this immunoglobulin so these platelets coated with immunoglobulin won't get destroyed

If Immunoglobulin is not affordable or refused by the pt we give prednisolone for no more than 21 days" you have to taber down in 14 wither it works or not "

If it didn't work we give rituximab (⅓ will respond for 6 months then relapse ⅓ respond for a year ⅓ don't respond)

We do splenectomy if 1- rituximab failed or 2- bleeding in lungs and in many sites.

splenectomy is absolute indicated if immediately if he bleed in the brain

The first thing to be consumed in DIC is platelets

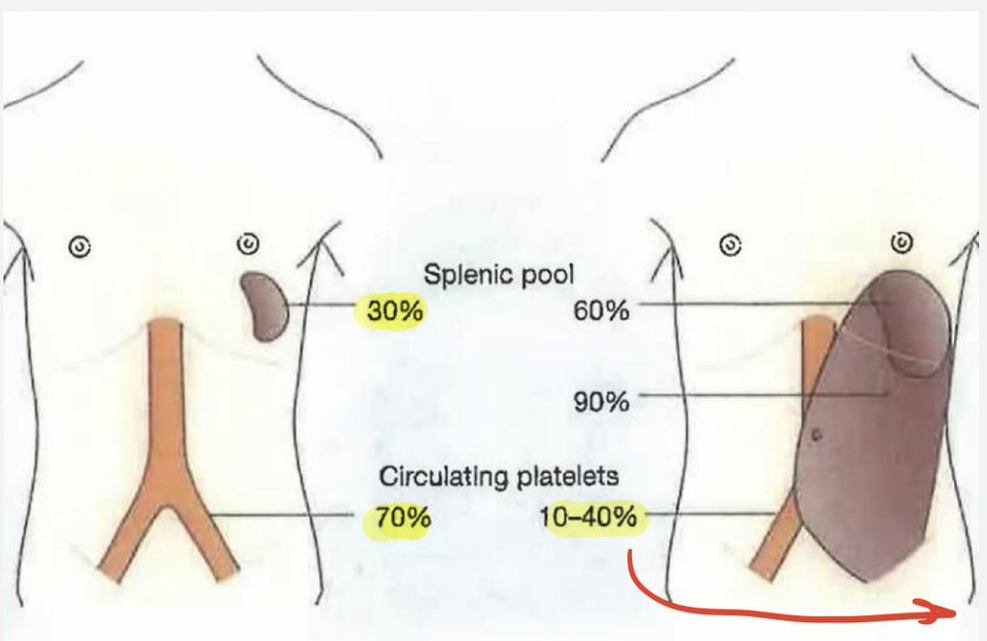


Figure 25.9 The platelet distribution between the circulation and spleen in normal individuals (left), and in patients with moderate or massive splenomegaly (right).

thrombocytopenia due to splenomegaly
here the spleen is huge due to others disease , this spleen will take 90% of the platelets and patient end up with thrombocytopenia due to hypersplenism

Vit k deficiency:
causes bleeding in newborn (factor 2,7,9,10 their function depend only on vit k which is synthesis in bowel, and the newborn bowel is sterile that we every newborn need 1mg IM injection of vit k)

Drug-induced Thrombocytopenia

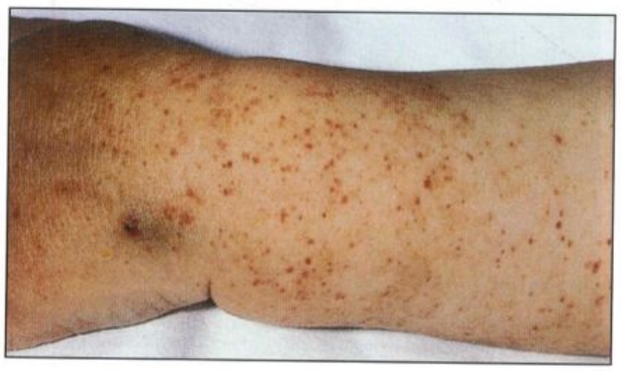
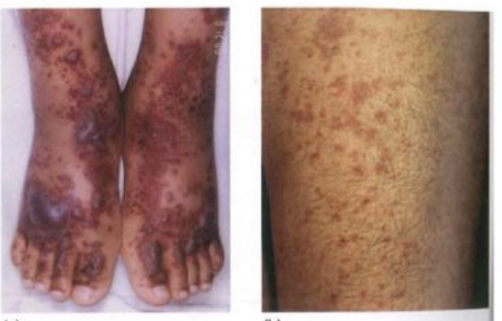


Figure 5-15. Cutaneous hemorrhage and purpura in a patient with drug-induced thrombocytopenia. Drug-induced thrombocytopenia can result from bone marrow suppression or peripheral immune destruction and clearance. Most patients with drug-induced thrombocytopenia present with mucocutaneous hemorrhage and purpua as shown here, similar to that of immune-mediated thrombocytopenic purpura. Immune thrombocytopenia induced by heparin and heparin-derived drugs rarely produces signs and symptoms suggestive of a bleeding diathesis; rather, there is a profound hypercoagulable state often associated with manifestations of venous and arterial thrombosis.



(a) (b)

Figure 25.2 Henoch–Schönlein purpura: **(a)** unusually severe purpura on legs with bulla formation in a 6-year-old child; and **(b)** early urticarial lesions.

- pt presented with malena arthralgia severe abdominal pain that can lead to intussusception if you didn't start steroid immediately
- Rash on the sucks distribution which is severe also in the buttocks area , ITP don’t do that

Book

Bleeding Disorders:

Diagnostic Approach:

- Identifying features in the clinical presentation:

Age of onset

- Neonate – in 20% of haemophilias, bleeding occurs in the neonatal period, usually with intracranial haemorrhage or bleeding after circumcision
- Toddler – haemophilias may present when starting to walk
- Adolescent – von Willebrand disease may present with menorrhagia

Family history

- Family tree – detailed family tree required
- Gender of affected relatives (if all boys, suggests haemophilia)

Bleeding history

- Previous surgical procedures and dental extractions – if uncomplicated, suggests bleeding tendency is acquired rather than inherited
- Presence of systemic disorders
- Drug history, e.g. anticoagulants
- Unusual pattern or inconsistent history – consider non-accidental injury

Pattern of bleeding

- Mucous membrane bleeding and skin haemorrhage – characteristic of platelet disorders or von Willebrand disease
- Bleeding into muscles or into joints – characteristic of haemophilia
- Scarring and delayed haemorrhage – suggestive of disorders of connective tissue, e.g. Marfan syndrome, osteogenesis imperfecta or factor XIII deficiency

- Initial laboratory screening tests:

1. Full blood count and blood film.
2. Prothrombin time (PT): tests for deficiencies intrinsic pathway involving factors II, V, VII and X.
3. Activated partial thromboplastin time (APTT): tests for deficiencies in the extrinsic pathway involving factors II, V, VIII, IX, X, XI and XII.
4. Thrombin time: tests for deficiency or dysfunction of fibrinogen.

if PT or APTT is prolonged, a 50:50 mix with normal plasma will distinguish between possible factor deficiency or presence of inhibitor.

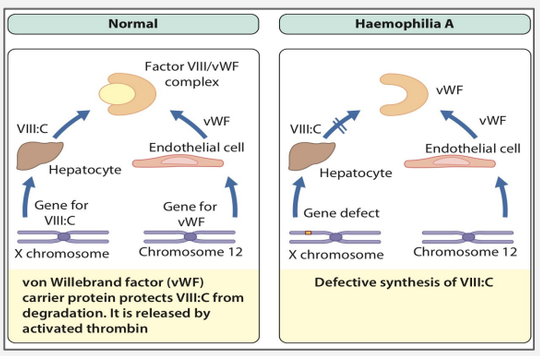
5. Quantitative fibrinogen assay.
6. D-dimers: to test for fibrin degradation products.
7. Biochemical screen, including renal and liver function.
8. Genetic analysis: for child and their parents to exclude an inherited coagulation factor deficiency.

In the neonate, the levels of all clotting factors except factor VIII (FVIII) and fibrinogen are lower; preterm infants have even lower levels. Therefore the results have to be compared with normal values in infants of a similar gestational and postnatal age.

Haemophilia

It is X-linked recessive inheritance.
Two types:

1. Haemophilia A: is FVIII deficiency.
2. Haemophilia B: is FIX deficiency.



Clinical features:

- Towards the end of the first year of life, when they start to crawl or walk (and fall over), children begin to develop muscle and joint bleeds.
- Almost 40% of cases present in the neonatal period, particularly with large cephalhaematomas, intracranial haemorrhage, bleeding post circumcision or prolonged oozing from heel stick and venepuncture sites.
- Large bruises from trivial pressure.

The hallmark of severe disease is recurrent spontaneous bleeding into joints and muscles, which can lead to crippling arthritis if not properly treated.

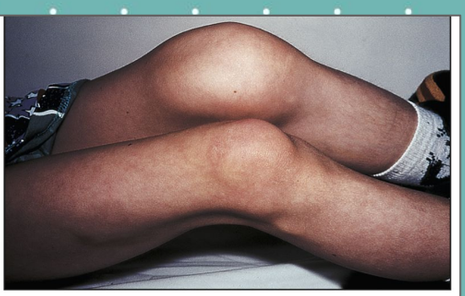


Figure 23.15 Severe arthropathy from recurrent joint bleeds in haemophilia. The aim of modern management is to prevent this from occurring.

Table 23.3 Severity of haemophilia

Factor VIII	Severity	Bleeding tendency
<1%	Severe	Spontaneous joint/ muscle bleeds
1%–5%	Moderate	Bleed after minor trauma
>5%–40%	Mild	Bleed after surgery

Management:

Investigations:

Table 23.2 Investigations in haemophilia A and von Willebrand disease

	Haemophilia A
PT	Normal
APTT	↑↑
Factor VIII:C	↓↓
vWF Antigen	Normal
RiCoF (activity)	Normal
Ristocetin-induced platelet aggregation	Normal
vWF multimers	Normal

Haemophilia

Treatment:

Prophylactic FVIII and IX given intravenously every 2-3 days. If peripheral venous access is poor, a central venous access device (e.g. Portacath) may be required.

Acute bleeding episodes, recombinant factor concentrate is given by prompt intravenous infusion. If recombinant products are unavailable, highly purified, virally inactivated plasma-derived products should be used. The quantity required depends on the site and nature of the bleed:
1- Raising the circulating level to 30% of normal is sufficient to treat minor bleeds and simple joint bleeds.
2- Major surgery or life-threatening bleeds require the level to be raised to 100% and then maintained at 30% to 50% for up to 2 weeks to prevent secondary haemorrhage.

Infusion Desmopressin (DDAVP), which stimulates release of endogenous FVIII and vWF, may allow mild haemophilia A to be managed without the use of blood products to enable minor surgery and dental extraction.
DDAVP is ineffective in haemophilia B.

Specialized physiotherapy is needed to preserve muscle strength and avoid damage from immobilization.

Box 23.5 Complications of treatment of haemophilia

Inhibitors, i.e. antibodies to FVIII or FIX

- Develop in 30% of patients with haemophilia A, but only 3% of patients with haemophilia B
- Reduce or completely inhibit the effect of treatment
- Usually treated with immune tolerance induction which involves regular exposure to large quantities of factor treatment for a long time

Transfusion-transmitted infections

- Hepatitis A, B, and C
- HIV
- Other, e.g. prions, parvovirus B19

Vascular access

- Peripheral veins – may be difficult to cannulate
- Central venous access devices may become infected or thrombosed

von Willebrand disease (vWD)

Von Willebrand factor (vWF) has two major roles:

- It facilitates platelet adhesion to damaged endothelium.
- It acts as the carrier protein for FVIII, protecting it from inactivation and clearance.

Von Willebrand factor (vWF) deficiency causes:

- This causes defective platelet plug formation.
- **Patients with vWD also are effectively deficient in FVIII.**

There are many different mutations in the vWF gene resulting in many different types of vWD. The inheritance is usually autosomal dominant.

Clinical features:

- Bruising.
- Excessive, prolonged bleeding after surgery.
- Mucosal bleeding such as epistaxis and menorrhagia.

In contrast to haemophilia, spontaneous soft tissue bleeding such as large haematomas and haemarthroses are uncommon.

Management:

Investigations:

	von Willebrand disease
PT	Normal
APTT	↑ or normal
Factor VIII:C	↓ or normal
vWF Antigen	↓
RiCoF (activity)	↓
Ristocetin-induced platelet aggregation	Abnormal
vWF multimers	Variable

Treatment: depends on the type and severity.

Type 1:	Treating with Desmopressin, which causes secretion of both FVIII and vWF
More severe types of vWD:	Treating with plasma-derived FVIII concentrate.

For both Haemophilia and vWD	Intramuscular injections, aspirin and nonsteroidal anti-inflammatory drugs should be avoided.

Acquired disorders of coagulation

The main acquired disorders of coagulation affecting children are those secondary to:

1. Liver disease.
2. Immune thrombocytopenia (ITP).
3. Disseminated intravascular coagulation (DIC).
4. Vitamin K deficiency, causing vitamin K deficient bleeding (haemorrhagic disease of the newborn).

Children may become deficient in vitamin K due to:

- Inadequate intake (e.g. neonates, long-term chronic illness with poor intake)
- Malabsorption (e.g. coeliac disease, cystic fibrosis, obstructive jaundice)
- Vitamin K antagonists (e.g. warfarin).

Vitamin K is essential for the production of active forms of factors II, VII, IX, X and anticoagulants such as protein C and protein S.

Summary

The child with abnormal bleeding
– into soft tissues, mucocutaneous or following surgery

Acquired disorders

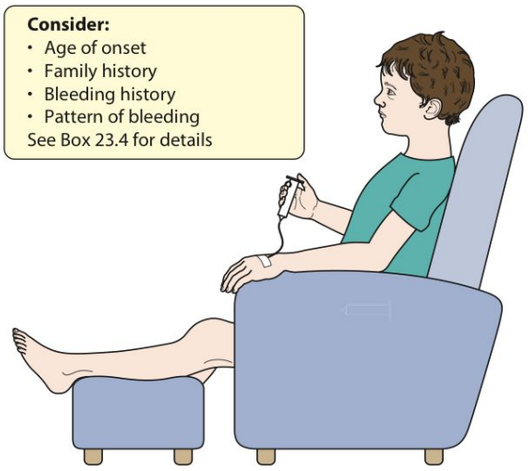
Vitamin K deficiency:
- mainly neonates or early infancy

Liver disease

Thrombocytopenia:
- immune, DIC, etc.

Consider:
- Age of onset
- Family history
- Bleeding history
- Pattern of bleeding

See Box 23.4 for details



Inherited disorders

Haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency):
- Are X-linked recessive disorders affecting males
- Presentation of severe disease – usually with recurrent spontaneous bleeding into joints and muscles at about 1 year of age
- Treatment – recombinant FVIII concentrate for haemophilia A or recombinant FIX concentrate for haemophilia B. Desmopressin (DDAVP) to treat mild haemophilia A
- Treatment complications – inhibitors and intravenous access

von Willebrand disease (vWD):
- Results from either a quantitative or qualitative deficiency of von Willebrand factor (vWF)
- Autosomal dominant
- Presentation – mucosal bleeding, e.g. epistaxis or menorrhagia in adolescence or excessive, prolonged bleeding after surgery
- Treatment – mild disease with DDAVP, severe disease with plasma-derived FVIII concentrate

Thrombocytopenia

Thrombocytopenia is a platelet count less than $150x10^9$/L.
The risk of bleeding depends on the level of the platelet count:

Mild thrombocytopenia	Moderate thrombocytopenia	Severe thrombocytopenia
platelets $50–150x10^9$/L	platelets $20–50x10^9$/L	platelets $<20x10^9$/L
Risk of a major operation or severe trauma bleeding.	Risk of excess bleeding during operations or trauma but low risk of spontaneous bleeding	Risk of spontaneous bleeding.

Thrombocytopenia may result in bruising, petechiae, purpura and mucosal bleeding. Major haemorrhage is much less common.

Table 23.4 Causes of purpura or easy bruising

Platelet count reduced, i.e. thrombocytopenia	
Increased platelet destruction or consumption	
Immune	Immune thrombocytopenic purpura (ITP) Systemic lupus erythematosus (SLE) Alloimmune neonatal thrombocytopenia
Non-immune	Haemolytic uraemic syndrome Thrombotic thrombocytopenic purpura Disseminated intravascular coagulation (DIC) Congenital heart disease Giant haemangiomas (Kasabach–Merritt syndrome) Hypersplenism
Impaired platelet production	
Congenital	Fanconi anaemia Wiskott–Aldrich syndrome Bernard–Soulier syndrome
Acquired	Aplastic anaemia Marrow infiltration (e.g. leukaemia) Drug-induced
Platelet count normal	
Platelet dysfunction	
Congenital	Rare disorders, e.g. Glanzmann thrombasthenia, Hermansky Pudlak syndrome type 2
Acquired	Uraemia, cardiopulmonary bypass
Vascular disorders	
Congenital	Rare disorders, e.g. Ehlers–Danlos, Marfan syndrome, hereditary haemorrhagic telangiectasia
Acquired	Meningococcal and other severe infections Vasculitis, e.g. Henoch–Schönlein purpura, SLE Scurvy

Immune thrombocytopenia (ITP):

- ITP is the most common cause of thrombocytopenia in childhood.
- It is usually caused by destruction of circulating platelets by antiplatelet IgG autoantibodies.
- It is acute, benign and self-limiting, usually remitting spontaneously within 6 weeks to 8 weeks.
- The following definitions are used in ITP based on duration:
  a. Newly-diagnosed ITP: Duration <3 months.
  b. Persistent ITP: Duration 3–6 months.
  c. Chronic ITP: Duration > 6 months.

Clinical features:

- Most children present between the ages of 2 years and 10 years, with onset often 1 week to 2 weeks after a viral infection or vaccination.
- Affected children develop petechiae, purpura, and/or superficial bruising , can also cause epistaxis and other mucosal bleeding

Thrombocytopenia

Management:

Investigations:

1- history.
2- clinical features.
3- blood film.

- Any atypical clinical features, such as the presence of anaemia, neutropenia, hepatosplenomegaly, or marked lymphadenopathy, should prompt a bone marrow

Treatment:

Most children do not need any therapy even if their platelet count is less than $10x10^9$/L but treatment should be given if there is evidence of major bleeding or persistent minor bleeding

The treatment options include:

1- oral prednisolone.
2- Intravenous immunoglobulin.
3- Platelet transfusions are reserved for life-threatening haemorrhage.

Chronic ITP:

Drug treatment is only offered to children with chronic persistent bleeding:

1- thrombopoietin receptor agonists (TPO- RA) such as:

- Eltrombopag (available as an oral daily dose.)
- Romiplostim (given as weekly subcutaneous injections).

2- Rituximab, a humanized monoclonal antibody directed against B cells, can also be given as second-line treatment.

3- Splenectomy can be effective for children who fail drug therapy as it significantly increases the risk of infection and patients require lifelong antibiotic prophylaxis.

- Regular screening for SLE should be performed, as the thrombocytopenia may predate the development of autoantibodies.

Anemia

- Anemia is defined as a Hb below the normal range. The normal range varies with age so anemia can be defined as:
- Neonate: Hb less than 140 g\L
- 1 month to 12 months of age: Hb less than 100 g\L
- 1 year to 12 years of age: Hb less than 110 g\L

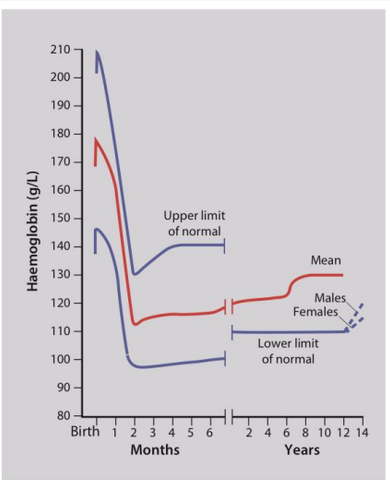


Figure 23.1 Changes in haemoglobin concentration with age, showing that the haemoglobin is high at birth, falling to its lowest concentration at 2 months to 3 months of age.

Table 23.1 Haemoglobins in haemoglobinopathies

	HbA	HbA_2	HbF	HbS
Newborn	25%	1%	74%	–
Adult	97%	2%	–	–
β-Thalassaemia trait	>90%	↑	↑	–
β-Thalassaemia major	–	↑	↑	–
Sickle cell trait	✓	✓	↑	✓
Sickle cell disease	–	✓	↑	✓

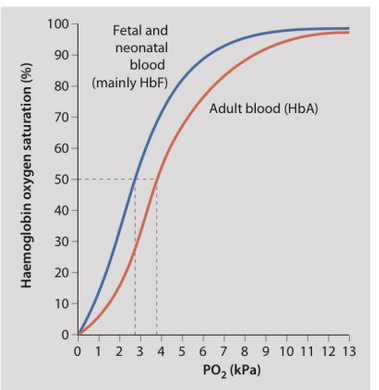
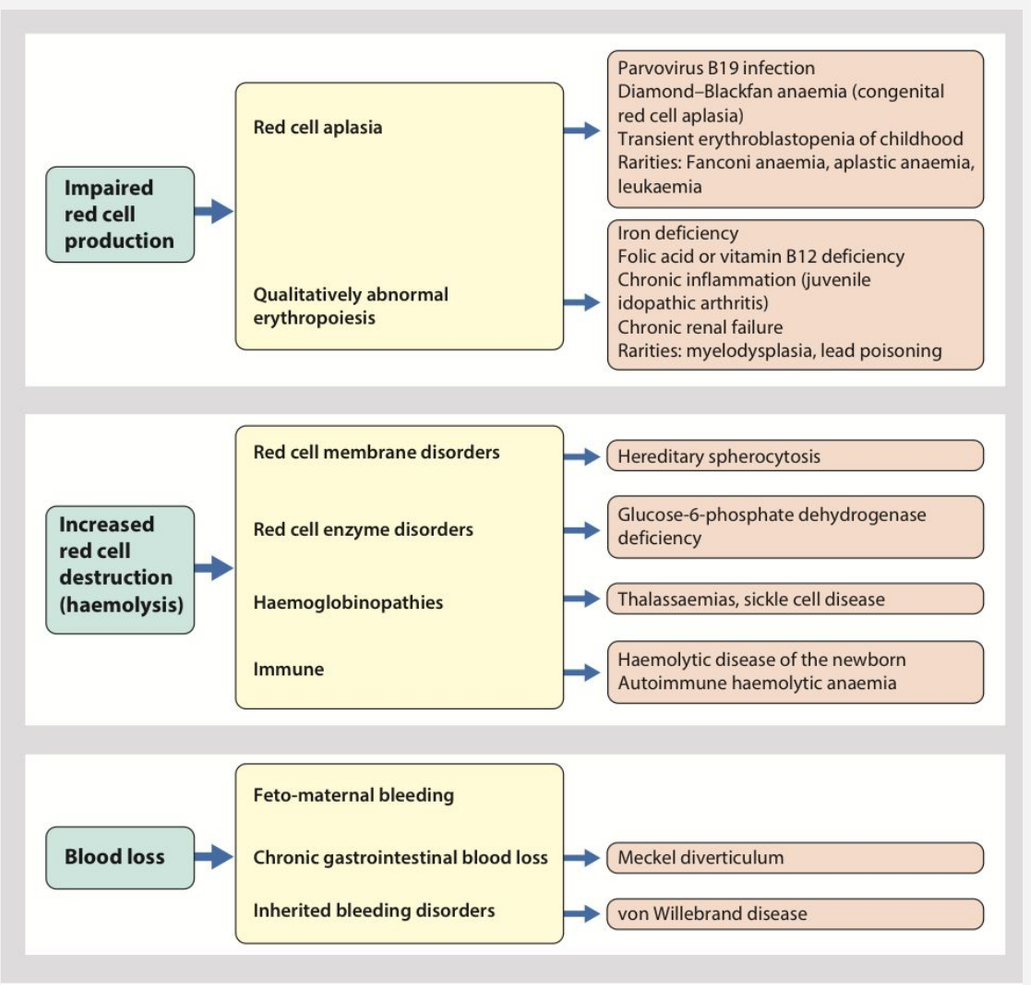


Figure 23.2 Oxygen dissociation curve showing the left shift of HbF compared with HbA. HbF-containing red cells have a higher affinity for oxygen and hold on to oxygen, delivering less to the tissues.

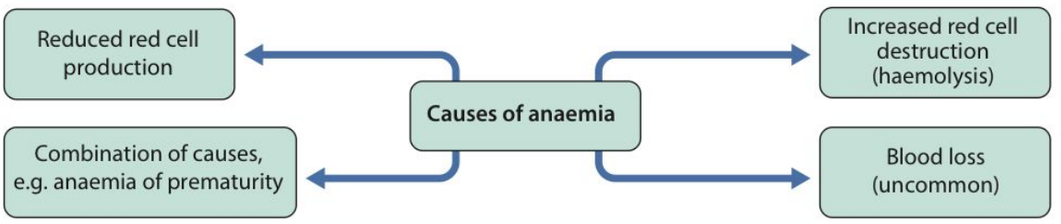
- Causes of anemia in infants and children:



Anemia

Summary

Anaemia



Reduced red cell production

Iron deficiency anaemia
- Common in infants and toddlers
- Usually dietary in origin
- Occurs because of high iron requirement for growth, nutrition and body stores
- Will not occur if infants are weaned at 6 months of age on to a mixed diet including iron-rich food
- Is diagnosed from a hypochromic microcytic anaemia and low serum ferritin
- Is treated with dietary advice and oral iron therapy for at least 3 months

Red cell aplasia
- Congenital red cell aplasia ('Diamond–Blackfan anaemia')
- Transient erythroblastopenia of childhood (TEC)
- Parvovirus B19 infection

Increased red cell destruction (haemolysis)

Hereditary spherocytosis
- Inheritance is autosomal dominant, but in 25% of cases there is no family history
- May cause early, severe jaundice in newborn infants
- Is often asymptomatic, but it may cause anaemia, jaundice, splenomegaly, aplastic crisis and gallstones
- Can usually be diagnosed from the blood film but confirmatory tests are usually undertaken
- Treatment is with folic acid, splenectomy if symptomatic

β-Thalassaemia major
- Mutation of the β-globin gene results in an inability to produce HbA ($\alpha_2\beta_2$)
- Clinical features: severe anaemia, faltering growth and hepatosplenomegaly
- Condition is fatal without regular blood transfusions, but blood transfusions cause iron overload
- Iron chelation therapy is essential in all patients to minimize iron overload

β-Thalassaemia trait and α-thalassaemia trait
- Can cause diagnostic confusion with mild iron deficiency

α-Thalassaemia major
- Deletion of all four α-globin genes, α-thalassaemia major is fatal in utero (Hb Barts) or within hours of birth

Isoimmune
- Haemolytic disease of the newborn

Immune haemolytic anaemia

G6PD deficiency
- Affects over 100 million people worldwide, usually of Mediterranean, Middle East, Far East and Central African ethnicity
- Is X-linked and therefore predominantly affects males, but females may be affected
- May present with neonatal jaundice
- Causes acute intermittent haemolysis precipitated by infection, certain drugs, fava beans (broad beans) and naphthalene in mothballs
- Parents should be given a list of drugs, chemicals and food to avoid

Sickle cell disease
- Family usually originates from tropical Africa or the Caribbean
- Autosomal recessive
- Sickled red cells result in ischaemia in organs or bones
- Main clinical features are: anaemia, infection, painful crises, sequestration crises, splenomegaly in some young children, growth failure, gallstones, and learning difficulties
- The most serious clinical complications are bacterial infection, acute chest syndrome, strokes and priapism
- Management: prophylactic penicillin and immunization; maintain good hydration
  Treat painful crises: analgesia, hydration, antibiotics, exchange or blood transfusion as indicated
  Long-term: hydroxycarbamide, blood transfusions or occasionally bone marrow transplant

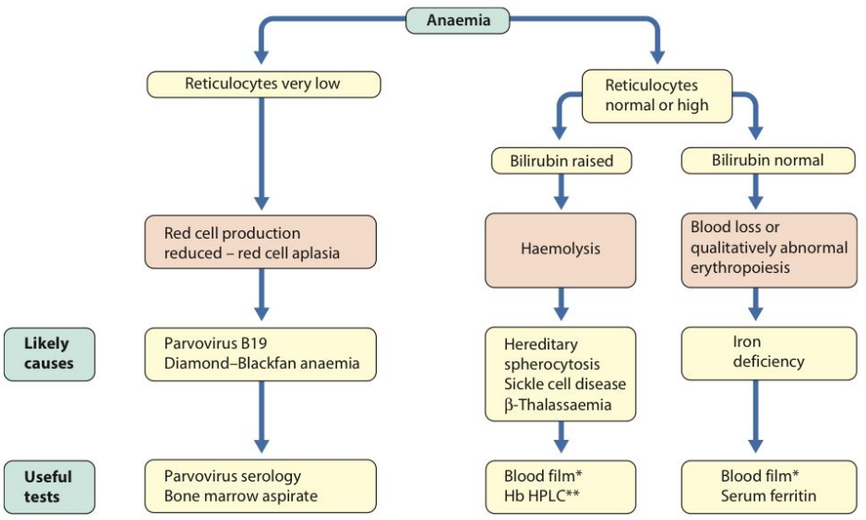


Figure 23.4 Simple diagnostic approach to anaemia in children.

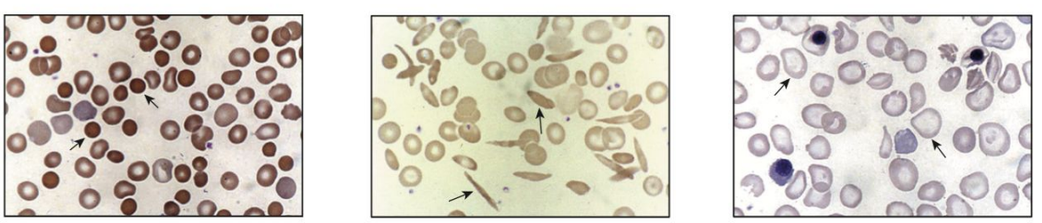


Figure 23.6 Abnormally shaped red blood cells help make the diagnosis in haemolytic anaemias. (**a**) Spherocytes (arrows) in hereditary spherocytosis; (**b**) sickle cells (arrows) in sickle cell disease; and (**c**) hypochromic cells (arrows) in thalassaemia.

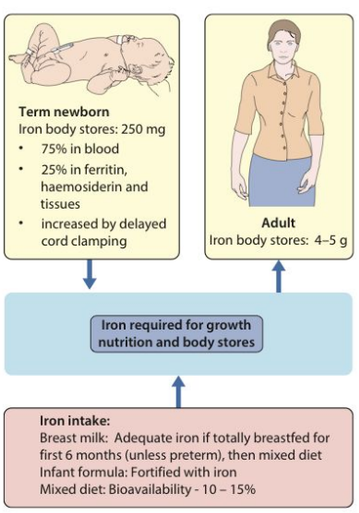


Figure 23.5 Iron requirements during childhood.

Box 23.1 Dietary sources of iron

High in iron
- Red meat – beef, lamb
- Liver, kidney
- Oily fish – pilchards, sardines, etc.

Average iron
- Pulses, beans, and peas
- Fortified breakfast cereals with added vitamin C
- Wholemeal products
- Dark green vegetables – broccoli, spinach, etc.
- Dried fruit – raisins, sultanas
- Nuts and seeds – cashews, peanut butter, etc.

Foods to avoid in excess in toddlers
- Cow's milk
- Tea: tannin inhibits iron uptake
- High-fibre foods: phytates inhibit iron absorption

Clinical features and complications of β-thalassaemia major (transfusion dependent thalassaemia)

Pallor

Jaundice

Bossing of the skull
Maxillary overgrowth

Splenomegaly and hepatomegaly

Need for repeated blood transfusions
Complications shown in Box 22.3

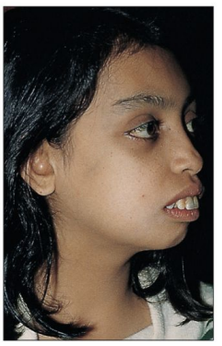


Figure 23.13 Facies in β-thalassaemia showing maxillary overgrowth and skull bossing in a child with β-thalassaemia intermedia, (non-transfusion dependent thalassaemia).

Box 23.3 Complications of long-term blood transfusion in children

Iron deposition – the most important (all patients)

- Heart – cardiomyopathy
- Liver – cirrhosis
- Pancreas – diabetes
- Pituitary gland – impaired growth and sexual maturation
- Skin – hyperpigmentation

Antibody formation (10%)

- Allo-antibodies to transfused red cells in the patient make finding compatible blood very difficult
- Infection – now uncommon

Infection – now uncommon

- Hepatitis A, B, C
- HIV
- Malaria
- Prions (e.g. new variant Creutzfeldt–Jakob disease)

Venous access (common problem)

- Often traumatic in young children
- Central venous access device (e.g. Portacath) may be required; these predispose to infection

Anaemia	All have moderate anaemia (usually Hb 60–100 g/L) with clinically detectable jaundice from chronic haemolysis
Infection	All have marked increase in susceptibility to infection from encapsulated organisms such as pneumococci and *Haemophilus influenzae*. There is also an increased incidence of osteomyelitis caused by *Salmonella* and other organisms. This susceptibility to infection is due to **hyposplenism** secondary to chronic sickling and **microinfarction** in the spleen in infancy. The risk of overwhelming sepsis is greatest in early childhood
Painful crises	**Vaso-occlusive crises** causing pain affect many organs of the body with varying frequency and severity. A common mode of presentation in late infancy is the hand-foot syndrome, in which there is dactylitis with swelling and pain of the fingers and/or feet from vaso-occlusion (Fig. 23.9). The bones of the limbs and spine are the most common sites. The most serious type of painful crisis is acute chest syndrome, which can lead to severe hypoxia and the need for mechanical ventilation and emergency transfusion. Avascular necrosis of the femoral heads may also occur. Acute vaso-occlusive crises may be precipitated by exposure to cold, dehydration, excessive exercise or stress, hypoxia or infection
Acute anaemia	Sudden drop in haemoglobin from **Haemolytic crises** – sometimes associated with infection **Aplastic crises** – haemoglobin may fall precipitously. Parvovirus infection causes complete, though temporary, cessation of red blood cell production **Sequestration crises** – sudden splenic or hepatic enlargement, abdominal pain and circulatory collapse from accumulation of sickled cells in spleen
Priapism	Needs to be treated promptly with exchange transfusion as it may lead to fibrosis of the corpora cavernosa and subsequent erectile dysfunction
Splenomegaly	Common in young children, but becomes much less frequent in older children
Long-term problems	**Short stature and delayed puberty** **Stroke and cognitive problems** – although 1 in 10 children with sickle cell disease have a stroke, twice that number develop more subtle neurological damage (Fig. 23.10), often manifest with poor concentration and school performance **Adenotonsillar hypertrophy** – causing sleep apnoea syndrome leading to nocturnal hypoxaemia, which can cause vaso-occlusive crises and/or stroke **Cardiac enlargement** – from chronic anaemia **Heart failure** – from uncorrected anaemia **Renal dysfunction** – may exacerbate enuresis because of inability to concentrate urine **Pigment gallstones** – due to increased bile pigment production **Leg ulcers** – uncommon in children **Psychosocial problems** – difficulties with education and behaviour exacerbated by time off school may occur

Figure 23.8 Clinical manifestations of sickle cell disease.

Box 23.2 Drugs, chemicals and food which can cause haemolysis in children with G6PD deficiency (British National Formulary for Children 2020).

Definite risk drugs

- Sulphonamides (including co-trimoxazole)
- Fluoroquinolones (ciprofloxacin)
- Nitrofurantoin

Possible risk drugs

- Quinine (acceptable in acute malaria)
- Chloroquine (acceptable in acute malaria and chemoprophylaxis)
- Aspirin (in high doses)
- Sulfonylureas

Chemicals and food

- Naphthalene in mothballs
- Fava beans (broad beans) in some G6PD variants

APPROACH TO THROMBOCYTOPENIA

Definition of thrombocytopenia: **platelet (PLT) count < 150,000/μL**

PRESENTATION

HISTORY

Bleeding Hx

- Provoked (trauma, surgery) or spontaneous
- Deep or superficial bleeds

Red Flag Symptoms

! Fever, weight loss, night sweats, bone pain, fatigue

- Prodromal illness
- Recent live vaccination (MMR)
- Recent travel
- Dietary History
- Family Hx of bleeding disorders
- Review Medications list
- If newborn ask about maternal PLT count, medical history and medications

PHYSICAL EXAM

- ABCs and vital signs (stable or unstable)
- Purpura, petechiae, ecchymoses, mucocutaneous bleeding
- Altered consciousness, abnormal pupils, slurred speech
- Lymphadenopathy (malignancy)
- Hepatosplenomegaly
- Swollen joints or rash

INVESTIGATIONS

CBC (isolated PLT vs. pancytopenia)

- Check previous PLT counts

Peripheral blood smear

Bone marrow examination ONLY IF:

! Red Flag Symptoms
! Involvement of other blood cell lines (anemia or neutropenia)
! Blasts on smear

SIGNS AND SYMPTOMS

Platelet (x 10^3 /μL)	Example of Bleeding Risk
> 100	Asymptomatic
50 - 100	Post-operative bleeding & bruising
20 - 50	Petechiae, purpura, ecchymoses
5 - 20	Epistaxis or gingival bleeding
< 10	GI bleeding, heavy menstrual bleeding or intracranial hemorrhage

IMMUNE THROMBOCYTOPENIA (ITP)

- **#1 etiology** in children
- Sudden severe drop in PLT count often associated with petechiae and mild bruising
- Ask about **recent viral illnesses** or **live vaccine** administration
- Majority recover with **observation**, however, may require **corticosteroids** or **IVIG**

DIFFERENTIAL DIAGNOSIS

Thrombocytopenia

PLT Destruction

Immune Mediated

- Immune Thrombocytopenia
- HIV, Hep C
- Neonatal alloimmune thrombocytopenia
- Lupus, Juvenile Idiopathic Arthritis
- Neonatal autoimmune thrombocytopenia

Consumptive

- Hemolytic Uremic Syndrome
- Disseminated Intravascular Coagulopathy

Decreased PLT Production

- Malignancy (leukemia, lymphoma)
- Medications (chemotherapy)
- Infectious (sepsis, viral)
- Nutritional deficiencies (B12, folate, iron)
- Inherited & Congenital (Wiskott-Aldrich Syndrome)

Splenic Sequestration

- Hypersplenism (infection, sickle cell, malignancy)
- Von Willebrand Disease

! DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC) !

- ↑ thrombosis & ↑ bleeding
- Prolonged PTT, INR
- Low fibrinogen
- Sick patient requiring PICU
- Identify and treat the underlying cause (e.g., sepsis, trauma or malignancy)
- PLT transfusion may be indicated if significant bleeding
- Transfusion thresholds vary based on clinical situation (<10-100 x 10^3/μL PLT)
- 5-10 mL/kg PLT transfusion (max 300 mL) over 1 hour

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Usman Ahmed (MD 2022, University of Alberta) & Dr. Mark Belletrutti (Pediatric Hematology and Clinical Associate Professor, University of British Columbia) for www.pedscases.com

Sickle Cell Disease: Overview

Definition

Sickle cell disease (SCD) is a group of inherited red blood cell disorders caused by abnormal hemoglobin resulting in acute and chronic complications.

Pathophysiology

- Point mutation in β-globin gene changing amino acid Glu → Val at position 6, resulting in HbS
- HbS polymerizes → red blood cell sickling → vaso-occlusion, changes in blood viscosity, hemolysis, endothelial dysfunction, and inflammation

Presentation

Acute Complications

- Vaso-occlusive Crisis (Acute Pain Episode)
- Acute Chest Syndrome
- Sepsis
- Splenic Sequestration
- Stroke
- Dactylitis
- Priapism

Chronic Complications

- Poor growth
- Renal disease
- Retinopathy
- Osteonecrosis
- Functional asplenia
- Cholelithiases
- Learning & cognitive difficulties
- Silent cerebral infarcts
- Chronic lung disease
- Pulmonary hypertension
- Congestive heart failure

Diagnosis

Newborn screening in many provinces
Hemoglobinopathy investigation

Management

Targeted towards managing & preventing complications

Involve hematology prior to any blood product transfusion or procedure

Education
Teach families splenic palpation and to urgently seek care with rapid splenic enlargement/fever

Prophylactic Penicillin
Prophylaxis against encapsulated organisms as functionally asplenic. Continue to minimum age 5 years

Immunizations
Routine immunizations + PPSV 23

Transcranial Doppler
Screening for stroke prevention begins at age 2

Hydroxyurea
Increases total fetal Hb, decreases WBC. Decreases admissions for Acute Chest Syndrome and pain episodes.

Red Blood Cell Transfusions
Simple or exchange transfusions. Indicated only in certain clinical situations as high risk alloimmunization. Reduces the HbS%.

Hematopoietic stem cell transplant
Currently, the only cure for SCD

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(Genie) Eugene Kwon (Medical Student, University of Alberta) and Dr. Catherine Corriveau-Bourque (Pediatric Hematologist, University of Alberta) for www.pedscases.com

Sickle Cell Disease: Acute Complications

Complications of sickle cell disease arise because Hemoglobin S polymerizes and becomes rigid upon deoxygenation, causing vaso-occlusion and hemolysis.

Triggers for hypoxic states include:


infection


dehydration


stress


extreme temps

Vaso-Occlusive Crisis (Acute Pain Episode)

Vaso-occlusion → hypoxic-ischemic and reperfusion injury

Presentation: Acute pain (commonly long bones, chest, abdomen).

Investigations: Usually a clinical diagnosis, but rule out other causes.

Initial Management:

- Analgesia: acetaminophen, NSAIDs, opioids
- IV fluids

Stroke

Ischemic stroke most common in children, hemorrhagic in adults. High risk of stroke recurrence (60-90%) without secondary prevention.

Presentation: Headache, nausea & vomiting, focal neurologic deficits, seizures, altered level of consciousness.

Investigations: CT/MRI

Initial Management:

- Stabilize vitals
- Red blood cell exchange transfusion

Sepsis

Primary cause of mortality in children. ↑ risk of sepsis from encapsulated organisms as functionally asplenic.

Presentation: Fever and unwell-appearing. Highest risk if <5 years old.

Investigations: CBC+diff, blood culture, other infectious workup as appropriate.

Initial Management:

- 3rd gen cephalosporin +/- vancomycin

Splenic Sequestration

Vaso-occlusion leads to trapping of erythrocytes with rapid painful enlargement of the spleen and acute drop in hemoglobin.

Presentation: Hypotension, tachycardia, LUQ pain, splenomegaly.

Investigations: CBC+diff with retic count

Initial Management:

- Transfusion of pRBCs in small aliquots (beware auto-transfusion from spleen).
- Reassess vitals, hemoglobin, and spleen size regularly.

**If recurrent or life-threatening, consider splenectomy after acute event has resolved.*

Acute Chest Syndrome

Clinically defined as new infiltrate on CXR with respiratory symptoms or fever. Often precipitated by infection.

⚠ May progress rapidly to respiratory failure

Presentation: Chest pain, cough, SOB, tachypnea, fever, hypoxia.

Investigations: CXR, CBC+diff with retic count

Initial Management:

- Optimize ventilation. Incentive spirometry.
- Hydration and analgesia.
- Antibiotics: 3rd generation cephalosporin and macrolide (cover *Mycoplasma, S. pneumoniae*).
- Simple or exchange red blood cell transfusion.

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(Genie) Eugene Kwon (Medical Student, University of Alberta) and Dr. Catherine Corriveau-Bourque (Pediatric Hematologist, University of Alberta) for www.pedscases.com