Hematology for Surgeons

6

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6.1 Coagulation Tests

6.1.1 Normal Process of Coagulation

Damaged and exposed endothelium allows:

1. Platelet adherence to collagen, aggregation, and activation (*via* surface glycoprotein and (Von-Willebrand factor—vWF[1])) with the release of thromboxane A2, V, and further vWF.
2. Formation of **"prothrombinase complex"** (*via* VII and exposed (tissue factor—tF) to produce initial **thrombin**.
3. Amplification and activation of XI, IX, and VIII to activate V and produce more thrombin **("thrombin burst").**
4. Thrombin polymerizes **fibrinogen** to form insoluble **fibrin**.

Inhibition of coagulation

5. Thrombin also activates ***protein C and S***, which cleaves V and VIII to inactive components.
6. *Thrombin* binds to ***antithrombin***—preventing its action.

[1] Erik Adolf von Willebrand (1870–1949) Finnish physician: described familial bleeding disorder in 1926.

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Table 6.1 Possible causes for abnormal coagulation tests

	Factors		Possible cause if isolated
PT	II, V, VII, X	Increase	Liver disease, Vit K deficiency, use of warfarin
APTT	VIII, IX, XI, XII	Increase	Hemophilia, Von-Willebrand[1] disease, use of heparin
TT	Reflects fibrinogen to fibrin time		Hypofibrinogenaemia

Notes:
Vitamin K (fat-soluble) dependent—factors II, VII, IX, and X
vWF, Von Willebrand factor[1]; tPA, tissue plasminogen activator; tF, tissue factor

7. Fibrinolysis, by action of ***plasmin*** (activated by tissue plasminogen activator—tPA) on fibrin into smaller soluble fragments (**fibrin degradation products**, of which D-dimers are one part) (Table 6.1).

Most coagulation screens would include Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen level, together with a platelet count (and function tests later if all the parameters are normal).

6.1.2 Hemophilia

- Hemophilia A, a well-known inherited bleeding disorder, arises due to congenital deficiency of coagulation factor VIII.
- Hemophilia B is due to congenital deficiency of coagulation factor IX.

Both of these are X-linked disorders affecting males, and their mothers and daughters are obligate carriers.

- Von-Willebrand disease is the most common inherited bleeding disorder, which is transmitted in an autosomal dominant fashion and is caused by the qualitative or quantitative defects in VWF (Von-Willebrand Factor).
- **Factor concentrates** (Recombinant) are required for replacement therapy immediately before the surgery to minimize the risk of intraoperative bleeding. The factor concentrates should be continued postoperatively to achieve target factor levels according to the type of surgery, aiming to normalize the factor level and maintain the hemostatic level until wound healing is achieved.
- **Desmopressin** (DDAVP) can be used for minor surgery in hemophilia and Von-Willebrand disease and can be given 1 h prior to the procedure to raise factor VIII activity levels for a short time. The peak effect of IV desmopressin is achieved in 30–60 min. Common adverse effects are fluid retention with hyponatremia, hypertension, and flushing.

- **Tranexamic acid** (Anti-fibrinolytic agent) can be given intravenously prior to the surgery, and it should be continued orally for a few days postoperatively.

Platelet Count and Bleeding

The relation of platelet count to bleeding risk is poorly defined because of inadequate clinical studies and also a lack of information about platelet function. In general, there is a risk of spontaneous bleeding with a platelet count <20,000/μL.

Generally, there is a concept of 50,000/μL for surgical hemostasis and prophylactic platelet transfusion for a count <10,000/μL. If the count falls <10,000/μL, then thrombin generation falls proportionately, and it remains maximal if platelets are >10,000/μL.

6.1.3 Blood Transfusion (UK Specific)

The practice of transfusion of whole blood into patients began with the French physician **Jean-Baptiste Denis's** account of a successful (surprisingly) transfusion of 9 oz. of lamb's blood into a 15-year-old boy in 1667.

This was followed by the obstetrician **James Blundell** who successfully transfused donated blood from a husband into his postpartum wife in 1818.

The key discovery of ABO blood groups was made by **Karl Landsteiner**, an Austrian Nobel laureate, in 1901, then later with his discovery of the Rhesus antigen in 1937.

Blood transfusion can be a lifesaving intervention in many surgical conditions. There are hazards of blood transfusion, and blood products are expensive; therefore unnecessary transfusions should be avoided. PBM (Patient Blood Management) is a patient-centered program in UK for good blood management during surgical procedures.

6.1.3.1 ABO System

Two RBC antigens (A and B), with four possible combinations *(AB, A, B, O)*. Plasma always contains contrary (IgM) antibodies (i.e., Group A will have anti-B antibody). Individuals with blood group O are considered universal donors as they do not have any antigens, but their plasma contains anti-A and anti-B, which can cause hemolysis, if present in high concentrations.

Marked racial variation—e.g., Norwegian (predominantly Gp A, 42%), Chinese (↑ Gp B, AB, 34%, invariably Rh(D) +ve).

Table 6.2 Group frequency in UK population

	Rhesus +ve (%)	Rhesus –ve (%)
O	37	7
A	35	7
B	8	2
AB	3	1

6.1.3.2 Rhesus (D) System

The Rh antigen is present in 83% of the population. If it is not present, then the anti-D (IgG) antibody is not normally present (unless there has been previous exposure, usually this is a mother from previous Rh (D) +ve fetus) (Table 6.2)

Women and girls of child-bearing age with Rh-negative blood group should not be transfused with Rh-positive blood unless there is an extreme emergency.

6.1.3.3 Minor Groups

E.g., Lewis (Le), Kell (K)

6.1.4 Need for Blood Transfusion

Any prescription for blood transfusion should include detail of the volume required, any special requirements, e.g., irradiated and rate of infusion.

A Type and Screen takes about 45 min and includes ABO group and a screen for alloantibodies (IAT).

- **Crossmatched blood**
- **Uncrossmatched blood**

One Unit: Single Donation

- Whole blood ~500 mL stored in citrate phosphate dextrose (CPD)
  - Life span ~35 days
- Packed red cells ~350 mL

In adults 1 unit should increase Hb by 1 g/dL—and is usually administered over 4 h, and must be infused within 4 h of removal from the fridge.

If a unit of blood is out from the fridge for more than 30 min, it should be returned to the transfusion laboratory.

- I.e., donor O +ve or O −ve (contains no antibodies). Latter preferred for children.

6.1.4.1 Platelets

No need for crossmatching

- 1 unit (~50 mL)—administered over 30 min

6.1.4.2 Fresh Frozen Plasma

Should be ABO compatible—no need for crossmatching

- 1 unit (150–250 mL), usually single donor—administered over 30 min

6.1.4.3 Cryoprecipitate

No need for crossmatching—Administered over 30 min
Fibrinogen and factors VII and VIII

- Unit (~20 mL)

6.1.5 Transfusion Reactions

- ***Hemolytic reaction (ABO incompatibility)***—invariably arises from a clerical error. The ABO incompatible transfusion occurs in 1:180,000 red cell units transfused. This is rare but causes rapid-onset chest pain, headache, vomiting with signs of shock, rigors, and hemoglobinuria. The patient becomes extremely unwell with shock, DIC, and acute renal failure.
  - **Management**:
    Stop transfusion.
    Resuscitation with ABC (Airway-Breathing-Circulation) protocol and maintain venous access using 0.9% sodium chloride.
    Use BP, pulse, and urine output to guide intravenous fluid management, and the patient can be catheterized if needed.
- ***Allergic Reactions (IgE-Mediated to Most Blood Components).*** Common skin reactions due to histamine release. Ranges from mild urticaria to life-threatening angioedema or anaphylaxis (bronchospasm, ↓ BP).
  - Management:
    Stop transfusion.
    Chlorpheniramine (for mild reaction).
    Hydrocortisone.
    If severe reaction or anaphylaxis—give Intramuscular Adrenaline rapidly effective, adult dose 0.5 mL of 1:1000 (500 μg).
- ***Febrile reaction (nonhemolytic) (anti-leucocyte antibodies)***—usually with a history of past transfusions, onset after few hours of pyrexia and tachycardia. As part of histamine release. Severe reactions may cause anaphylaxis.
  - Management:
    Stop transfusion
    Paracetamol,
    Hydrocortisone/chlorpheniramine (if severe)
    Blood culture and start broad-spectrum antibiotic
- ***Delayed Extravascular Hemolysis*** *(recipient antibody-mediated, e.g., Duffy, Kell)*—manifest as an unexpected fall in Hb at 7–10 days, ↑ jaundice, +ve Coombs' test.

- **TRALI (Transfusion-related acute lung injury**): Occurs when the patient's neutrophils or monocytes react with antibodies in the blood, causing leakage of plasma into alveolar spaces resulting in pulmonary edema. Treatment is supporting with oxygen and ventilator support.
- **TACO (Transfusion-associated circulatory overload):** Occurs in elderly patients with other medical conditions. Treatment is supportive with oxygen therapy and diuretics.
- **TaGVHD (Transfusion-associated Graft-versus-Host disease):** Can occur in immunosuppressed patients due to engraftment of viable T-lymphocytes, which can cause widespread tissue damage. It can be prevented by giving irradiated blood products.

6.1.6 Alternatives to Blood Transfusion (Jehovah's Witness)

- Erythropoietin
- Iron supplementation
- Preoperative autologous transfusion
- Intraoperative and postoperative cell salvage

6.1.7 Coombs' Test[2]

- **Direct antiglobulin test (DAT)**—detects preformed IgG antibodies (usually) on the red cell. +ve DAT can be
  - Immune-mediated (e.g., transfusion reactions, Rhesus disease, drug-induced hemolytic anemia)**.**
- **Indirect antiglobulin test (IAT)**—detects preformed IgG and IgM antibodies in serum. Is used as a screening test for transfused blood, and during pregnancy. A +ve IAT can be caused by Minor blood group incompatibility (Rh, Lewis, Kell, etc.)

6.1.7.1 Transmissible Hazards of Blood Transfusion

- Hepatitis B (1 in 250,000 in USA) (< 1 in 1.2 million donations in UK).
- Hepatitis C (1 in 13,000 in USA) (< 1 in 28 million in UK).
- HIV (1 in 2 million in USA) (<1 in 7 million in UK).
- Variant Creutzfeldt-Jakob[3,4] disease, (vCJD) (no known cases but export of blood products from UK banned since 1999). Leucodepletion of all blood products in UK since 1999.

[2] Robin Coombs (1921–2006)—British immunologist.

[3] Heinz Gerhard Creutzfeldt (1885–1964) German neuropathologist.

[4] Alfons Maria Jakob (1884–1931) German neurologist.

6.1.8 Sickle Cell Disease

- >200,000 new cases worldwide.
- Sickle cell disease (SCD) includes a number of hemoglobinopathies causing chronic hemolytic anemia and painful episodes associated with the sickle cell gene (valine substitution for glutamic acid at position 6 on β-globin chain).
- Homozygous SCD (Hb SS).
- Compound heterozygotes with Hb C (Hb SC) (milder phenotype).
- Heterozygotes with H β-thalassemia (Hb Sβ).

The abnormal Hb provokes a change in red cell shape (sickle) which tends to cause small vessel occlusion in a wide variety of vascular beds.

6.1.8.1 Sickle Cell Crisis

Not usually seen in the first year but may manifest as

- Dactylitis[5] (i.e., pain/swelling in fingers and toes).
- Long bone pain (younger children).
- Abdominal pain (older children and adolescence.
  - Difficult to differentiate from surgical pathology (e.g., gallstones, appendicitis, intussusception).
  - SCD—↓ incidence of appendicitis.

6.1.8.2 Clinical Features

- Stroke (commonest cause in childhood) (up to 10% of affected children)
- Acute chest syndrome (the commonest cause of death)
- **Sequestration**—causing acute hemolytic anemia and splenomegaly. A similar phenomenon can be seen in the liver in older children
- Orthopedic, e.g., avascular necrosis of hip, osteomyelitis
- Gallstones—causing cholecystitis and choledocholithiasis
- Priapism[6]

6.1.9 Surgery in the Child with SCD

Children with SCD may well require surgical intervention either as a result of their pathology or incidentally. The process, whether elective or emergency, needs to be safe, and various areas of best practice are highlighted.

Preoperative planning for transfusion(s) to reduce the incidence of postoperative sickle cell complications.

[5] Daktylos δάχτυλο—Greek for "finger"

[6] Priapus—minor Greek fertility god, always denoted with permanently erect penis.

- Formerly the key component of preparation was to dilute the sickle cells within a more morphologically normal RBC population (typically aiming for a sickle cell percentage of <30%).
- Latterly, a more tolerant attitude has been adopted whereby the aim has been to aspire to a target hematocrit of >30%.
  - If Hb < 80 g/L, a **simple top-up transfusion** can suffice to increase the hematocrit and oxygen-carrying capacity and helps in diluting the HbS percentage. Simple transfusion—for major procedures (e.g., open cholecystectomy).
  - **Exchange transfusion** is usually arranged a week before surgery for those with Hb > 80 g/L needing major surgery and have severe phenotype (ACS, stroke, etc.).
- Hypothermia
  - Use of warming blankets, warmed intraoperative fluids, and temperature monitoring is reasonable standards to avoid peripheral vasoconstriction.
- Tourniquet
  - **Avoid** in operations such as hypospadias, hand surgery, and orthopedic procedures.

6.1.10 Acute Chest Syndrome

Definition—"the onset of a new lobar infiltration on chest X-ray, excluding atelectasis, accompanied by fever >38.5 °C, respiratory distress or chest pain."

The cause is multifactorial, including infection, pulmonary sickling and sequestration and fat embolism secondary to bone infarction.

Not uncommon complication (~10%) of invasive surgery (e.g., laparotomy) due to sickling in the pulmonary vasculature. Typically occurs 2–3 days post-surgery with increasing dyspnoea and high temperature. It may be limited by aggressive chest physiotherapy and early mobilization.

6.1.10.1 Management

- Oxygenation and ventilatory support
- Bronchodilators
- Broad-spectrum antibiotics
- Transfusion, possible exchange transfusion in severe cases
- Pain management

6.1.11 Leucocytosis or Neutropenia

While leucocytosis can be an indicator of infection, neutropenia can predispose to infection. CRP is a gold standard marker of inflammation.

Antimicrobial therapy might be indicated for treating the infection or for infection prophylaxis in case of neutropenia.

Further Reading

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2. Firth PG. Anaesthesia for peculiar cells—a century of sickle cell disease. Br J Anaesth. 2005;95:287–99.
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