Common pediatric hematological diseases

Disclaimer:
This lecture was taken from the doctors handouts + the notes given.
The notes are very important but the lecture content is not comprehensive of the topics.

Study the original handouts here

Know hemophilia, vWF Disease, and ITP

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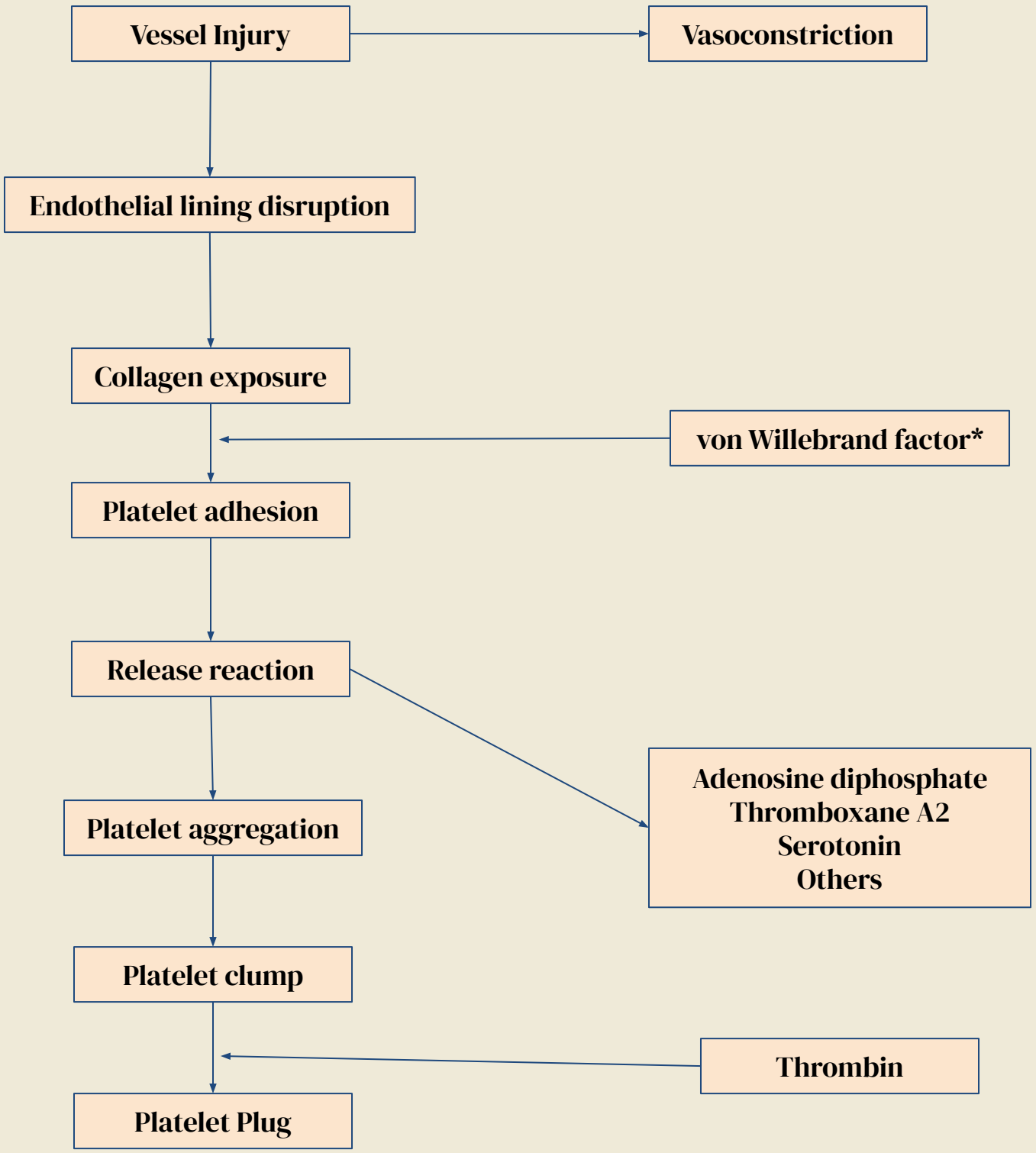
Special thanks to team 437 & Faisal alsaif

Notes

Important

Book

Primary Hemostasis (Formation of platelet plug)



*Defective von Willebrand factor will prevent platelet adhesion from happening.

Normal bleeding takes 6-8 min to stop bleeding, max time to stop bleeding normally is 8 min .

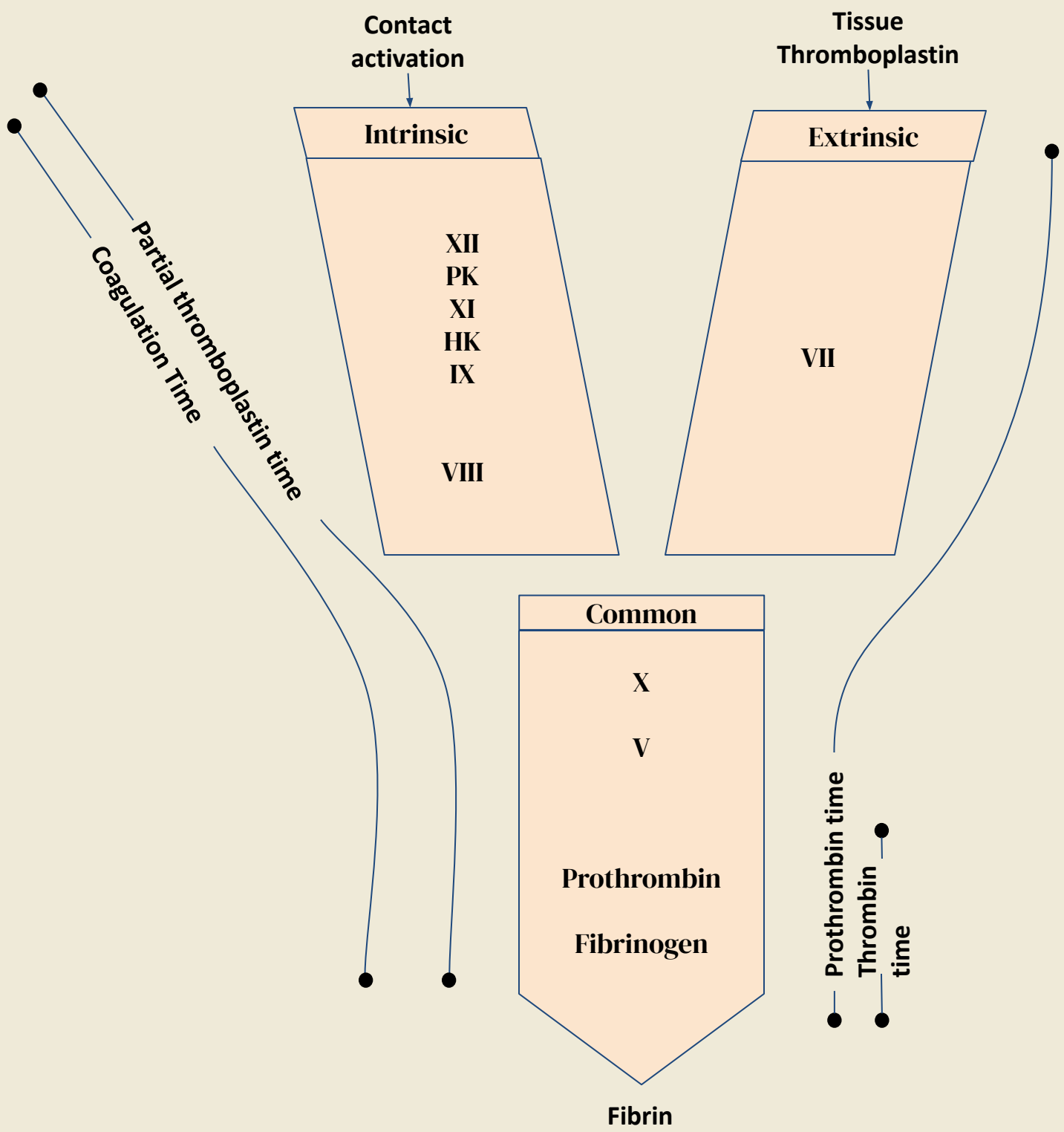
- How children stop bleeding mechanism (normal child)?

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

Secondary Hemostasis (Coagulation cascade)



- **pT prolongation:** VII deficiency
- **pTT prolongation:** XII, XI, IX, VIII
    - XII is Hageman factor, no effect on health but will show a prolonged pTT if its absent
    - XI deficiency is extremely rare, found in ashkenazi jews.
    - IX and VIII are the ones most commonly deficient with prolonged pTT
- **pT and pTT prolongation:**
    - Common pathway pathology: X, V, prothrombin, thrombin

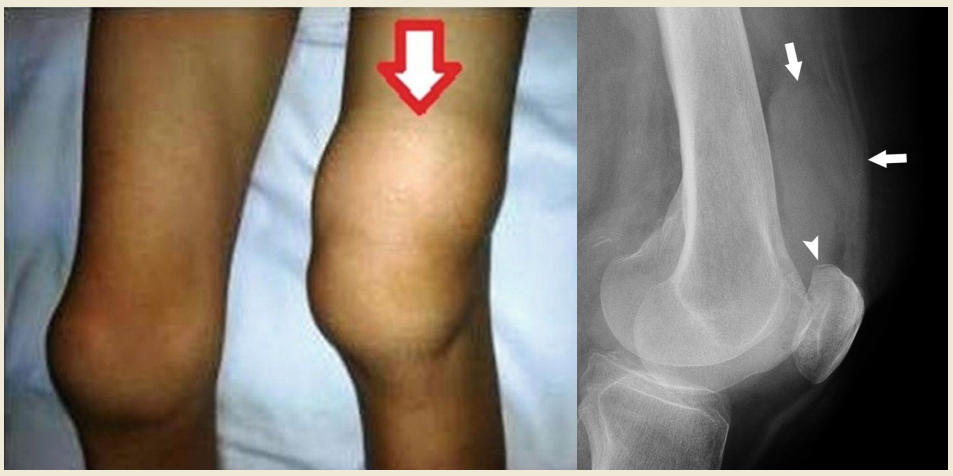
Hemophilia

- Hemophilia is a defect in factor VIII(A) or IX(B)
- 85% of hemophilias are A
- The inheritance pattern is X linked recessive
- The hallmark is hemarthrosis
- First presentation can be bleeding after circumcision or easily bruising.
- Labs show prolonged pTT, Specific factor assay is the confirmatory test

Relationship of factor levels and severity of clinical manifestations of Hemophilia A and B

Type	Percentage (of function) factor VIII/IX	Types of hemorrhage
Severe	<1	Spontaneous; hemarthrosis and deep tissue hemorrhages
Moderate	1-5	Gross bleeding following mild to moderate trauma; some hemarthrosis; seldom spontaneous hemorrhage
Mild	5-25	Severe hemorrhage only following moderate to severe trauma or surgery.
High risk carrier females	30-50	Gynecologic and obstetric hemorrhage

- Hemophilic patients have normal number of factor VIII/IX, they only have a defect in their function.
- Mild types are usually diagnosed after surgeries.



Hemarthrosis

von Willebrand Disease

Differences between von Willebrand Disease and Hemophilia A:

	Von Willebrand Disease	Hemophilia A
Symptoms	Bruising and epistaxis Menorrhagia or mucosal bleeding	Joint bleeding Muscle bleeding
Sexual distribution	Male = females	Males
Frequency	1:200 to 1:500	1:6000 males
Abnormal protein	vWF	Factor VIII
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
Inhibitor frequency	Rare	14 – 25% of patients
History	Abnormal	Abnormal
aPTT	Normal or prolonged	Prolonged
Factor VIII activity	Borderline or decreased	Decreased or absent
-vWF Ag	Decreased or absent	Normal or increased

- If bleeding time is increased. its vWF disease,
- If the bleeding time is normal, Its hemophilia
- vWF disease is more common than hemophilia A/B, remember than vWF can present with low levels of factor 8
- Type 1 vWF disease is the most common
- **Make sure to differentiate between vWF disease and hemophilia**

Type 1	Type 3
The commenset 95% of all VWB deficiency caese	Rarest
Autosomal dominant, one of the parent have it One of them will give the disease to the child	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

Summary

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

Acquired disorders

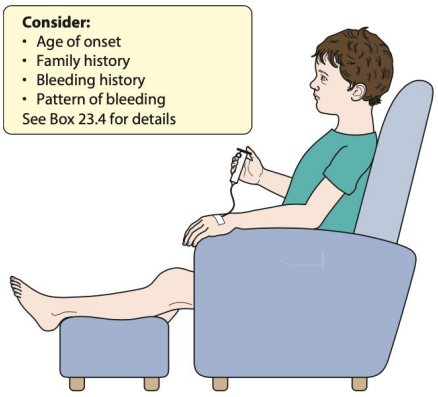
Vitamin K deficiency:
- mainly neonates or early infancy

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

von Willebrand Disease

Differences between von Willebrand Disease and Hemophilia A:

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

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

Treatment of hemophilia:

- ❖ 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.

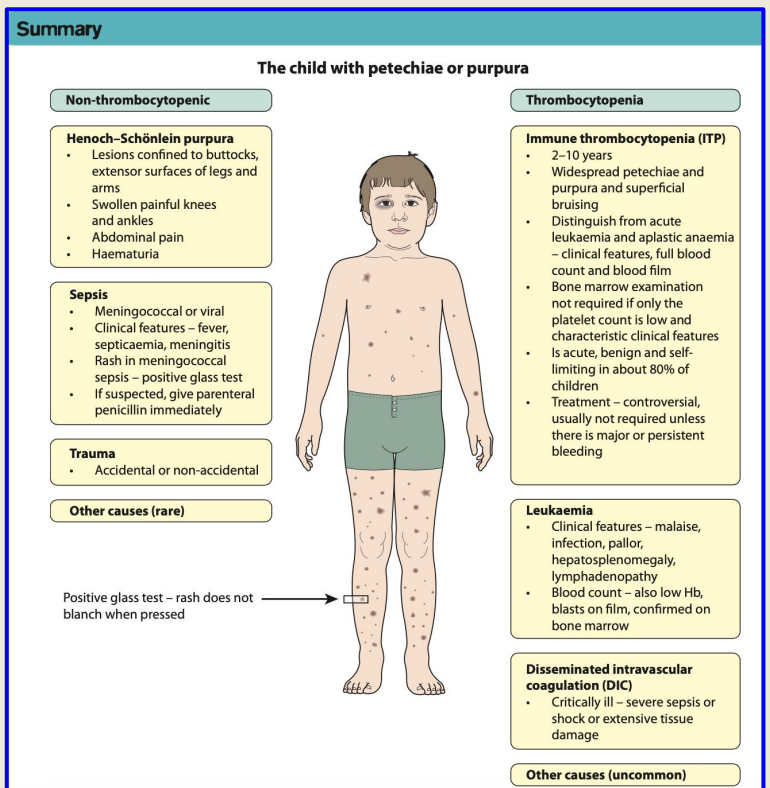
Treatment of von Willebrand Disease : depends on the type and severity.
Type 1: Treating with Desmopressin, which causes secretion of both FVIII and vWF
More severe types of vWD: Treating with plasma-derived FVIII concentrate.

Immune Thrombotic Purpura ITP

- 90-99% of platelet disorders are ITP
- It is a state of low PLT
- Remember, the first thing to be consumed in a sick child are platelets. They might go through DIC
- Acute ITP is less than a year, Chronic >1 year.
- Brain hemorrhages occur within the first month of ITP
- the most common cause is a **viral infection** (1-4 weeks back)
- **Medications** can cause ITP.
- **ITP only occurs in healthy patients. there NEEDS to be a completely clean history, physical and CBC except for the low PLT MCQ**
- **If the spleen is palpable this is leukemia not ITP**
- CBC will be normal in ITP except for the low PLT
- **Admit the patient if PLT <20,000 MCQ**
- **PLT >40,000 follow up after one week MCQ**
- Check T4 and TSH to look for thyroiditis
- ANA, C3, C4 levels for an autoimmune cause
- **Management:**
  - PLT Transfusion is **contraindicated**
  - Give **Immunoglobulins**; administer hydrocortisone and paracetamol before to prevent meningismus and brain hemorrhages.
  - Drug of choice for ITP is **Prednisolone MCQ**
  - **since prednisone takes time to work. Give IgG first with the Prednisolone.**
  - If treatment fails, Go for **Rituximab**

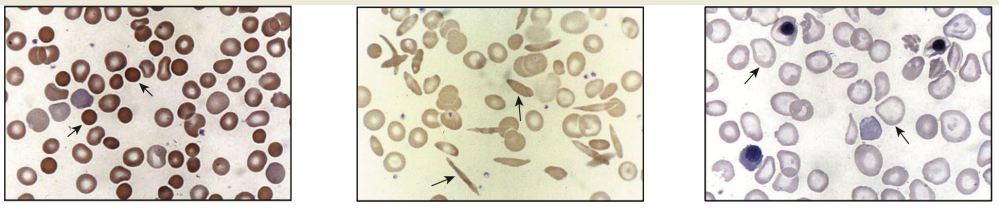
Chronic ITP: Drug treatment is only offered to children with chronic persistent bleeding:
1- thrombopoietin receptor agonists (TPO- RA)
such as: Eltrombopag (available as an oral daily dose.)
● Romiplostim (given as weekly subcutaneous injections).
2- Rituximab, a humanized monoclonal antibody directed 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.



Approach to Anemia
(Tutorial notes)

- Congenital anemia shows up within 1 year
- **Nutritional anemia usually before the age of 5 ask about nutrition (osce). focus on red meat intake**
- Approach to anemia:
  - If the cause is production:
    - Pathology is most commonly neutrotional
    - Most commonly its iron deficiency (microcytic)
    - B12 and folate (macrocytic)
    - No palpable spleen
  - If the cause is RBC destruction (hemolysis):
    - RBCs are destroyed in the spleen, so check for splenomegaly
    - The causes for hemolysis are either:
      - a membrane abnormality
      - hemoglobin abnormality
      - Enzymatic abnormality
    - CBC should show low Hb but normal plt and wbc. otherwise think of systemic diseases like leukemia
    - Peripheral blood smear can show:
      - Spherocytosis: very small and dense RBCs.
      - Elliptocytosis: elongated RBCs.
      - Stomatocytosis: RBCs with fish mouth appearance
      - All will be destroyed by the spleen



(a) (b) (c)

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.

    - Splenectomy should be done at 6 years of age. not before to avoid pneumococcal infections
    - **After the splenectomy the RBCs are still abnormal. MCQ**
    - we remove the spleen to stop the hemolysis but we don't fix the RBCs
    - Reticulocyte count in hemolysis is very important
  - Retics reflect production.
  - **Anemia with a low retic count and no splenomegaly → Bone marrow biopsy MCQ**
  - Sickle cell disease:
    - Present before 9 months
    - Hand foot syndrome is the usual first presentation
    - S Hemoglobin is rigid and gets stuck in capillaries causing a vaso-occlusive crisis
    - treat vaso occlusive crisis with IV fluids (double the maintenance) + analgesia + IV Abx
    - Hb electrophoresis will show one of two types
      - Hb s is 80-90; The african variant. Severe disease. Found along the red sea
      - Hb s Is 50-60; The indian variant. More mild. Found in the eastern province

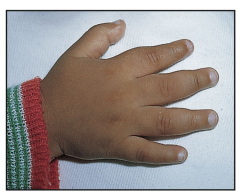
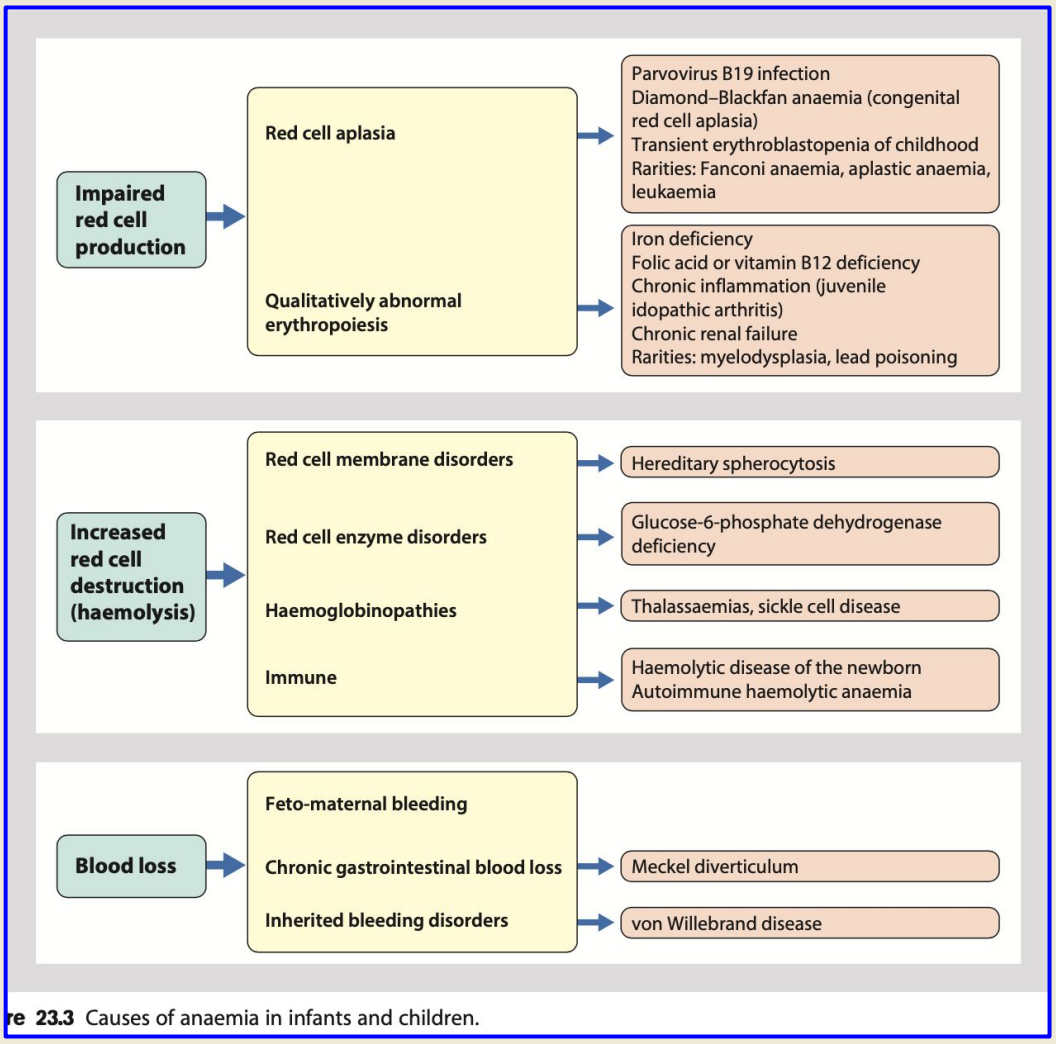


Figure 23.9 Dactylitis in sickle cell disease.

Approach to Anemia
(Tutorial notes)



re **23.3** Causes of anaemia in infants and children.

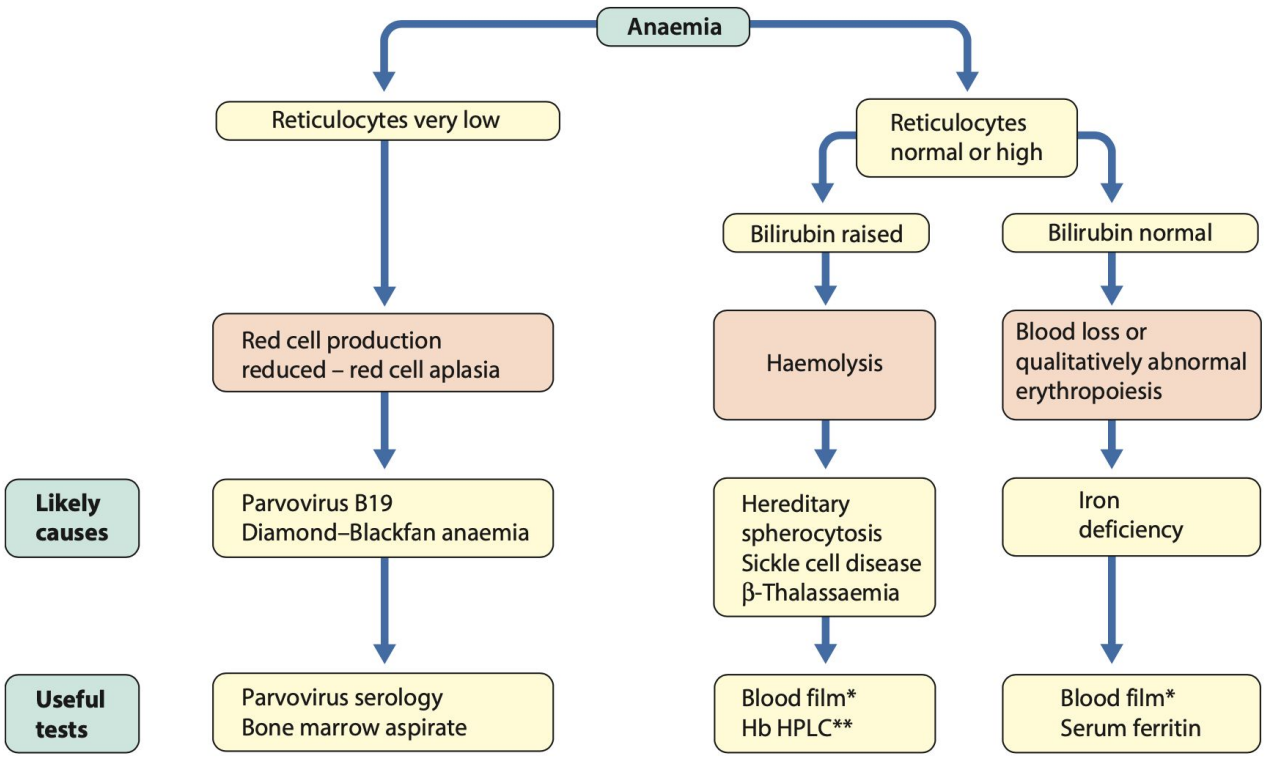
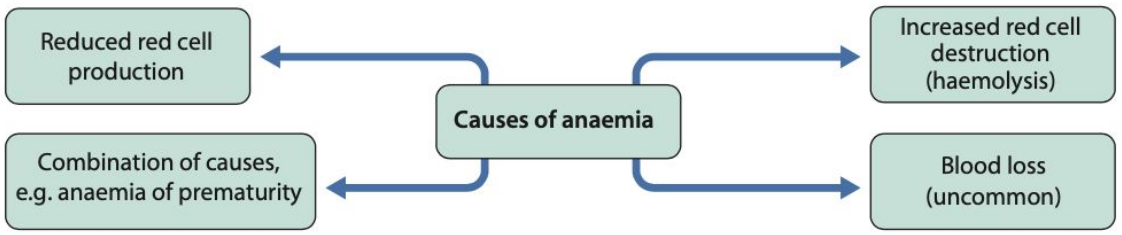


Figure 23.4 Simple diagnostic approach to anaemia in children.

Approach to Anemia
(Tutorial notes)

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