Transfusion Guide for Clinicians

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Forewords
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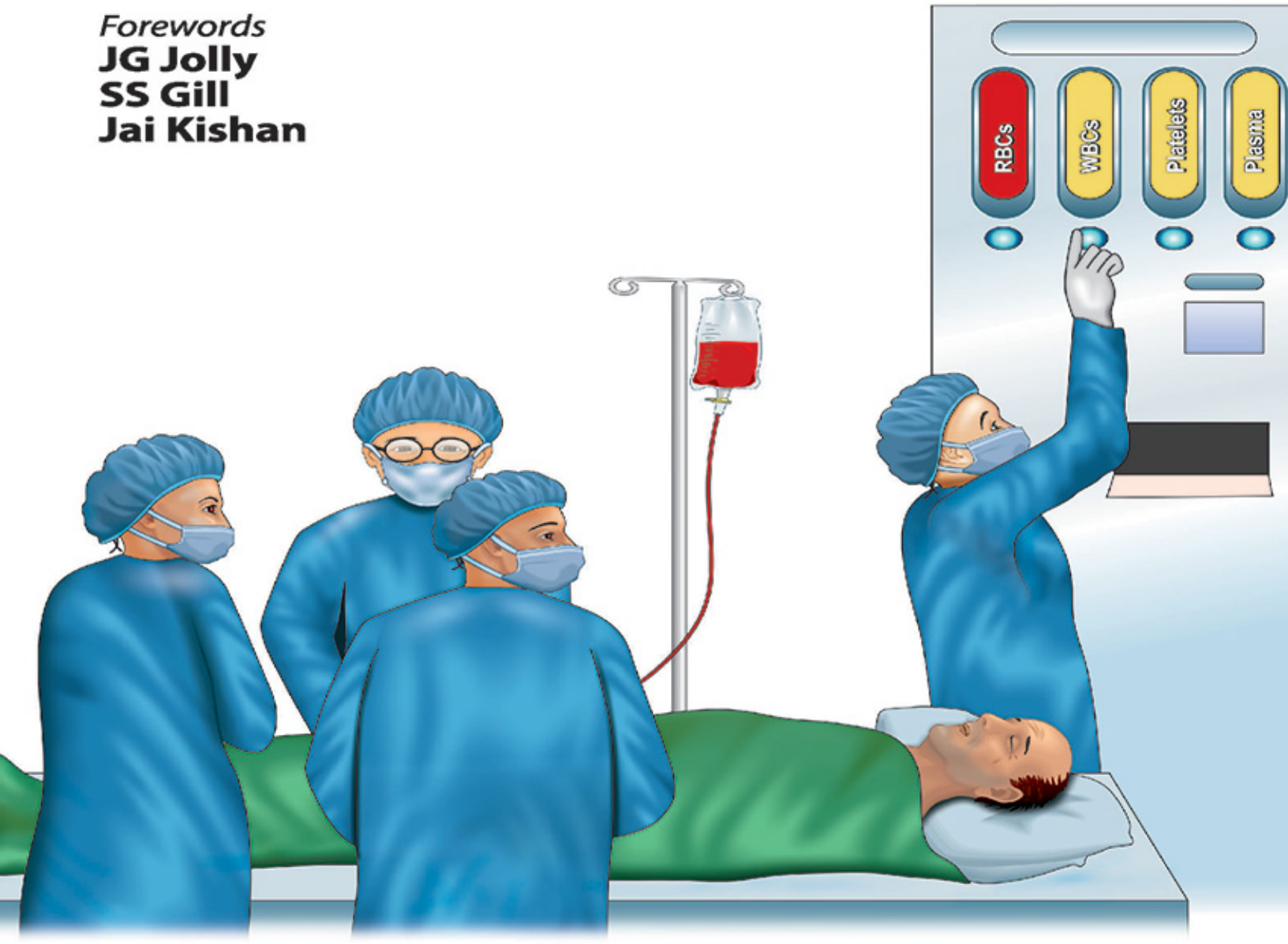

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4 Transfusion in Clinical Medicine

MASSIVE TRANSFUSION

This is defined as transfusion of one, or more than one, blood volume in 24 hrs or transfusion of 10 units of whole blood of 450 ml in 24 hrs or 20 units of PRBCs in 24 hrs or transfusion of blood equal to 50% of blood volume within in 3 hrs or less or a rapid transfusion at more than 150 ml/minute or 70 ml/kg in adults or 80-90 ml/kg in children or infants.

Ultra massive transfusion: Transfusion of blood equal to or more than five times one's own blood volume.

Clinical Settings with Massive Transfusion

1. **Traumatic**
   - Trauma to major blood vessels.
   - Pelvic or femoral fracture.
2. **Non-traumatic**
   - Gastro-intestinal bleed, e.g. variceal bleed.
   - Ante-partum hemorrhage, e.g. abruptio placenta, placenta previa.
   - Post-partum hemorrhage, e.g. Atonic uterus, inversion of uterus.
   - Cardio-pulmonary bypass surgery.
   - Exchange transfusion.

Sequelae of Massive Transfusion

- Hypothermia: Hypothermia can cause leftward shift of the oxygen dissociation curve, impairs platelet functions, increases chances of hypocalcemia and causes ventricular arrhythmias. The patient is kept warm, warmed blood may be used by administering blood through standardized blood warmers.
- Coagulopathy: Carefully monitor coagulation profile (PT, APTT).
- Dilutional thrombocytopenia: Managed by platelet transfusions. This effect is clinically significant when the patient receives 15-20 units of blood.
- Pulmonary insufficiency: Due to microvascular blockage by micro aggregates in stored blood.
- Graft versus host disease.

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- DIC.
- Citrate toxicity: More when several FFP units are transfused.
- Electrolyte imbalance: Monitor serum electrolytes closely.
- D-lactate encephalopathy syndrome.

Indications for Components

- Platelets are to be transfused with platelet counts between 50,000–1,00,000/µl in the presence of micro-vascular bleed.
- FFP is to be transfused when PT or PTTK > 1.5 times the normal value (give ABO compatible) in a dose of 15 ml/kg.
- Cryoprecipitate is given when APTT is prolonged and fibrinogen < 100 mg/dl (give ABO compatible) in a dose of 10-15 packs in an adult in addition to FFP, if factor VIII/fibrinogen concentrate is not available.

The policy of release of blood in emergency is given in Table 4.1.

Table 4.1: Cross matching policies in emergency release of blood

Time of release of blood	*Policy*
Within 5 minutes of receipt of sample	O negative packed red cells
Within 15 minutes of receipt of sample	Type specific uncrossmatched blood
Within 45 minutes of receipt of sample	Type specific crossmatched blood

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation (DIC) is an acquired coagulopathy. It is caused by abnormal and uncontrolled activation and consumption of coagulation factors, fibrinogen and platelets, causing small thrombi within the vascular system throughout the body. Free thrombi in the vascular systems are the cause of DIC. There is over production of fibrinolytic enzymes, which break down the clots formed, leading to an increase in fibrin degradation products. All the coagulation factors, platelets, and fibrinogen are consumed faster than they are replaced, resulting in widespread bleeding.

Causes of DIC

- Trauma
- Septicemia
- Disseminated malignancy
- Obstetric complications
  - Premature separation of placenta
  - Retained products of conception
  - Retained dead fetus
  - Amniotic fluid embolism.
- Hemolytic transfusion reaction

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- Neonatal DIC secondary to sepsis and necrotizing enterocolitis
- Prolonged hypoxia or hypovolemia including shock.

Symptoms

- Severe/sudden bleeding from many sites in the body
- Sudden onset of bruising
- Oozing from venipuncture site.

Microvascular thrombi may cause organ dysfunction leading to:

- Respiratory distress
- Renal failure
- Jaundice and
- Coma.

Laboratory Findings

- Thrombocytopenia: Platelet count is less than 50 x 10^9/L and the patient is bleeding
- Peripheral smear shows fragmented cells
- Prolonged PT—1.5 to 1.8 times of control (N = 10—14 sec.)
- APTT—1.5 to 1.8 times of control (N = 25—35 sec.)
- Reduced fibrinogen
- Elevated fibrin degradation products (FDP), D-dimers are more specific (N < 10 mg/L).

If laboratory tests are not available, use the following simple clotting test for DIC:

1. Take 2-3 ml of venous blood into a clean plain glass test tube (10 x 75 mm).
2. Hold the tube in your closed fist to keep it warm (i.e. body temperature).
3. After 4 minutes, tip the tube slowly to see if a clot is forming. Then tip it again every minute until the blood clots and the tube can be turned upside down.
4. The clot will normally form between 4 and 11 minutes but, in DIC, the blood will remain fluid well beyond 15 to 20 minutes.

If DIC is suspected, do not delay treatment while waiting for the results of coagulation tests.

Management

- Correct any reversible cause.
- If patient is anemic, replace red cell losses with the freshest whole blood available as it contains fibrinogen and most other coagulation factors.
- Closely monitor coagulation profile, aPTT, PT, TT, fibrinogen levels and platelet count.
- Maintain hemostatic functions:
  - If PT and APTT are prolonged and the patient is bleeding, give FFP (15 to 20 ml/kg body wt.)

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- If fibrinogen is low (< 80 mg/dl), TT is prolonged, give cryoprecipitate (6 to 12 units/kg body wt. or 8-10 packs in adults). 1 unit would raise levels of fibrinogen by 50 mg/dl.
- If the platelet count is less than 50×10^9/L, and the patient is bleeding, give platelet concentrates 4-6 units or one unit of apheresis platelet.

The use of heparin is not recommended in bleeding patients with DIC.

- Exchange transfusion may be an effective therapy for infants who suffer severe symptomatic DIC following birth asphyxia.

Monitoring of the case is done by estimating:

- Prothrombin time (PT)
- Activated partial thromboplastin time (APTT)
- Fibrinogen level
- Hb and Hct.

MULTI-TRANSFUSED PATIENTS

Multiple transfusions are the repeated transfusions of whole blood or red cell concentrate over a long period of time (months or years).

Indications

1. Hypoproliferative anemias:
   - Aplastic anemia
   - Drug induced hypoplastic anemias
   - Radiation induced marrow depression.
2. Hemolytic anemias:
   - Thalassemia major
   - Sickle cell anemia
   - Autoimmune hemolytic anemia
   - Paroxysmal nocturnal hemoglobinuria.
3. Anemias of chronic disorder:
   - Renal insufficiency
   - Hepatic failure
   - Chronic inflammation
   - Malignancy.

In hematological conditions like thalassemia, aplastic anemia and hemophilia, and some hemato-oncologic malignancies, the patient is often transfusion dependent. Certain considerations need to be kept in mind during therapy in such situations.

Guidelines for multiple transfusion:

- Compatibility testing should be done carefully by indirect antiglobulin technique.
- Before commencing the transfusion regime, the patient must be vaccinated for hepatitis B virus infection.

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- Packed red cells are preferred to whole blood.
- Leuco-reduced red cells must be used to minimize the febrile transfusion reactions and red cell alloimmunisation.
- Patient receiving regular multiple transfusions should be given iron chelating agents to prevent hemosiderosis.
- Careful monitoring for development of any transfusion transmissible infections.

SICKLE CELL ANEMIA

Oxygen affinity and 2, 3–DPG levels of RBCs of sickle cell disease are elevated. Symptoms of anemia are usually less.

Indications for Transfusion Therapy in Sickle Cell Disease

- Severe infection
- Severe vaso-occlusive or painful crisis refractory to medical management
- Acute splenic sequestration
- Stroke
- Chronic leg ulcer
- Priapism
- Liver infarction.

Laboratory Investigations

- Hb of 5 -11 g/dl (usually low in relation to symptoms of anemia).
- Blood film to detect sickle cells, target cells and reticulocytosis.
- Sickle solubility or slide test to identify sickle cells.
- HbF quantitation to detect elevation of HbF.
- Hemoglobin electrophoresis to identify abnormal hemoglobin patterns. In homozygous HbSS, no normal HbA is detectable.

Transfusion in Sickle Cell Crisis

For Prevention of Crisis

1. Transfusion is not indicated purely to raise a low Hb. Patients with SCD are well-adapted to Hb of 7-10 g/dl and are at risk of hyperviscosity if the Hb is raised significantly above the patient's normal baseline without a reduction in the proportion of sickle cells.
2. Aim is to maintain a sufficient proportion of normal HbA (about 30% or more) in the circulation to suppress the production of HbS containing red cells and minimize the risk of sickling episodes.
3. Regular red cell transfusion has a role in reducing the frequency of crisis in (homozygous) SCD and preventing recurrent strokes. It may also assist in preventing recurrent life-threatening acute lung syndrome and chronic sickle cell lung disease.

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4. Stroke occurs in 7-8% of children with SCD and is a major cause of morbidity. Regular transfusions can reduce recurrence rates for stroke from 46-90% to less than 10%.
5. Long term effects of multiple transfusions like iron overload, transfusion transmitted infections & alloimmunization occur.

For Treatment of Crisis and Severe Anemia

1. Transfusion is indicated in severe acute anemia (Hb < 5 g/dl or > 2 g/dl below the patient's normal baseline).
2. Prompt transfusion in sequestration crisis and aplastic crisis can be life-saving. Aim is to keep the Hb level of 7-8 g/dl.

Sequestration Crisis

1. The patient presents with the equivalent of hypovolemic shock due to loss of blood from the circulation into the spleen.
2. The circulating blood volume must be urgently restored with intravenous fluid.
3. Transfuse blood if needed.

Aplastic Crisis

Aplastic crisis is usually triggered by infection: e.g. parvovirus B19. There is transient acute bone marrow failure and transfusions may be needed until the marrow recovers.

Management of Pregnancy and Anesthesia in SCD

1. In bad obstetric history or frequent crisis, routine transfusions are given during pregnancy.
2. Transfusion aiming to bring the proportion of HbS below 30% during preparation for delivery or surgery with anesthesia.
3. Anesthetic techniques and supportive care should ensure that blood loss, hypoxia, dehydration and acidosis are minimized.

Transfusion of Fresher RBCs

Fresher RBCs (less than 6 days old) from non-sickle cell donors, 10-15 ml/kg body weight is given every 12 hours until the hemoglobin levels increases to 12-13 g/dl.

Exchange Transfusion

- Simple transfusion is time consuming and increases the risk of fluid overload and congestive heart failure.
- So partial exchange transfusion is advised as an alternative, which is more rapid and effective method to decrease the level of HbS.

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- Partial–exchange transfusion in sickle cell anemia is indicated in:
  - Painful crisis
  - Heart disease
  - Cerebrovascular accidents (stroke).

THALASSEMIA

Considerable progress has been made in transfusion therapy for patients with homozygous β-thalassemia (Thalassemia major)

1. Aim to transfuse red cells regularly early in the course of disease in sufficient quantity to suppress erythropoiesis to prevent skeletal deformities, improve O_2 delivery to tissue and inhibit iron absorption from GIT.
2. Small transfusions are preferred because they need less blood and suppress red cell production more effectively.

Management

1. Blood transfusion: The aim is to prevent anemia and to maintain sufficient hemoglobin level so as to suppress the endogenous erythropoiesis.
   Management of complications of blood transfusion:
   - Immediate transfusion reactions:
     - Non-hemolytic Febrile Transfusion Reaction (NHFTR).
     - Alloimmunization.
   - Iron overload:
     - Cardiac complications
     - Endocrine abnormalities—e.g. hypogonadism, growth retardation:
   - Infections: HIV, HCV, HBV.
   - Psychological.
2. Iron chelation with vitamin C and folate
3. Neocytes
4. Splenectomy
5. Bone marrow transplantation
6. Modulation of HbF
7. Gene therapy.

Blood Products Used in Thalassemics

- RBC should be < 6 days old.
- Leukocyte: Reduced packed red cells are preferred.
- Filtered blood products
- Saline washed red cells.
- Neocyte transfusion

Transfusion regimens are given in Table 4.2.

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Table 4.2: Transfusion regimens in thalassemia	
Regimens	*Pre-transfusion hemoglobin (g/dl)*
Super transfusion	≥ 12
Hyper transfusion	≥ 10

Hyper transfusion regimen is preferred presently, where the mean Hb of the patient is maintained at 12 g/dl. This is useful as it ensures good physical development, ensures freedom from intercurrent infections, prevents hepatosplenomegaly and excess iron absorption from GIT.

Post transfusion hemoglobin should not exceed 15 g/dl to prevent thromboembolism.

Dose: 10-20 ml/kg body weight every 3-4 weeks. (8 ml PRBCs / kg raise the Hb by 1 g/dl in children)

Rate of transfusion depends upon the cardiac status and base line hemoglobin value is given in Table 4.3.

Table 4.3: Rate of transfusion depending on cardiac status and wbaseline Hb		
Status	*Rate of transfusion*	*Amount of blood transfused*
No cardiac problem	5-7 ml/kg/hr	15-20 ml/kg
Cardiac problem present or Hb < 5 g/dl	2 ml/kg/hr	5 ml/kg

Transfusion interval—every 3-4 weeks

Complications of BT

- Transmission of blood transmissible infections
- Isoimmunization
- Iron overload.

Prevention

- Use blood of voluntary repeat donor
- Screening of HIV, hepatitis B and C should be done by sensitive and specific tests
- Immunize all newly diagnosed thalassemics against hepatitis B.

Iron Overload

As a result of multiple transfusions, transfusion hemosiderosis develops. About 200 mg of iron accumulates with each unit of transfused blood.

Iron Chelation in Thalassemia

- Desferrioxamine, the most effective iron-chelating agent which is given subcutaneously by infusion pump (1.5-2 gm over 8-12 hrs) for 5-6 nights to produce adequate iron chelation.
- It is started as early as possible (at 3 years of age).

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- Oral iron chelating agent Deferiprone (Kelfar) has been recently been introduced and is likely to help these patients.

Vitamin C

It converts ferric form of the iron to ferrous form and facilitate mobilization of iron stores to free iron.

Neocytes Transfusion

Neocytes are young RBCs with low specific gravity. Survival of neocytes is 100 days, while that of red cell survival is 60 days. Neocyte transfusion (1) reduces blood requirement (2) increases transfusion intervals and (3) reduces iron overload.

Splenectomy

- It should be done in children more than 5 years of age
- Pre-surgical prophylaxis with penicillin, pneumococcal and hepatitis B vaccine should be given.

Indications

1. RBC consumption annually increases to more than 1.5 times of previous requirement.
2. Cytopenias leading to infection or bleeding.
3. Massive splenomegaly leading to pain in abdomen or there is an imminent risk of rupture of spleen.
4. Chromium studies indicating RBC survival of less than 15 days.

Prevent Isoimmunization

- Screen all patients for irregular antibodies
- Compatibility testing should be done by antihuman globulin technique
- Use of leucocyte filters.

Bone Marrow Transplantation

Success rate post BMT is 70-80%. The outcome depends upon the following factors:

- Adequate iron chelation
- Presence of liver fibrosis
- Hepatomegaly.

HEMOPHILIA

- Second most common hereditary X-linked recessive bleeding disorder affecting male. The typs hemophilia depending on the activity of deficient factr is given in Table 4.4.

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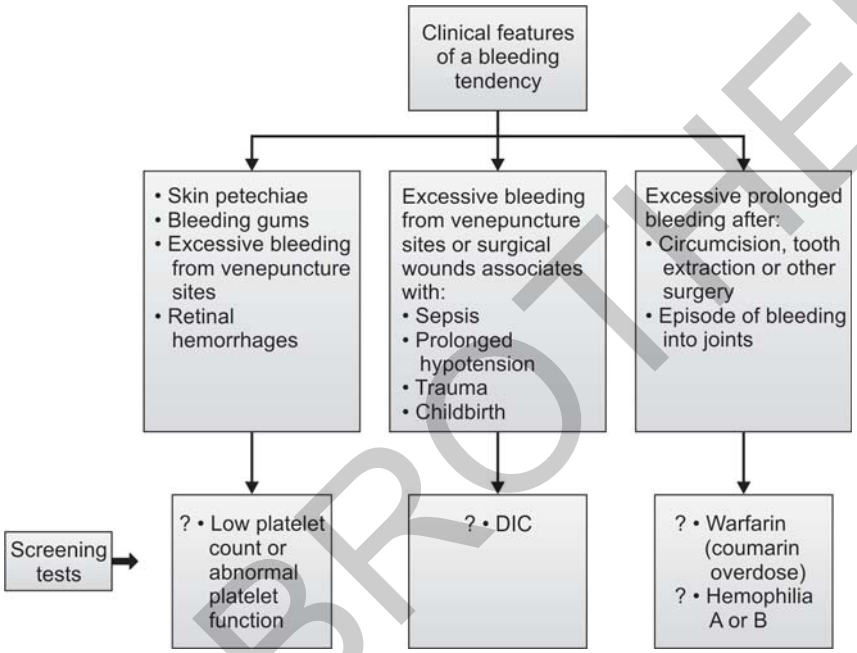
Flow chart 4.1: Source of bleeding suggesting the cause



- Normal levels of factor VIII levels in plasma is 0.5–2.0 IU/ml.
- Sign and symptoms suggestive of bleeding disorder.

Source of bleeding usually suggests the most likely cause (Flow chart 4.1):

- Bleeding from mucous membranes suggests low platelet count or platelet abnormalities or von Willebrands disease or vascular defects.
- Muscle and joint bleeding or bruising suggest hemophilia A or B.

Lab Findings

- Normal PT
- Prolonged APTT—corrects with the addition of normal plasma

Table 4.4: Types of hemophilia

Factor VIII or IX activity (%age)	*Type of hemophilia*	*Incidence*	
		Hemophilia A	*Hemophilia B*
6-30	Mild	15	20
1-5	Moderate	15	30
< 1	Severe	70	50

Laboratory investigations in bleeding disorder with typical results are given in the Table 4.5.

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Table 4.5: Laboratory investigations in bleeding disorders—typical results

	Thromb-ocytopenia	*Heparin*	*DIC*	*Fibrinolytic therapy*	*von Willebrands disease*	*Liver disease*	*Warfarin*	*Hamophilia A*	*Hamophilia B*	*Massive transfusion*
Platelet count	↓	N	↓	N	N/↓	N/↓	N	N	N	↓
PT	N	N	↑	↑	N	↑ severely	↑	N	N	↑
APTT	N	↑	↑	↑	↑	↑	↑	↑	↑	↑
TT	N	↑	↑	↑	N	↑	N	N	N	N/↑
Fibrinogen conc.	N	N	↓	↓	N	↓	N	N	N	N/↓
FDP	N	N	↑	↑	N	N/↑	N	N	N	N/↑

N = Normal

Reversal of prolonged TT by protamin indicates heparin is present

PBF fragmentated RBCs

Ristocetin cofactor activity decreased BT ↑ (template method)

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Blood Products Used:

Packed RBCs (< 5 days old) preferably leucodepleted.

Treatment

Acute hemorrhage

- Local methods—pressure and ice packs
- Desmopressin for mild to moderate hemophilia
- Anti fibrinolytic agents, e.g. amino caproic acid, tranexamic acid.

Replacement Therapy

- Use virus-inactivated factor concentrates to prevent the risk of transmission of HIV and hepatitis B and C
- If coagulation factor concentrates are not available, use the following:
  - Hemophilia A: Cryoprecipitate (Cryo)
  - Hemophilia B: Fresh frozen plasma (FFP)

  Dosage of factor VIII, factor IX and alternatives for treatment are given in Tables 4.6 and 4.7.

Table 4.6: Dosage of factor VIII and alternatives for treatment of hemophilia A

Severity of bleed	*Dosage*	*Supplied as:*	
		Factor VIII concentrate (500 IU/bottle)	*Cryoprecipitate (80-100 IU/pack)*
Mild bleed: Nose, gums, etc.	14 IU/kg	1-2 bottles (adult)	1 pack/6 kg
Moderate bleed: joint, muscle, gastrointestinal tract, surgery	20 IU/kg	2-4 bottles (adult)	1 pack/4 kg
Major bleed: e.g. cerebral	40 IU/kg	4-6 bottles (adult)	1 pack/2 kg
Prophylaxis for major surgery	60 IU/kg	6-10 bottles (adult)	1 pack/1kg

1. Cryoprecipitate pack containing 80-100 IU of Factor VIII, usually obtained from 250 ml of FFP.
2. For a mild, moderate or severe bleed, repeat dose 12-hourly if bleeding persists or swelling is increasing.
3. With more severe bleeds, it is usually necessary to continue treatment with half of total daily dose 12-hourly for 2-3 days or occasionally longer.
4. For prophylaxis for major surgery, start therapy 8 hours before surgery. Continue 12 hourly therapy for 48 hours postoperatively. If no bleeding occurs, gradually slow down over next 3-5 days.

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5. As adjunct to factor replacement in mucosal or gastrointestinal bleeding and surgery, give fibrinolytic inhibitor: Tranexamic acid (oral): 500-1000 mg 3 times/day. Do not use for hematuria.
6. In an emergency, if none of the above is available, use FFP to treat bleeding in hemophiliacs (give 3 packs initially).
7. Careful assessment of the patient's fluid intake is important to avoid fluid overload when using FFP or large doses of cryoprecipitate.

Table 4.7: Dosage of factor IX for treatment of hemophilia B

Severity of bleed	*Dosage*	*Supplied as*	
		Factor IX concentrate (500 IU/bottle)	Fresh frozen plasma
Mild bleed	15 iu/kg	2 bottles (adult)	1 pack/15 kg
Major bleed	20-30 iu/kg	3-6 bottles (adult)	1 pack/7.5 kg

Note:

1. Repeat in 24 hours if bleeding continues.
2. Factor VIII concentrate and cryoprecipitate are not useful for hemophilia B, so accurate diagnosis is essential.
3. As adjunct to replacement therapy.
4. Tranexamic acid (oral): 500-1000 mg three times/day, as for hemophilia A.

VON WILLEBRAND'S DISEASE

There is deficiency of von Willebrand's factor (vWF). It is an autosomal dominant disease affecting both males and females

Clinical Features

- Mucocutaneous bleeding like epistaxis
- Easy bruising
- Menorrhagia
- Bleeding after dental extraction
- Post traumatic bleeding.

Lab Investigations

- BT prolonged because of abnormal platelets plug formation which is because of partial deficiency of factor VIII. Decreased ristocetin cofactor activity suggests deficiency of vWF
- APTT prolonged

Management

To normalize bleeding time, following steps are taken:

- Increasing endogenous vWF levels with desmopressin or
- Replacing vWF using intermediate purity factor VIII product that is known to contain some vWF (Humate-P) or with Cryo, which also contains vWF.

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Transfusion Guide for Clinicians

Salient Features

- Written in a simple language
- Useful for all clinical and critical care specialists involved in the transfusion practice
- For promotion of rational use of blood by updating the clinical fraternity about the present scenario of transfusion service
- Knowledge about transfusion practice will ensure patients' safety and safeguard the practicing clinicians from legal tangles, as this book is as per national guidelines on the clinical use of blood
- Gives an overview of the recent advances in this field
- Acquaints the undergraduates with the transfusion practice
- Covers all the aspects of transfusion practice ranging from general guidelines for clinical transfusion procedures, blood components, apheresis, transfusion practice in clinical medicine, surgery, trauma and hemorrhage, obstetrics, transplantation and cardiopulmonary bypass surgery, autologous transfusion, transfusion transmitted infections, transfusion reactions, umbilical cord blood, recent advances in transfusion, plasma derivatives and substitutes, alternatives of transfusion and frequently asked questions about transfusion.
- Comprises of 21 chapters with tables, flow charts and diagrams for the ease of the readers.



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