Chapter 3

Hemostasis and Blood Component Therapy

A. Bleeding and Hemostasis

3.1 Postoperative Monitoring of Hemostasis and Chest Tube Drainage

Use continuous suction with a catheter inserted into the chest tubes until drainage seizes or drainage is scanty. It is especially done in neonates and infants to prevent blood accumulation / tamponade.

May evaluate the collections of blood in pleural space by chest roentgenogram.

i) Blood drainage of 1.5 mL – 2 mL/kg/hour:

It is acceptable in the immediate postoperative period.

ii) Blood drainage of > 2 mL/kg/hour for consecutive 4 hours or more:

Need assessment of bleeding.

iii) Blood drainage of > 5 mL/kg/hour for consecutive 4 hours or more:

Represents loss of 25% of blood volume.

May be associated with hemodynamic alterations.

Warrants re-exploration.

iv) Blood drainage of > 10 mL/kg/hour:

Require immediate exploration.

Result in loss of 40%-50% blood volume in succeeding 3 hours.

Accompany severe homodynamic changes.

v) Indication for exploration in a large adolescent or adult (65-70 kg):

Blood drainage of 100 mL/hour for consecutive 4-6 hours.

Immediate exploration: Blood drainage of 300 mL to 500 mL/any hour.

3.2 Assessment of Moderate to Significant Postoperative Bleeding

3.2.1 Exclude Caogulopathy

Clinical diagnosis of coagulopathy:

Diffuse oozing from surgical sites.

Bleeding around vascular access sites.

Mechanism of coagulopathy:

Dilution - platelets, dilution of factors VIII and V.

Consumption - fibrinogen and platelets.

3.2.2 Clues from Immediate Clinical History

Massive transfusion.

Physiological status: Temperature, pH.

Duration of hypotension.

Extent of resuscitation.

Cardiopulmonary bypass (CPB).

Platelet effects:

Activation and loss of GPIb (platelet receptor), plasmin, elastase and calpain.

Aprotinin: Given for repeat valvular surgery and septic endocarditis.

(Usual dose: 2 million KIU pre incision and 0.5 million KIU/hour during CPB).

3.2.3 Patient History

1) Family history:

The hemophiliac follow a pattern of X linked recessive inheritance.

30% of cases of hemophilia A are spontaneous mutations with no family history.

Von Willebrand's disease is difficult to diagnose due to:

Variability in the level of Von Willebrand factor (VWF), and variability of inheritance exists in patients.

Lowest levels of VWF present in type O and the highest in type AB blood groups.

Prior surgical or traumatic events or other triggering events without unusual bleeding may be best evaluated of their coagulation system.

2) Frequency of abnormal bleeding:

3) Duration of abnormal bleeding:

Coagulopathy manifests as moderate bleeding over a prolonged period but not as bleeding at an excessive rate. The location of abnormal bleeding suggests the following:

Platelet disorders: Bleeding from skin and mucous membranes tends to occur.

Hemophiliacs: Bleeding in joints and muscles tends to occur.

4) Associated medical diseases:

Liver disease, renal disease, hematological malignancy, vitamin K deficiency, vitamin C deficiency, and solid organ malignancy.

5) Medication history:

Aspirin, coumadine, and heparin.

3.2.4 Exclude Surgical Causes of Bleeding

Occurs due to suspected flaws in surgical technique.

3.3 Blood Coagulation

Activation of either intrinsic or extrinsic pathways of clotting leads to a common pathway that culminates in formation of a fibrin clot.

i) The intrinsic pathway (intravascular pathway):

It is activated by a contact of collagen (from damaged or injured vessel) by factor XII forming active factor XIIa.

Active factorXIIa initiates a cascade resulting in activation of successive coagulant factors such as factor XI, IX, and VIII, which lead to a common pathway (i.e. formation of active factor Xa or stage I clotting).

ii) The extrinsic pathway:

It is initiated by tissue thromboplastin (III), which in presence of Ca++ activates factor VII, this in turn leads to common pathway or formation of active factor Xa or stage I clotting.

iii) Common pathway: Active factor Xa and factor V in presence of Ca++ and platelet factor 3 converts prothrombin (II) to thrombin or stage II clotting.

iv) Thrombin converts soluble fibrinogen (I) to fibrin gel (clot) or stage III clotting.

v) Thrombin:

It plays an essential role in coagulation. Early after injury, activation of extrinsic pathway generates small amounts of thrombin.

Thrombin is a key factor in interaction of extrinsic and intrinsic pathways.

Thrombin accelerates intrinsic pathway by activating factor VIII and V.

Thrombin activates factor XIII which with Ca++ stabilizes fibrin gel (see Table 3.1).

Table 3.1 *Formation of hemostatic plug.*

Thrombin → Release of ADP from platelets → Formation of platelet aggregates
↓
Presence of other platelet factors → *Stable clot*

Hemostatic plug is formed by platelet aggregates impregnated in insoluble fibrin gel.

vi) Regulators (Inhibitors) of Coagulation:

The cascade of events that normally regulate the coagulation are shown in table 3.2

Table 3.2 *Regulators of coagulation cascade.*

i) Antithrombin III & heparin → Inhibits: XIIa, XI a, IXa, Xa and thrombin
ii) Thrombin →Protein C and Protein S → Protein Ca (activated protein C)
Protein Ca →Inhibits VIIIa and thrombin
iii) Fibrin production → Tissue plasminogen activators
↓
iv) Plasmin: Plaminogen →Plasmin
↑↓
Prekallekrins→ Inhibits fibrin, degrades V, VIII and IX, forms (FDP)
v) Fibrin split products (FDP)
↓
Inhibits thrombin, fibrin monomer polymerization and platelet function.

Note: (*Arrow heads*= leads to, promotes production or activates)

3.4 Tests of Coagulation

Monitor the following during the post operative period:

Routine: Activated clotting time (ACT), APTT (partial thromboplastin time), prothrombin time (PT), platelet count, fibrinogen, FDP, and bleeding time.

Specifics: Tests mentioned below are done only in certain circumstances in some patients.

D-dimers, thrombin time, reptilase time, euglobulin clot lysis time, platelet 3 factor, and factor assays (VIII, VII, and heparin).

Other tests: Plasminogen activator inhibitor (PAI-1), lupus anticoagulant etc,

A. Whole blood clotting time:

5 mL of blood is placed in a glass tube kept at body temperature.

Observe for a clot that should occur normally in 5 to 15 minutes.

Prolonged clotting time is suggestive of deficiency of any of the coagulation proteins.

The clot should retract in 30 to 60 minutes.

A weak, poorly retracted and friable clot suggests hypofibrinogenemia.

Early dissolution of a clot suggests enhanced fibrinolysis.

B. Platelet count:

Normal number 150, 000 to 400,000/cmm.

Poor platelet preservation techniques and specimens stored for more than 24 hours allow aggregation of platelets resulting in abnormally low results.

Hemolyzed red cell fragments may be identified as platelets.

Low platelet counts (Thrombocytopenia):

Increased peripheral destruction.

Post cardiopulmonary bypass/mechanical prosthetic valves.

Sepsis / disseminated intravascular coagulation.

Thrombotic thrombocytopenic purpura / hemolytic uremic syndrome.

Presence of platelet antibodies:

Post transfusion - HLA directed, or drug induced- such as penicillin, etc.

Immune thrombocytopenic purpura.

Dilutional: - Massive blood transfusion, CPB.

Decreased platelet production:

Hypocellular bone marrow: Aplastic anemia.

Hypercellular bone marrow: Megaloblastic anemia.

Myelodysplastic / myelophthisic: e.g.: Myelofibrosis,

C. Platelet aggregation test:

Addition of an agonist to platelet rich plasma exhibits a biphasic response, i.e., Reversible aggregation (occurs due to agonists) is followed by irreversible aggregation → Destruction of platelets.

Platelet agonists: (thrombin, ADP, adrenaline, collagen, ristocetin, and arachidonic acid).

D. Hess test:

BP cuff is inflated between systolic BP and diastolic BP for 10 minutes.

Normally less than 15 petechiae occur in a 5 cm diameter circle.

Inference: In vivo assessment of platelet adhesion, aggregation, collagen matrix, and vascular endothelium.

E. Prothrombin time and International Normalized Ratio (INR):

A mixture of anticoagulant (3.8% tri-sodium citrate) and blood in 9:1 ratio is centrifuged to produce platelet poor plasma. Complete thromboplastin is then added with calcium. Fibrin strand formation is measured by photo-optical device or electromechanical device.

Every batch of thromboplastin reagent has a "calibration value" (international sensitivity index).

The INR = (patient's prothrombin time / Laboratory's control prothrombin time).

A normal INR is between 0.9 and 1.2

Tests the extrinsic pathway of stage I clotting and factors II and III.

Prolonged INR: Deficiency of factor I, II, V, VII or X (it is most sensitive to decreases in factor VII vitamin K dependant).

Coumarin anticoagulation therapy, vitamin K deficiency, severe liver disease, massive blood transfusions, disseminated intravascular coagulation and (DIC) high dose heparin therapy.

F. Activated partial thromboplastin time (APTT):

Partial thromboplastin or "cephalin" (phospholipids) is added to a specimen and exposed to a negatively charged substance (kaolin, celite, or ellagic acid).

Normal 25 to 35 seconds.

Tests the intrinsic pathway of Stage I clotting and factors II and III.

Prolonged APTT: A decrease to less than 30% activity of all the coagulation factors:

1) Especially decrease in factor VIII, IX, and XI.

2) Heparin therapy and haemophilia.

3) Massive blood transfusions and high dose coumarin anticoagulation.

G. Thrombin time:

Thrombin is added to plasma and the time taken to form a clot is recorded.

Tests the Stage III clotting.

Normal: < 15 seconds.

Prolonged: Inhibition of thrombin, presence of abnormal fibrinogen, heparin, fibrin degradation products, and lupus anticoagulant.

H. Reptilase time:

Reptilase is added to plasma, and time taken to form a clot is recorded.

Normal: < 14-19 seconds.

Prolonged reptilase time: Inhibition of reptilase by presence of lupus anticoagulant, protamine in blood, and abnormal fibrinogen.

I. Fibrinolytic system and tests of fibrinolysis:

Fibrin is the final response to vascular injury, and is deposited in tissues and blood vessels. Once fibrin is no longer needed for hemostasis in vivo, the fibrinolytic system is activated and converts fibrin to its soluble degradation products, i.e. (FSP or FDP). Fibrinolysis is precisely regulated by activators, inhibitors, and cofactors in physiologic states.

Components of the fibrinolytic system: Plasminogen, plasminogen activator, and plasminogen activator inhibitors.

i) Plasminogen:

Synthesized in liver, and converted into plasmin (active) for activation.

Plasmin degrades fibrin into soluble degradation products.

Decreased: (DIC), liver disease, fibrinolytic therapy, and plasminogen deficiency.

Presence of plasminogen deficiency increases the risk of thrombosis.

Half of patients with plasminogen deficiency have other co-factor deficiencies such as protein C, and protein S.

Laboratory testing of plasminogen activity is fibrin plate test.

ii) Fibrin Plate Test:

Estimates fibrinolytic potential (plasminogen activity) by agar gel diffusion method. Test is positive within 24 hours of significant fibrinolysis.

In primary hyperfibrinogenolysis (as in hemorrhage complicating CPB) the test is positive within 2 hours.

iii) Plasminogen activators: Tissue plasminogen activator (t-PA).

Synthesized mainly in the endothelial cells and facilitates conversion of plasminogen to plasmin.

Decreased t-PA → thrombosis.

Increased t-PA levels → excessive fibrinolysis and bleeding episodes.

Laboratory testing:

Plasminogen activator inhibitor (PAI-1) rapidly binds to t-PA and inhibits its activity. It is necessary to acidify the patient's plasma to determine active t-PA.

iv) Plasminogen activator inhibitor (PAI-1):

Synthesized by endothelial cells, platelets, and hepatocytes.

Decreased levels: Autosomal recessive disorder and is associated with hemorrhages.

Elevated levels: Deep-vein thrombosis, myocardial infarction, pregnancy, and sepsis.

v) Fibrin degradation products (FSP/FDP):

These are end products of fibrinogen and cross-linked fibrin on action by plasmin.

These are detected by latex agglutination.

Elevation of FSP (> 10 ug/mL) denotes fibrinolysis.

Primary hyperfibrinogenolysis --- CPB, liver disease.

Secondary hyperfibrinogenolysis --- DIC.

vi) Protamine sulphate test / fibrin monomers:

Soluble fibrin monomers are formed by thrombin activity (i.e. DIC) with (+) test.

Useful for detecting secondary hyperfibrinogenolysis (DIC) with elevated FSP.

Not detected in primary hyperfibrinogenolysis (as in CPB hemorrhage).

vii) D-dimer (DD) assay:

It is an antigen formed when plasmin digests cross-linked fibrin.

Elevated levels are seen in secondary fibrinolysis (DIC) rather than in primary fibrinolysis.

A single global test for fibrinolysis is measurement of D-dimers in serum (s-DD).

Test accuracy correlates in many conditions except in pregnancy.

Correlates well with other fibrinolytic parameters such as euglobulin lysis time (ELT) and activity of type 1-plasminogen activator inhibitor (PAI-1).

viii) Euglobulin Clot Lysis time (ELT):

It is a qualitative test for fibrinolysis.

A mixture of plasma, fibrinogen, plasminogen, and plasminogen activators are allowed to form a clot and time for lysis of the clot is measured.

Shortened clot lysis time demonstrates fibrinolysis.

J. Antithrombin III (AT III) activity assay:

1) Decreased by consumption as in:

Sepsis, disseminated intravascular coagulation, deep vein thrombosis, and pulmonary embolism.

2) Decreased due to low levels of AT III molecule secondary to decreased synthesis of a normal AT III molecule (autosomal dominant) or production of a dysfunctional AT III molecule (autosomal dominant).

3) CPB hemorrhage complicating primary hyperfibrinogenolysis doesn't affect AT III levels except in hemodilution.

K. Factors assay (II, V, VII, VIII, IX, X, XI, XII):

Performed in special situations to pinpoint the bleeding disorder due to specific factor deficiency as in hemophilia and other suspected factor deficiencies.

L. Von Willebrand factor and Von Willebrand’s disease:

It is a large multimer glycoprotein acts as a carrier for factor VIII in plasma.

Synthesized in endothelial cells and megakaryocytes.

Acts as a bond between platelets and sub endothelial components such as collagen and heparin

M. Fibrinogen (factor I):

Performed to confirm deficiency states, secondary and primary hypofirinogenemia.

N. Fitzgerald factor assay:

The test is performed to detect kininogen deficiency.

The patients have prolonged PTT with no bleeding, but some patients may manifest thromboembolic episodes.

O. Fletcher factor assay:

Detects prekallikrein factor deficiency. The patient has prolonged PTT, but has no bleeding tendency.

It is an autosomal recessive pattern, and some patients may have thromboembolic episodes.

P. Factor Inhibitor Assay:

Factor VIII inhibitors:

May be present in hemophilia A patient that has received blood component transfusions. Patient develops a severe coagulopathy that is difficult to manage.

May also occur in unrelated conditions with coagulopathy, but levels are variable and disappear spontaneously.

Q. Lupus Anticoagulant:

It is directed against the Xa-V-phospholipid complex.

There is no tendency of increased bleeding, but markedly prolongs the APTT.

Patients have tendency towards excessive thrombosis and occurs in a variety of conditions:

i) Normal patients, lupus disease 5-10%, and infectious disease.

ii) Lymphoma and acquired immune deficiency syndrome.

iii) Drug exposure - chlorpromazine, procainamide and antibiotics.

Laboratory tests to isolate the lupus anticoagulant:

Reptilase test and kaolin clotting time.

R. Template bleeding time:

The bleeding time is unable to predict aspirin usage.

There is no predictive correlation with the platelet count.

There is no correlation with surgical bleeding.

Prolonged bleeding time:

i) Von Willebrand factor abnormality or deficiency, ii) Platelet deficiency or abnormality, iii) Heparin, iv) Aspirin, and v) Anemia.

S. Activated coagulation time (ACT):

Fresh whole blood is added to a tube containing negatively charged particles, and is timed for the formation of a clot.

The type of negatively charged particle affects the "normal" length of ACT.

E.g.: Celite = 100-170 seconds.

Used with high circulating levels of heparin as in cardiopulmonary bypass.

Aprotinin prolongs the "normal" ACT.

Prolonged ACT: heparin effect, hypothermia, platelet dysfunction, hemodilution, cardioplegic solutions, hypofibrinogenemia, and factor deficiencies.

T. Thromboelastograph:

Useful for diagnosis of CPB hemorrhage when other tests are inconclusive.

A sample of celite activated whole blood (0.4 mL) is placed into a pre-warmed cuvette. A pin suspended from a torsion wire is lowered into the cuvette, and the cuvette is rotated in a small arc fashion (see Figure 7.A).

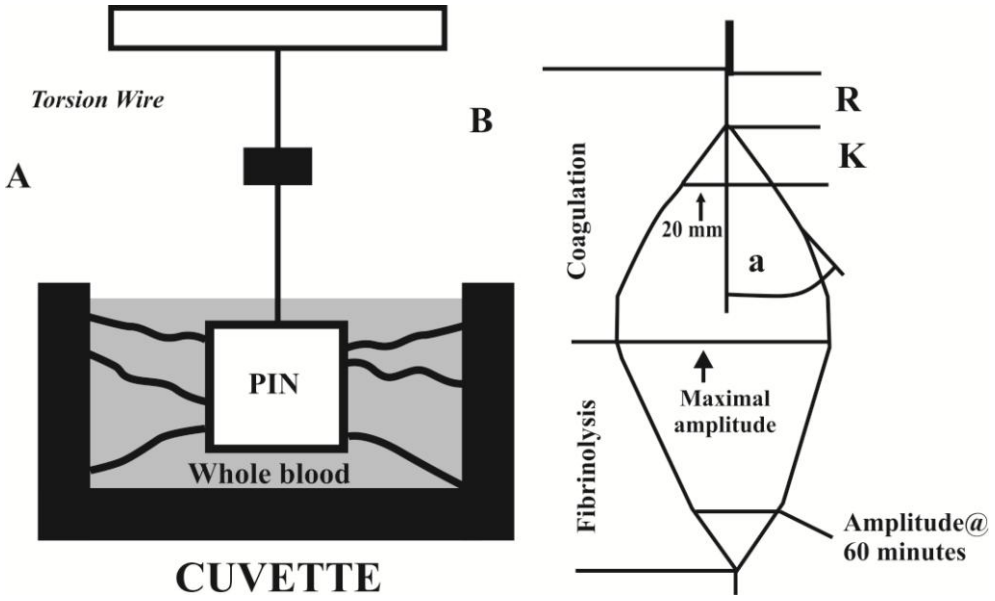

Figure 7 *Thromboelsatograph. A. Blood cuvette for performing thromboelsatograph: A sample (0.4 mL) of celite activated whole blood is placed into a pre warmed cuvette, and a pin suspended from a torsion wire is lowered into the cuvette. The cuvette is rotated in a small arc fashion. B. Interpretation of thromboelastograph: R value: Time period from initiation of the test to the initial fibrin formation and pin movement; K value: Time from beginning of clot formation until the amplitude of the TEG reaches 20 mm; α (alpha) angle: Angle between the line in the middle of and the line tangential to "body" (slope) of the TEG tracing; Maximal amplitude: Greatest amplitude of the TEG tracing; Amplitude at 60 minutes: TEG tracing 60 minutes after the maximal amplitude is recorded; Clot Lysis Index: Amplitude at 60 minutes expressed as a percentage of the maximal amplitude.*

As the fibrin strands interact with the activated platelets on the surface of the pin, the rotational movement of the cuvette is transmitted to the pin. The stronger the clot the more the pin moves. Hemoscope is connected to a computer to display the coagulation profile as an outline of a thromboelastograph and interpreted (see Figure 7B).

Interpretation of Thromboelastograph (TEG):

R value: Time period from initiation of the test to the initial fibrin formation and pin movement.

K value: Time from beginning of clot formation until the amplitude of the TEG reaches 20 mm.

α (alpha) angle: Angle between the line in the middle of and the line tangential to "body" of the TEG.

Maximal Amplitude: Greatest amplitude of the TEG tracing.

Amplitude at 60 minutes: TEG tracing 60 minutes after the maximal amplitude is recorded.

Clot lysis index: Amplitude at 60 minutes expressed as a percentage of the maximal amplitude.

Alterations of the normal TEG pattern:

i) Coagulation factor activation - R value: Reaction time to initial fibrin formation (normal 5-10 minutes). It is a test of extrinsic and intirinsic coagulation.

ii) Coagulation factor amplification - k value: “Kinetic time” for fibrin cross linkage to reach 20 mm clot strength (normal 1-2 minutes). Alpha angle is an angle between the line in the middle of and the line tangential to "body" (or slope) of the TEG. It represents clot formation (normal 53 to 72 degrees). Both K value and alpha angle measure fibrinogen and platelet numbers.

iii) Maximal amplitude (normal 50-70 mm): It is a measure of platelet aggregation and function.

iv) Amplitude at 30 to 60 minutes after maximal amplitude (MA) represents fibrinolysis. Clot lysis at 30 minutes (Ly 30) following MA is normally 0-3%.

Thromboelastography may also be used to guide blood product administration in bleeding patients as below:

R time > 10: Transfuse fresh frozen plasma. K time > 3: Transfuse cryoprecipitate.

Alpha angle < 53: Transfuse platelets. MA < 50: Transfuse platelets.

LY30 > 3%: Administer tranexamic acid or amicar (aminocaproic acid).

Rotational thromboelastometry (ROTEM) provides a trace similar to that of the TEG with related parameters including clotting time (CT), maximum clot firmness (MCF), tests similar to APTT, PT, and additional tests to detect heparin effect, qualitative analysis of fibrinogen, and detection of thrombin inhibitors.

3.5 Interpretation of Coagulation Tests and Diagnosis of Bleeding Disorder

1) Normal PT and prolonged PTT:

Intact stage II (factor II) and stage III (factor I) clotting and intact common pathway (factor V, X of stage I clotting).

Indicates defects in intrinsic pathway (factors XII, XI, IX and VIII) of stage I clotting.

2) Normal PTT and prolonged PT:

Intact stage II and stage III clotting, intact common pathway, but indicates defects in extrinsic pathway of stage I clotting, i.e., (factor VII, tissue thormboplastin, and prothrombin).

3) Prolonged PTT and prolonged PT with normal TT (thrombin time):

Indicates defects in common pathway and either intrinsic or extrinsic pathways.

Normal stage II and stage III clotting.

4) Prolonged thrombin time (TT):

Occurs due to heparin effect, hypofibrinogenemia, and fibrinolysis. Differentiate the etiology of prolonged TT (see Table 3.3)

Table 3.3 *Analysis of prolonged thrombin time.*

Primary Fibrinolysis	Heparin effect
Elevated FDP	Little or no FDP
Reptilase time prolonged	Reptilase time normal
Circulating Plasmin++	No circulating Plasmin
Clot Lysis in 5 minutes	No clot lysis

5) Heparin assay:

Detects excessive heparin and heparin rebounds as cause of excessive bleeding.

Administer 25% of initial calculated dose of protamine every 30 minutes until bleeding ceases.

Excess protamine rarely may cause bleeding, and is detected by:

Prolonged thrombin time and reptilase time, no clot lysis, and no FDPs.

6) Qualitative platelet abnormalities and thrombocytopenia:

Require administration of platelet concentrates for two to three days.

7) Primary hyperfibrinogenolysis (PHF):

a) Increased fibrinolysis (PHF) occurs after CPB though fibrinolytic activity is inhibited after any surgical procedure.

b) Hypofibrinogenemia and degradation of coagulation proteins (V, VIII, IX and Fibrin) occurs by activated plasmin.

c) FDPs interfere with thrombin, and platelet function.

Both b and c interfere with hemostasis.

E-aminocaproic acid, an antifibrinolytic may be used routinely for CPB hemorrhage.

3.6 Cardiopulmonary Bypass (CPB) Hemorrhage

If CPB hemorrhage is moderate to severe:

With evidence of hematuria, oozing from vein -punctures, mucous membranes and are associated with petechiae → Coagulation disorder.

If bleeding is moderate to severe without above findings and only blood drainage from chest tubes → Surgical bleeding.

The CPB hemorrhage is managed by an orderly approach and the summary of management is shown (see Figure 8).

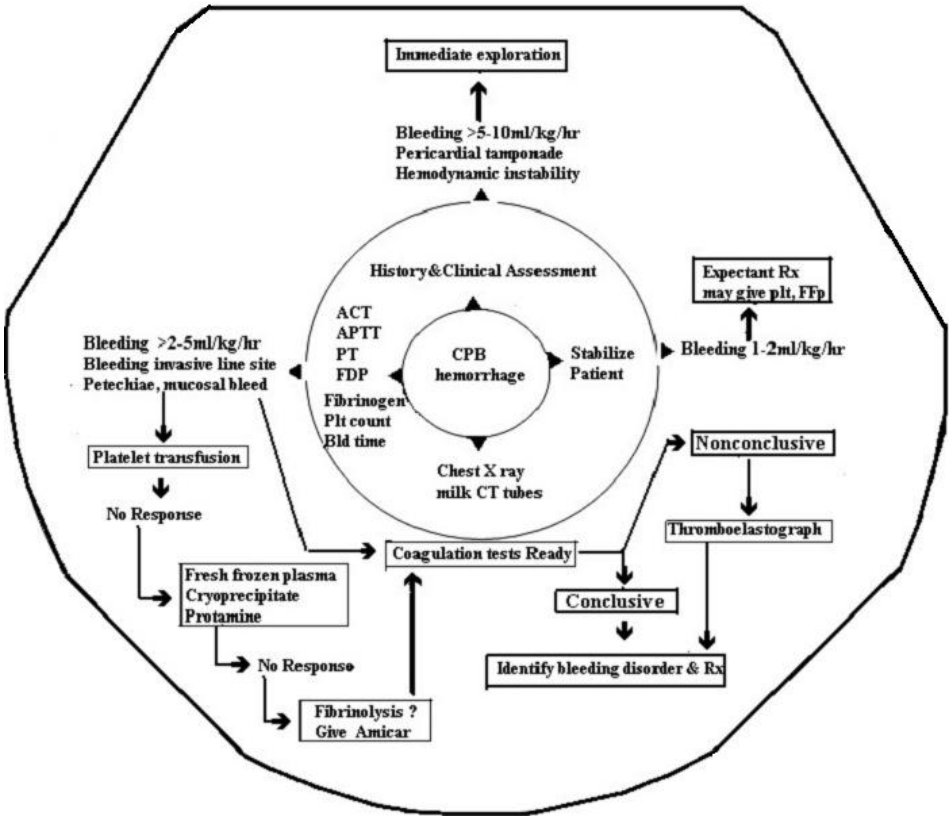

Figure 8 *Management algorithm in a patient with a postoperative (post cardiopulmonary bypass) hemorrhage. CPB= cardiopulmonary bypass, ACT= activated clotting time, APTT= Activated partial thromboplastin time, PT= prothrombin time, FDP= fibrin degradation (split) products, FFP=fresh frozen plasma, CT= chest tubes, Plt=platelet, Bld=bleeding.*

Order and evaluate coagulation tests discussed in section 3.4 and also do peripheral blood smear. May order specific tests for suspected specific causes, i.e., thrombin time, reptilase time, and fibrin split products to differentiate primary fbrinolysis and excess protaime in blood.

♥ Platelet defects are one of the most common causes of CPB hemorrhage.

Require correction by fresh platelets before coagulation test results are available.

If there is no response to platelets→ Give fresh frozen plasma (F), cryoprecipitate (C), and additional protamine (P).

If there is no response to FCP →probable fibrinolysis with increased plasmin and FSP.

↓

Give amicar.

3.7 Von Willebrand's Disease and Hemorrhage

The disease is caused by the deficiency Von- Willebrand's factor (vWf) and affects platelet adhesiveness with qualitative and quantitative abnormality of factor VIII.

Type 1: Decreased vWf is most common disorder.

Type 2: Markedly decreased vWf, but non-functional subunits are present.

Type 3: Absent vWf.

Diagnosis: Normal platelet count, normal PT and PTT, and increased bleeding time.

Confirmation: Abnormal ristocetin assay, reduced vWf in plasma, and reduced factor VIII coagulation activity.

DDAVP (Desmopressin): Synthetic analogue of the natural hormone vasopressin, but has no pressor effect.

Indicated in bleeding due to type I vW disease, not in type III or II B. Administration of DDAVP releases vWf from endothelial cells.

Effect is immediate, with 2-6 fold ↑ plasma concentrations of coagulation factor VIII, Von Willebrand factor, tissue plasminogen activator, and ↑ in platelet adhesiveness.

Usage: In patients with mild hemophilia A, Von Willebrand's disease, congenital or acquired platelet dysfunction (due to uremia or intake of drugs such as aspirin), or to reduce surgical blood loss without known bleeding diathesis.

Optimal hemostatic effect is achieved with a dosage of 0.3 ug/kg given intravenously. Other routes of administration are subcutaneous injection or intranasal spray.

3.8 Disseminated Intravascular Coagulation (DIC)

It is characterized by massive systemic activation of coagulation and consumption of platelets and coagulation proteins. May be associated by suppression of physiologic anticoagulant pathways and systemic generation of thrombin with impaired fibrinolysis.

Diagnosis:

Patient has risk factors for DIC.

CBC: Decreased platelets.

Prolonged clotting times.

PT – increased (may be normal in chronic DIC).

PTT – increased (may be normal in chronic DIC).

Thrombin time – increased.

Increased levels of fibrin-related markers.

D-dimers – increased in acute and chronic DIC.

Decreased – coagulation proteins, platelet count, and fibrinogen.

B. Blood Component Therapy

3.9 Blood Components

The blood components consist of packed red cells, whole blood, fresh frozen plasma, platelets, cryoprecipitate, and coagulation factor concentrates (Factor VIII, Factor VII). Fresh frozen plasma unit size issued depends on volume required. All donations should be from single donors. Familiarize with the following indications for administration of these components. Observe for adverse reactions / complications, and use caution during administration.

3.9.1 Blood Volume

In infants and children it is estimated by combined height and logarithmic weight values. Blood volume is read directly from height and weight by constructed nomograms. In young infants and children it varies with weight and body surface area.

Approximate blood volume in infants and children varies between:

80 mL to 90 mL/kg of body weight, or

1350 to 1860 mL/square meter of body surface area.

The volume percent of cells varies from 35 to 40.

Normal values in infants are lower than in adults for the following:

1. Blood volume estimated by global end-diastolic volume index (GEDVI).

2. Total intrathoracic blood index (ITBI).

Approximate values for blood volume by age and body weight are shown in Table 3.4.

Table 3.4 *Blood volume by Age and Body weight.*

Premature infants:	90-105 mL/kg	1 month-12 months:	73-78 mL/kg
Newborn:	78-90 mL/kg	1 year-3 years:	74-82 mL/kg.
4-6 years:	80-86 mL/kg	7-18 years:	83-90 mL/kg
Adults: 70-88 mL/kg			

3.9.2 Packed Cell Volume

Usual hematocrit (Hct) of PRBC (packed red blood cells) is 65%.

Infuse PRBC no faster than 2-3 mL/kg/hour / or infuse 10 mL/kg aliquots over several hours.

In chronic blood loss as in anemias infuse 1 mL/kg/hour.

$$\text{Required volume of PRBC} = \frac{estimated\ \ blood\ \ volume\ \times desired\ \ Hct\ change}{Hct\ of\ PRBC}$$

3.9.3 Fresh Frozen Plasma

Plasma is separated from whole blood and is frozen within 18 hrs after collection. Unit volume ranges from 150 to 300 mL.

Compatibility testing is not required. ABO compatible plasma should be used if possible.

Restrict group O recipients to group O plasma.

Group AB plasma can be used for all groups in an emergency.

Indications for administration to FFP(fresh frozen plasma):

Acute disseminated intravascular coagulation and INR or APTT are high.

INR or APTT are high with excessive bleeding.

INR or APTT are high before, during, or after major surgery.

Emergency surgery and/or massive blood loss, and warfarin effect is present in a patient and INR is high.

Before an invasive procedure and INR or APTT are high.

Associated liver disease before major surgery or invasive procedure and INR or APTT are high.

INR or APTT are high with a liver failure.

Correction of single factor deficiency when a specific factor was not available.

Treatment of thrombotic thrombocytopenic purpura.

3.9.4 Platelets

Platelet Transfusion:

1) Prepared by pooling platelet components separated from multiple units of whole blood (platelets pheresis or single donor platelets). / or

2) Single donor platelet-pheresis procedure ("Platelets pheresis" or "single donor platelets").

A unit of single donor platelets usually contains the equivalent of six or more platelet concentrates (dose commonly administered for a single platelet transfusion in an adult).

The plasma of a platelet component should be ABO compatible with the recipient's red cells, particularly if the recipient is a child.

3) The risk in multiple platelet transfusions is the development of a platelet-refractory state due to platelet alloimmunization. In vitro demonstration of platelet antibodies (HLA antibodies or platelet-specific antibodies) confirms the diagnosis.

4) A platelet count should be performed at 10-60 minutes post-transfusion.

A corrected count increment (CCI)* of > 7,500 indicates an acceptable response after transfusion.

If the CCI is < 7500, it suggests alloimunization in the absence of infection, splenomegaly or other causes of platelet destruction.

* Calculation of CCI:

$$CCI=\frac{(Post\ transfusion\ \ count-Pre\ transfusion\ \ count)\ 10^{11}\times Body\ surface\ \ area\ (M^2)}{Units\ of\ platelets\ \ transfused\ \times 10^{11}}$$

One unit of platelet concentrate averages $0.7\ \times\ 10^{11}$ platelets.

One unit of single donor platelets averages $4.0\ \times\ 10^{11}$ platelets.

"Illustration: A child (BSA $0.6M^2$) has a pre- transfusion platelet count of 5000/uL, post-transfusion platelet count of 35000/uL, and has received one unit of a single donor pheresis platelets. The CCI is

$$=\frac{(35000-5000)10^{11}\times 0.6}{4.0\times 10^{11}} = \frac{30000\times 0.6}{4} = 4500/\text{ul}/M^2$$

The 60 minutes post transfusion CCI of > 7500 and 24 hours post transfusion CCI of < 7500 is suggestive of platelet consumption rather than immune reaction."

Indications for platelet transfusion:

Excessive bleeding and surgical procedure on CPB.

Massive hemorrhage/transfusion and platelet count < 50 000/ul.

Prophylaxis for major surgery or invasive procedure and platelet count < 50 000/ul.

Bone marrow failure and platelet count < 10000/ul.

Bone marrow failure and platelet count < 20000/ul with risk factors.

3.9.5 Cryoprecipitate

Cryoprecipitated antihemophilic factor is a cold-insoluble portion of fresh frozen plasma (FFP) that precipitates when FFP is thawed at refrigerator temperatures (1-6 ℃). It contains clotting factor proteins from a single donor resuspended in approximately 10 to 15 mL of plasma. Each unit contains a minimum of 80 IU of factor VIII and at least 150 mg of fibrinogen, in addition to significant amounts of von Willebrand factor and factor XIII.

Indications for cryoprecipitate transfusion:

A. If fibrinogen test result is available and fibrinogen level is < 1.0 g/L, and is associated with clinical bleeding.

Trauma or invasive procedure.

Disseminated intravascular coagulation.

B. Hypofibrinogenemia or afibrinogenemia association with bleeding or prior to an invasive procedure:

Causes of hypofibrinogenemia: Lack of synthesis (e.g., liver disease), consumption (e.g., disseminated intravascular coagulation [DIC], dilution (e.g., massive transfusion or intensive plasma exchange), and inheritable defect.

C. In the following and in association with bleeding or prior to surgery:

Von Willebrand disease (If DDAVP or von Willebrand factor-containing concentrates are ineffective).

Hemophilia A (DDAVP and factor VIII concentrate are unavailable in an emergency.

Dysfibrinogenemias (inherited and acquired).

Factor XIII deficiency.

3.10 Complications of Blood Component Therapy

3.10.1 Transfusion Related Acute Lung Injury (TRALI)

It is a clinical diagnosis of exclusion. It is characterised by acute respiratory distress and bilaterally symmetrical pulmonary edema. Hypoxemia develops within 2 to 8 hours after a transfusion. The Chest X ray depicts interstitial or alveolar infiltrates with no cardiogenic or other cause of pulmonary edema.

The pulmonary vascular effects are due to cytokines in the transfused product and / or from interaction between patient white cell antigens and donor antibodies (or vice versa).

3.10.2 Volume Overload

Infants and patients with cardiopulmonary disease are at risk, especially during rapid transfusion. Avoid unnecessary fluids and use appropriate infusion rates.

3.10.3 Hypothermia

Rapid infusion of large volumes of stored blood contributes to hypothermia.

Infants are particularly at risk during exchange or massive transfusion.

Blood warmers should be used during massive or exchange transfusion.

Additional measures may also be used such as 1) warming of other intravenous fluids, 2) use of devices to maintain patient body temperature.

3.10.4 Citrate Toxicity

Rapid administration of large quantities of stored blood may cause hypocalcaemia and hypomagnesaemia as citrate binds calcium and magnesium.

Patients with liver dysfunction or neonates with immature liver function having rapid large volume transfusion are most at risk. May result in myocardial depression or coagulopathy. Use replacement therapy for symptomatic hypocalcaemia or hypomagnesaemia.

3.10.5 Hemolytic Reactions

Patient develops an antibody directed against an antigen on transfused red cells.

The antibody may cause shortened red cell survival, and a delayed hemolytic reaction occurs. Most delayed hemolytic reactions produce few symptoms or may go unrecognised. A few hemolytic reactions produce clinical features of fever, jaundice, and lower than expected hemoglobin following transfusion.

There are reports of serious consequences occurring in critically ill patients.

3.10.6 Hyperkalemia

Occurs due to rapid and massive transfusion of older red cell units in small infants and children. Blood less than 7 days old is generally used for rapid large volume transfusion in small infants, (e.g., cardiac surgery, ECMO, and exchange transfusion). Stored red cells leak potassium proportionately throughout their storage life.

3.10.7 Antibody Screen

Should be performed as part of pre-transfusion testing. If antibody is detected, it is identified and appropriate antigen negative blood is provided.