بسم الله الرحمن الرحيم

Pediatric Hematologic Emergency

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K.U.M.S

- Blood product and Emergency side effects
- Hemolytic Anemia(Favism)
- Hemophylia
- ITP

WHOLE BLOOD

Indication

- Acute , active blood loss with hypovolaemia
- Exchange transfusion

Contraindication

- Risk of volume overload : Chronic anaemia
  Incipient cardiac failure

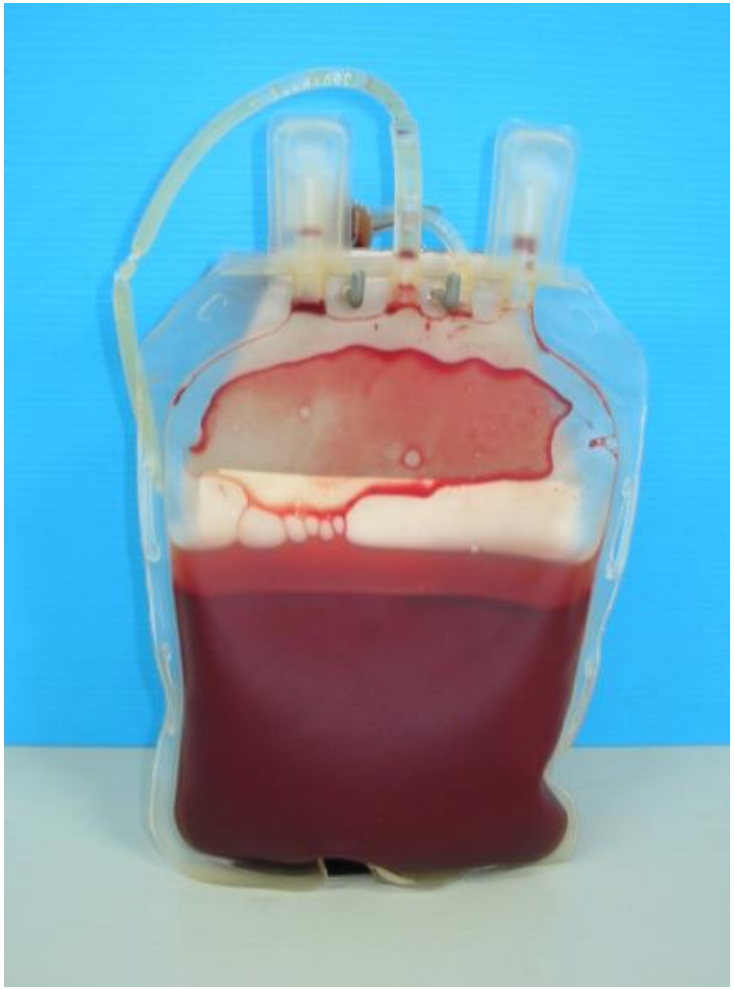
WHOLE BLOOD

Administration

- Must be ABO and RhD compatible
- Never add medication to a unit of blood
- Use blood administration set

Dosage

Packed red cell



Packed Red Cells (in plasma)

Indication

- Replacement of red cells in anaemic patients
- Use with crystalloid or colloid solution in acute blood loss

Dosage 10 - 15 ml / kg

PRC 1 unit → Hct 3 % or Hb 1 g/dL

Duration

TABLE 470-1. Guidelines for Pediatric Red Blood Cell Transfusions*

CHILDREN AND ADOLESCENTS

Acute loss of >25% at circulating blood volume
Hemoglobin of <8.0 g/dL† in the perioperative period
Hemoglobin of <13.0 g/dL and *severe* cardiopulmonary disease
Hemoglobin of <8.0 g/dL and *symptomatic* chronic anemia
Hemoglobin of <8.0 g/dL and *marrow failure*

INFANTS WITHIN THE FIRST 4 MO OF LIFE

Hemoglobin of <13.0 g/dL and *severe* pulmonary disease
Hemoglobin of <10.0 g/dL and *moderate* pulmonary disease
Hemoglobin of <13.0 g/dL and *severe* cardiac disease
Hemoglobin of <10.0 g/dL and *major* surgery
Hemoglobin of <8.0 g/dL and *symptomatic* anemia

*Words in *italics* must be defined for local transfusion guidelines.
†Hematocrit estimated by Hb g/dL × 3.

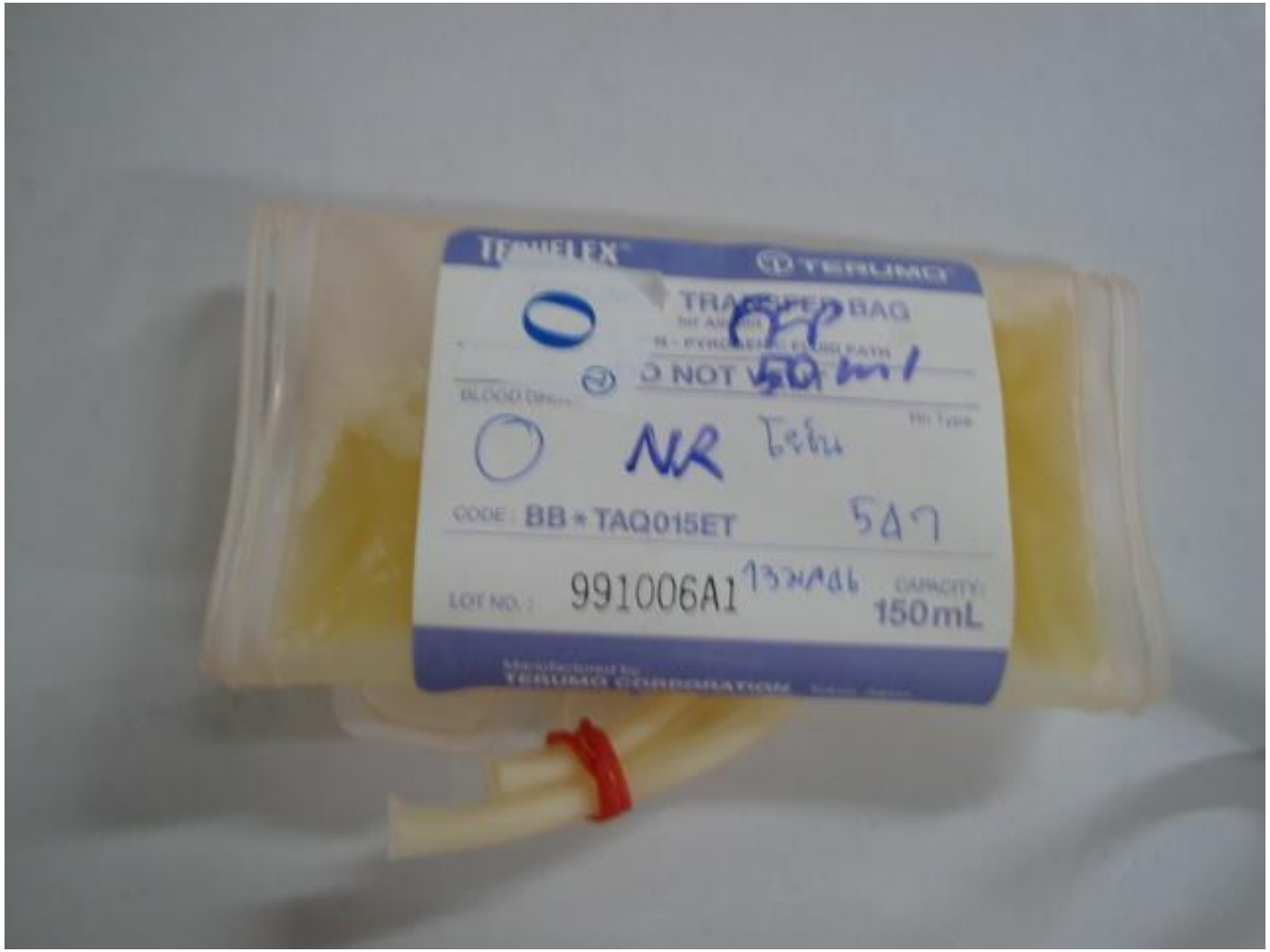
- The traditional use of relatively fresh RBCs «7 days of storage)has been halted in many centers in favor of diminishing donor exposure by using a single unit of RBCs to obtain aliquots for transfusing each infant throughout its permitted duration of storage (currently 42 days).

- Neonatologists who insist on transfusing
- only fresh RBCs generally are fearful of the rise in the plasma potassium (K+) level that occurs in RBC units during extended storage. After 42 days of storage, plasma K+levels are approximately 50 mEq/L (0.05 mEq/mL), a value that, at 1st
- glance, seems alarmingly high. However, the actual dose of K+ transfused in the extracellular fluid is tiny.

- However,the safety of stored RBCs may not apply to large-volume(>25 mL/kg) transfusions infused rapidly, in which greater doses of K+may be harmful.

FRESH FROZEN PLASMA

PEDIATRIC FFP



FRESH FROZEN PLASMA

Indication

- Clinically significant deficiency of Factors II, V, X, XI
- Replacement of multiple coagulation

factor deficiencies :-

liver disease , warfarin treatment,

dilutional and consumption coagulopathy

FRESH FROZEN PLASMA

Contraindication

- Volume expansion
- Immunoglobulin replacement
- Nutritional support
- Wound healing

FRESH FROZEN PLASMA

Precaution

- Acute allergic reaction are common
- Anaphylactic reaction may occur

Dosage

Initial dose of 15 - 20 ml / kg

FRESH FROZEN PLASMA

Administration

- Must be ABO compatible
- Infuse as soon as possible after thawing

  (within 6 hrs)
- using standard blood administration set

TABLE 473-1. Guidelines for Pediatric Fresh Frozen Plasma Transfusions*

INFANTS, CHILDREN, AND ADOLESCENTS

Severe clotting factor deficiency and bleeding

Severe clotting factor deficiency and an invasive procedure

Emergency reversal of warfarin effects

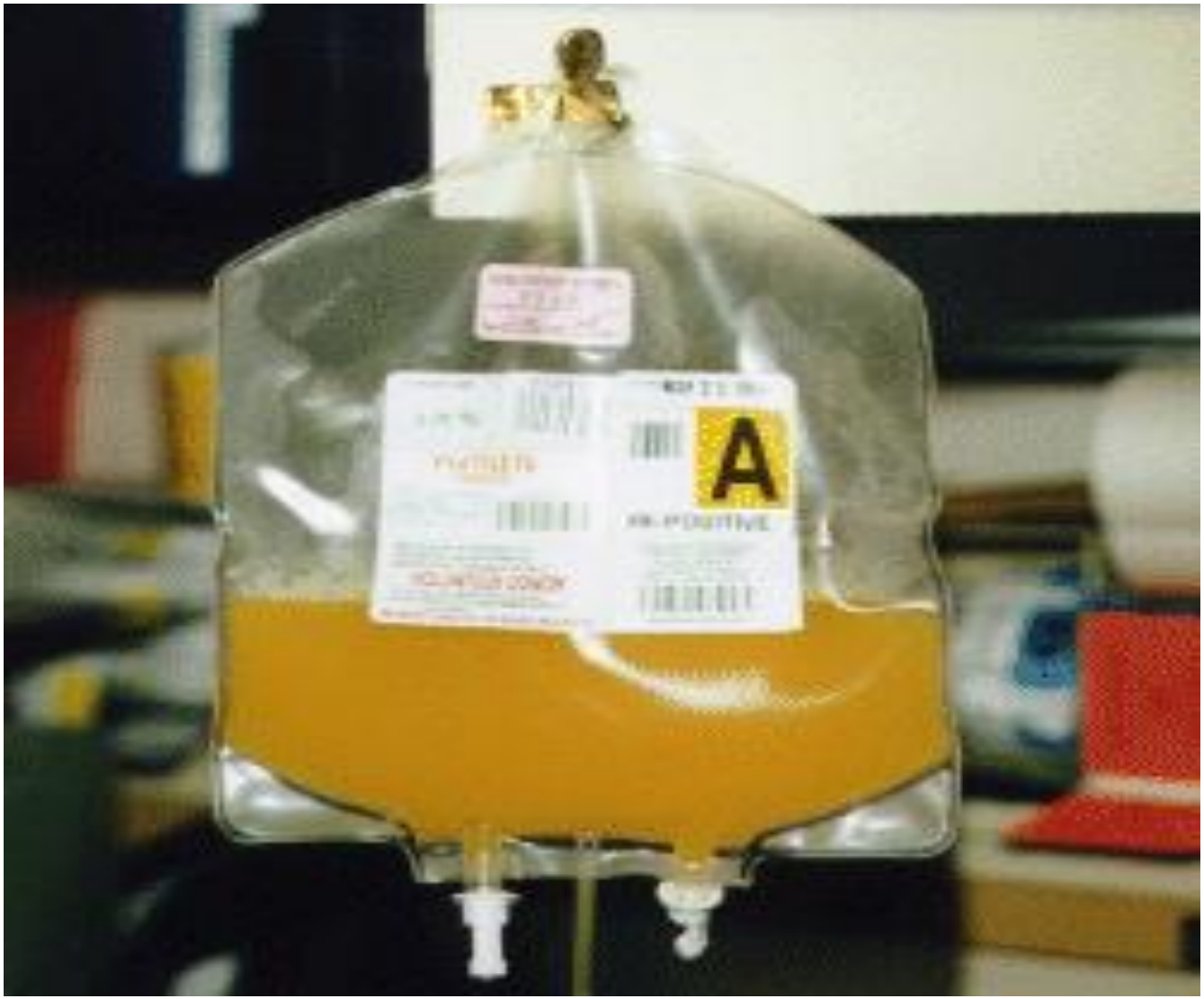
Dilutional coagulopathy and bleeding

Anticoagulant protein (antithrombin III, proteins C and S) replacement

Plasma exchange replacement fluid for thrombotic thrombocytopenic purpura

*Words in *italics* must be defined for local transfusion guidelines.

Platelet concentrate



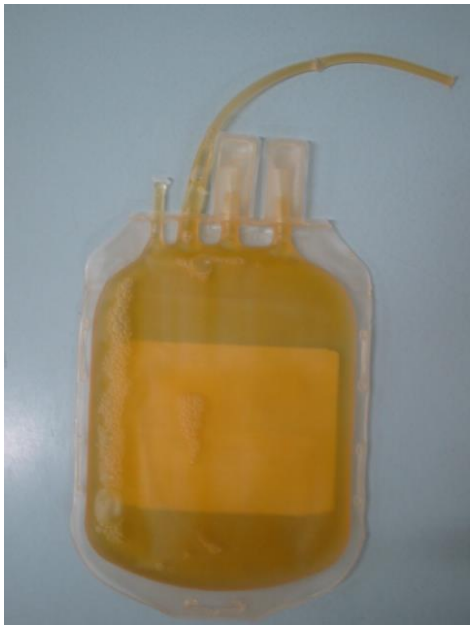
PLATELET CONCENTRATE

- Indications

  Treatment of bleeding due to

  - Thrombocytopenia
  - Platelet Dysfunction
  - Prevention of bleeding

PLATELET CONCENTRATE



- Dosage
  - 1 unit of PC / 10 kg B.W.
  - Increment will be less in
    - Spleenomegaly
    - DIC
    - Septicemia

1 unit of PC → Platelet 5000-10,000 / ul

PLATELET CONCENTRATE

Administration

- should be ABO & Rh compatible
- After pooling, should be infused as soon as possible
- Use blood administration or platelet infusion set
- Must not be refrigerated before infusion

Platelets Concentrate

Random donor Platelets

Whole blood ๑ unit → Platelet Concentrate ๑ unit

↓

≥ ๕.๕ x ๑๐^{๑๐} platelets in

๕๐ - ๗๐ ml of plasma

Single donor platelets

๑ Donor → Platelet concentrate

↓

≥ ๓ x ๑๐^{๑๑} platelets in

~ 3๐๐ ml of plasma

Single Donor Platelet

- Indication
  - same as random PC
  - special requirement → obtain from selected donor
- Dosage

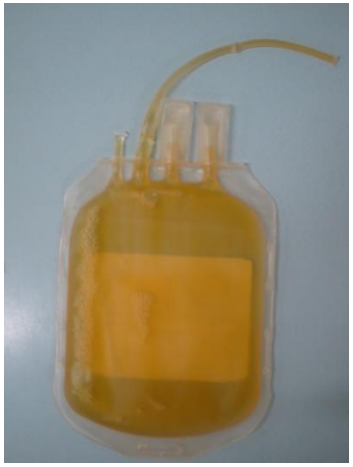
  Usually 1pack of SDP = 1 therapeutic dose

Single Donor Platelet

- Administration

  same as random PC , but ABO compatible is more important

Vol ~ 300 ml



Vol ~ 50 – 70 ml

TABLE 471-1. Guidelines for Pediatric Platelet Transfusions*

CHILDREN AND ADOLESCENTS

PLTs $< 50 \times 10^9$/L and bleeding

PLTs $< 50 \times 10^9$/L and an *invasive* procedure

PLTs $< 20 \times 10^9$/L and *marrow failure* with hemorrhagic risk factors

PLTs $< 10 \times 10^9$/L and *marrow failure* without hemorrhagic risk factors

PLTs at any count, but with PLT dysfunction plus bleeding or an invasive procedure

INFANTS WITHIN THE FIRST 4 MO OF LIFE

PLTs $< 100 \times 10^9$/L and bleeding

PLTs $< 50 \times 10^9$/L and an invasive procedure

PLTs $< 20 \times 10^9$/L and *clinically stable*

PLTs $< 100 \times 10^9$/L and *clinically unstable*

PLTs at any count, but with PLT dysfunction plus bleeding or an invasive procedure

*Words in *italics* must be defined for local transfusion guidelines.

PLTs, platelets.

Platelets

- Platelets have both the ABO and HLA antigens. ABO compatibility is ideal but not required. (incompatibility will shorten the life span of the platelet)

- It is important to minimize repeated transfusion of group 0 PLTs to group A or B recipients because passive anti-A or anti-B in group 0 plasma can lead to hemolysis.

Storage

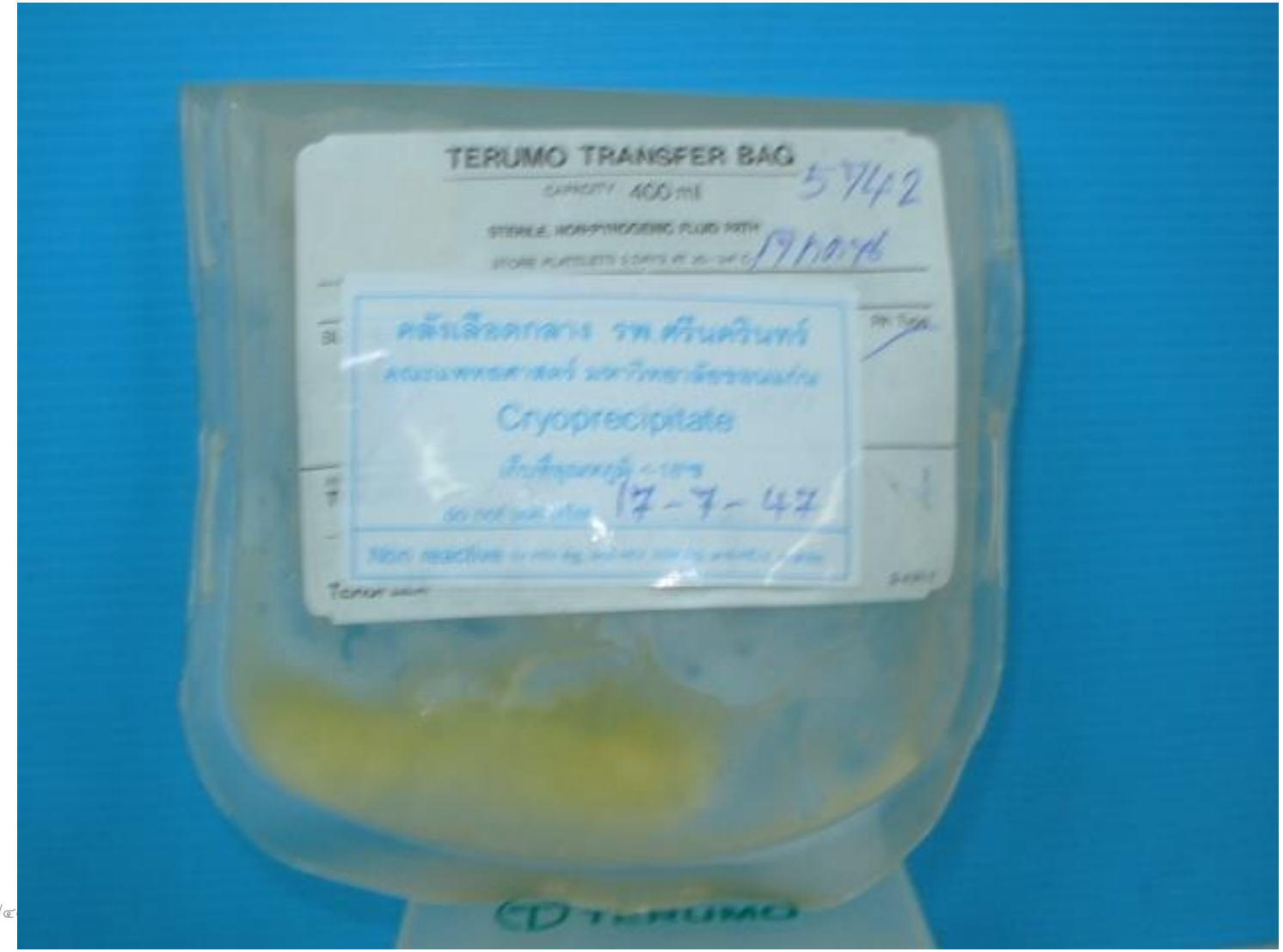
- Up to 72 hours at 20 – 24^0c with constant agitation.
- Max. period of storage is 3 to 5 days.
- Must not be refrigerated as this will reduce platelet function.

Plateletpheresis

- A portion of donor's platelet and some plasma is removed with the return of donor's RBCs, WBCs and remaining plasma.
- A routine procedure takes 1 to 1.5 hours.
- The product is prepared in closed system and can be stored for 5 days.

2
COBE Spectra

CRYOPRECIPITATE



Cryoprecipitate

Cryoprecipitate is the cold - insoluble portion of plasma that precipitates

when FFP is thawed between ๑-๖ ° C

FFP ๑ unit → Cryoprecipitate ๑ unit

(Volume ~ 10 - 15 ml)

Cryoprecipitate ๑ unit contains

- F VIII:c ๘๐ - ๑๕๐ IU
- Fibrinogen ๑๕๐ - ๒๕๐ mg
- F XIII (๒๐-๓๐% of WB level)
- vWF (๔๐-๗๐% of WB level)

CRYOPRECIPITATE

Indication

- Quantitative and Qualitative Fibrinogen Deficiency : DIC
- von Willebrand Disease
- Factor XIII deficiency
- Uremic Coagulopathy
- Factor VIII (haemophilia A)

CRYOPRECIPITATE

Administration

- ABO compatible if possible
- no compatibility testing required
- After thawing & pooling, infuse as soon as possible through blood admin. set
- must be infused within 6 hours of thawing

Transfusion Risks

- Risks of blood transfusion can be divided into two catagories
- Infectious
- Non-Infectious

Infectious Risks

- The transmittable risks are numerous and include:
- Hepatitis A, B, C, D, E
- Human T-cell lymphotropic viruses (HTLV-1 & HTLV-2)
- HIV-1 & HIV-2
- Cytomegalovirus
- Epstein-Barr virus

Infectious Risks

- Parvovirus B19
- GBV-C virus (also called hepatitis G)
- Transfusion-transmitted virus (TTV)
- Prions including Creutzfeldt-Jakob and variant
- Lyme Disease
- Bacterial infections including: malaria, Chagas disease, ehrlichiosis, babesiosis, and syphilis.

Bacterial Contamination

- Bacterial Contamination occurs at a much higher frequency than any other infections and is associated with substantial mortality.
- Rate of bacterial infection/contamination:

RBCs 1 in 30,000

Platelets 1 in 2,000

Bacterial Contamination

- The patient who receives contaminated blood will rapidly experience some combination of fever, chills, tachycardia, emesis, and shock. The patient may also develop DIC and acute renal failure.
- If the index of suspicion is high then the blood transfusion should be stopped immediately and blood cultures taken.

Exposure Estimates

- Hepatitis B 1 in 350,000
- Hepatitis C 1 in 2,000,000
- HIV 1 in 2,000,000
- HTLV 1 in 2,900,000
- Bacterial reactions from

  RBC 1 in 30,000

  Platelets 1 in 2,000

Noninfectious Risks

- The noninfectious risks associated with blood products are generally immunologically mediated.
- Reactions can occur as a result of the antibodies that are constitutive (Anti-A or Anti-B) or ones that have been formed as a result of prior exposure to donor RBCs, WBC, platelets, or proteins.

Noninfectious Risks

- The noninfectious adverse reaction with their approximate incidences are:
- Acute hemolytic transfusion reaction 1 in 25,000 to 50,000
- Delayed hemolytic transfusion reaction 1 in 2,500
- Minor allergic reactions 1 in 200 to 250
- Anaphylactic/-toid reactions 1 in 25,000 to 50,000
- Febrile reactions 1 in 200
- Transfusion related acute lung injury 1 in 5,000

Acute Hemolytic Transfusion Reactions (AHTR)

- Hemolysis of donor RBC's often leads to acute renal failure, DIC, and death
- Of the >300 antigens on the RBC, only several will produce these reactions: anti-A, anti-B, anti-Kell, anti-Kidd, anti-Lewis, and anti-Duffy

Signs and Symptoms of AHTR

- Fever
- Chills
- Nausea and Vomiting
- Diarrhea
- Rigors
- Hypotension
- Flushed appearance and dyspneic
- Chest pain and back pain
- Pt is restless, and has a headache
- Hemoglobinuria, and possible diffuse bleeding

Management of AHTR

- If a reaction is suspected, the transfusion should be stopped and the identity of the patient and the labeling of the blood rechecked.
- Management has 3 main objectives:
- Maintenance of systemic blood pressure
- Preservation of renal function
- Prevention of DIC

Management of AHTR

- Lab tests should include a repeat crossmatch and a direct antiglobulin (Coombs) test.
- The direct antiglobulin test is the definitive test for an acute hemolytic transfusion raction.
- It examines recipient RBCs for the presence of surface immunoglobulins and complement. Patient serum is also examined for antibodies that react with donor cells

Delayed Hemolytic Transfusion Reaction (DHTR)

- This reaction occurs when the donor RBCs have an antigen to which the recipient has been previously exposed by transfusion or pregnency, however over time the antibodies fall to levels too low to be detected by compatibility testing
- When re-exposure occurs the pt. undergoes an anamnestic response and produces more antibody that eventually lyses the foreign RBCs

DHTR

- Evidence of hemolysis is usually evident by the first or second week after exposure
- Symptoms are a low grade fever, increased bilirubin with or without jaundice, and a reduction in hemoglobin
- Diagnosis confirmed by a Coombs test
- The reaction is self-limiting and the clinical manifestations resolve as the transfused cells are removed

Minor Allergic Reactions

- Allergic reactions to *proteins* in donor plasma can cause urticarial reactions in 0.5% of all transfusions
- The reaction is almost always associated with FFP administration
- The pt. may have itching, swelling, and a rash as a result of histamine release
- Treatment is with diphenhydramine

Febrile Reactions

- Patients who receive multiple transfusions often develop antibodies to the HLA antigens on the *passenger leukocytes*
- During subsequent RBC transfusions, febrile reactions may occur as a result of antibody attack on donor leukocytes
- The response occurs in 1-2% of all RBCs transfused
- Temperature increase of greater than 1 degree centigrade within 4 hours that resolves within 48 hrs

Transfusion-Related Acute Lung Injury (TRALI)

- TRALI is a noncardiogenic form of pulmonary edema associated with blood product administration
- It is associated with administration of all blood products but occurs most frequently with RBCs, FFP, and platelets
- The incidence is 1 in 5000 units transfused
- TRALI has a mortality of 5 to 8%

TRALI

- TRALI occurs when agents present in the plasma phase of donor blood activate *leukocytes in the host*
- Those agents are usually antileukocyte antibodies in donor blood formed as a result of a previous transfusion or pregnancy
- TRALI usually requires a preexisting condition such as sepsis, trauma or surgery

TRALI

- The clinical appearance is similar to adult respiratory distress syndrome (ARDS)
- Symptoms usually begin within 6 hours after the transfusion and often more rapidly, the patient develops dyspnea, cyanosis, chills, fever, hypotension and noncardiogenic pulmonary edema
- CXR reveals bilateral infiltrates
- Severe pulmonary insufficiency can develop

TRALI

- Treatment is largely supportive
- The transfusion should be stopped if the reaction is recognized in time
- The patient should receive oxygen and ventilatory support as necessary, usually with a low tidal volume strategy

HEMOLYTIC ANEMIA

Definition

- An essential feature of hemolytic anemia is a reduction in the normal red cell survival of 120 days. Premature destruction of red cells may result from:

  Corpuscular abnormalities

  membrane,enzymes, or hemoglobin;
  Extracorpuscular abnormalities,

  immune or nonimmune mechanisms.

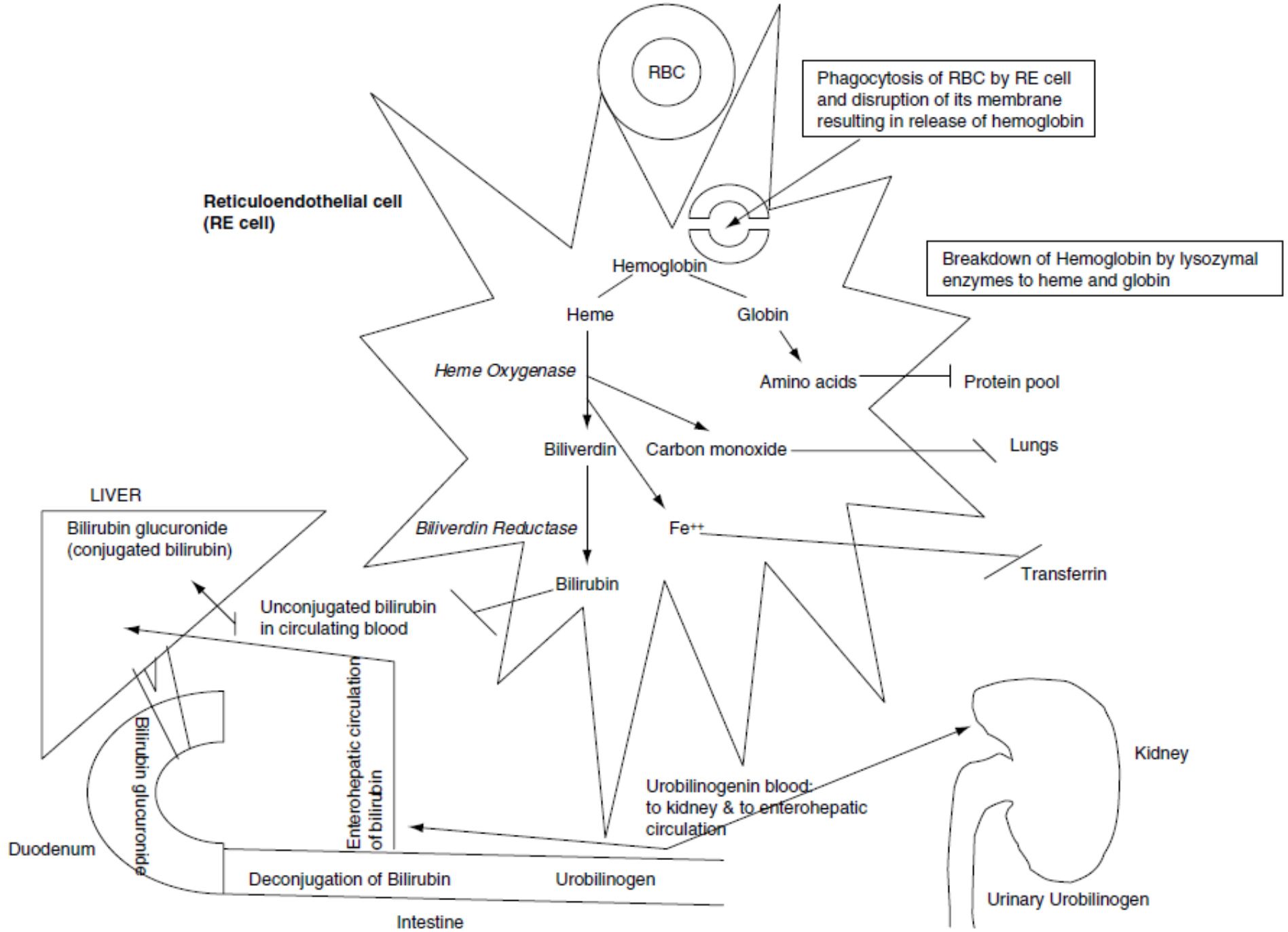
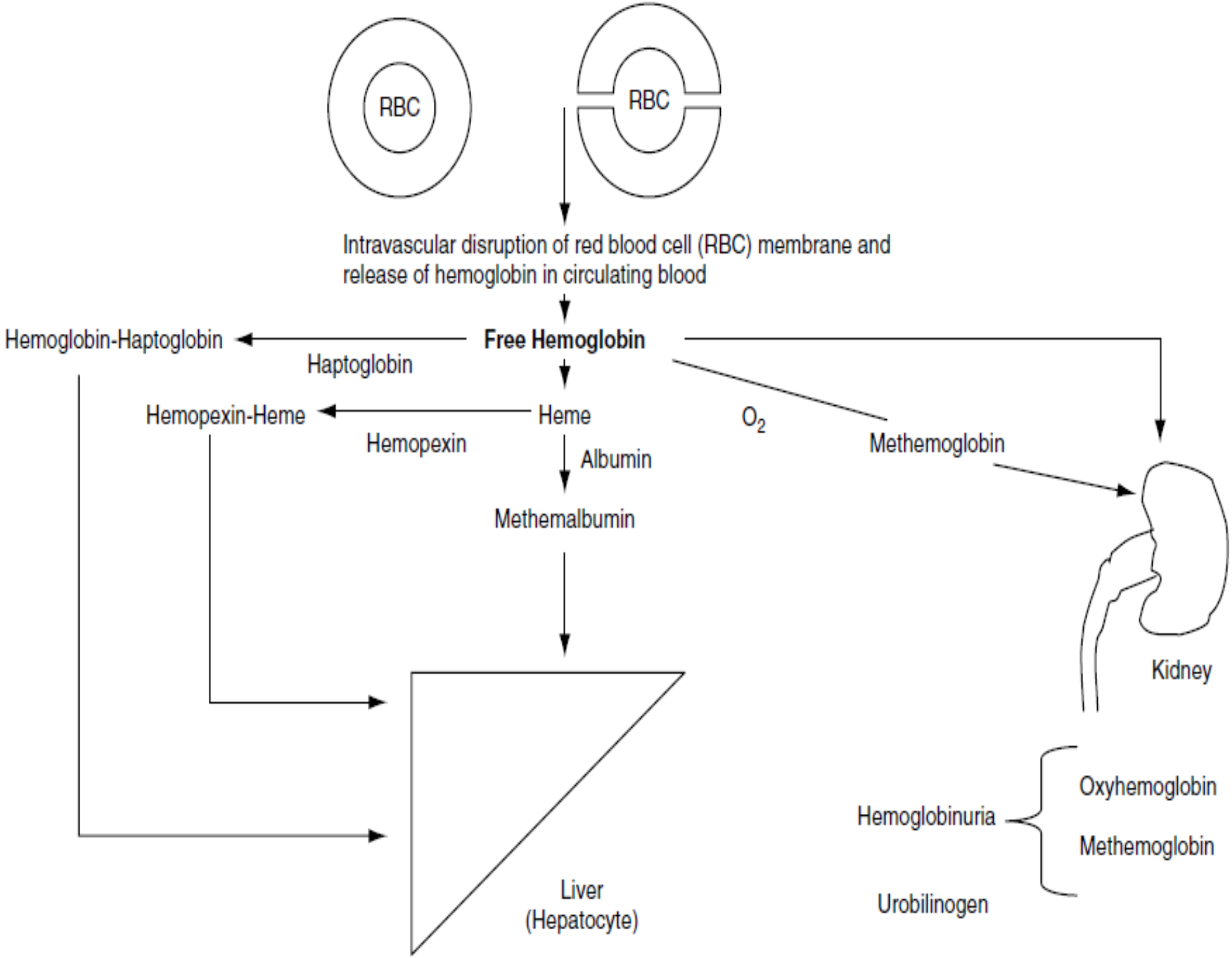


Fig. 7-1. Extravascular hemoglobin catabolism following extravascular destruction of the RBC.


RBC
RBC
Intravascular disruption of red blood cell (RBC) membrane and release of hemoglobin in circulating blood
Free Hemoglobin
Hemoglobin-Haptoglobin
Haptoglobin
Hemopexin-Heme
Hemopexin
Heme
Albumin
Methemalbumin
O_2
Methemoglobin
Kidney
Hemoglobinuria
Oxyhemoglobin
Methemoglobin
Urobilinogen
Liver
(Hepatocyte)

Clinical Features

- 1. History of anemia, jaundice, or gallstones in family
- 2. Persistent or recurrent anemia associated with reticulocytosis
- 3. Anemia unresponsive to hematinics
- 4. Intermittent or persistent indirect hyperbilirubinemia
- 5. Splenomegaly
- 6. Hemoglobinuria
- 7. Presence of multiple gallstones
- 8. Chronic leg ulcers
- 9. Development of anemia or hemoglobinuria after exposure to certain ***drug***

Laboratory Findings

- Laboratory findings of hemolytic anemia consist of:
- 1. Reduced red cell survival and evidence of accelerated hemoglobin catabolism
- 2. Evidence of increased erythropoiesis.

Accelerated Hemoglobin Catabolism

- *Signs of extravascular hemolysis:*
- 1. Increased unconjugated bilirubin
- 2. Increased fecal and urinary urobilinogen
- 3. Increased rate of carbon monoxide production

Accelerated Hemoglobin Catabolism

- *Signs of intravascular hemolysis:*
- 1. Raised plasma hemoglobin level
- 2. Hemoglobinuria
- 3. Low or absent plasma haptoglobin
- 4. Raised plasma methemalbumin (albumin bound to heme; unlike haptoglobin,albumin does not bind intact hemoglobin)
- 5. Raised plasma methemoglobin (oxidized free plasma hemoglobin) and raised levels of hemopexin-heme complex in plasma.

Increased Erythropoiesis

- 1. *Reticulocytosis*
- 2. Increased mean (MCV) due to the presence of reticulocytosis and increased (RDW) as the hemoglobin level falls
- 3. Increased normoblasts in peripheral blood

Increased Erythropoiesis

- 5. Erythroid hyperplasia in bone marrow
- 6. Expansion of marrow space in chronic hemolysis resulting in:

  a. Prominence of frontal bones

  b. Broad cheekbones

  c. Widened intratrabecular spaces, hair-on-end appearance of skull radiographs

Causes of Hemolytic Anemia Due to Corpuscular Defects

I. Membrane defects
   A. Primary membrane defects with specific morphologic abnormalities
      1. Hereditary spherocytosis
      2. Hereditary elliptocytosis/pyropoikilocytosis
      3. Hereditary stomatocytosis with:
         a. Increased osmotic fragility (high Na^+, low K^+)
         b. Decreased osmotic fragility (high Na^+, low K^+)
         c. Normal osmotic fragility
         d. Rh_{null}
      4. Congenital hemolytic anemia with dehydrated red cells (high Na^+, low K^+, decreased osmotic fragility)
   B. Secondary membrane defects: abetalipoproteinemia

II. Enzyme defects

A. Energy potential defects (Embden–Meyerhof: anaerobic; ATP-producing pathway deficiencies)
   1. Hexokinase
   2. Glucose phosphate isomerase
   3. Phosphofructokinase
   4. Triosephosphate isomerase
   5. Phosphoglycerate kinase
   6. 2,3-Diphosphoglyceromutase (polycythemia and no hemolysis)
   7. Pyruvate kinase

B. Reduction potential defects (hexose monophosphate: aerobic; NADPH-producing pathway deficiencies)
   1. G6PD[a]
   2. 6-Phosphogluconate dehydrogenase (6PGD)
   3. Glutathione reductase
   4. Glutathione synthetase
   5. 2,3-Glutamyl-cysteine synthetase

C. Abnormalities of erythrocyte nucleotide metabolism
   1. Adenosine triphosphatase deficiency
   2. Adenylate kinase deficiency
   3. Pyrimidine 5′-nucleotidase (P5N) deficiency
   4. Adenosine deaminase excess

Causes of Hemolytic Anemia Due to Corpuscular Defects

III. Hemoglobin defects
   A. Heme: congenital erythropoietic porphyria
   B. Globin
      1. Qualitative: hemoglobinopathies (e.g., Hb S, C, H, M)
      2. Quantitative: α- and β-thalassemias

IV. Congenital dyserythropoietic anemias
   A. Type I
   B. Type II
   C. Type III
   D. Type IV

Causes of Hemolytic Anemia Due to Extracorpuscular Defects

I. **Immune**
   A. Isoimmune
      1. Hemolytic disease of the newborn
      2. Incompatible blood transfusion
   B. Autoimmune: IgG only; complement only; mixed IgG and complement
      1. Idiopathic
         a. Warm antibody
         b. Cold antibody
         c. Cold–warm hemolysis (Donath–Landsteiner antibody)
      2. Secondary
         a. Infection, viral: infectious mononucleosis—Epstein–Barr virus (EBV), cytomegalovirus (CMV), hepatitis, herpes simplex, measles, varicella, influenza A, coxsackie virus B, human immunodeficiency virus (HIV); bacterial: streptococcal, typhoid fever, *Escherichia coli* septicemia, *Mycoplasma pneumoniae* (atypical pneumonia)
         b. Drugs and chemicals: quinine, quinidine, phenacetin, *p*-aminosalicylic acid, sodium cephalothin (Keflin), penicillin, tetracycline, rifampin, sulfonamides, chlorpromazine, pyradone, dipyrone, insulin; lead
         c. Hematologic disorders: leukemias, lymphomas, lymphoproliferative syndrome, associated idiopathic thrombocytopenic purpura (Evans syndrome), paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria
         d. Immunopathic disorders: systemic lupus erythematosus, periarteritis nodosa, scleroderma, dermatomyositis, rheumatoid arthritis, ulcerative colitis, agammaglobulinemia, Wiskott–Aldrich syndrome, dysgammaglobulinemia, IgA deficiency, thyroid disorders, giant cell hepatitis, Evans syndrome, autoimmune lymphoproliferative syndrome (ALPS), common variable immune deficiency
         e. Tumors: ovarian teratomata, dermoids, thymoma, carcinoma, lymphomas

Causes of Hemolytic Anemia Due to Extracorpuscular Defects

II. Nonimmune
   A. Idiopathic
   B. Secondary
      1. Infection, viral: infectious mononucleosis, viral hepatitis; bacterial: streptococcal, *E. coli* septicemia, *Clostridium perfringens, Bartonella bacilliformis;* parasites: malaria, histoplasmosis
      2. Drugs and chemicals: phenylhydrazine, vitamin K, benzene, nitrobenzene, sulfones, phenacetin, acetinalimide; lead
      3. Hematologic disorders: leukemia, aplastic anemia, megaloblastic anemia, hypersplenism, pyknocytosis
      4. Microangiopathic hemolytic anemia: thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, chronic relapsing schistocytic hemolytic anemia, burns, post cardiac surgery, march hemoglobinuria
      5. Miscellaneous: Wilson disease, erythropoietic porphyria, osteopetrosis, hypersplenism

Glucose-6-Phosphate Dehydrogenase Deficiency

- Glucose-6-phosphate dehydrogenase (G6PD) is the first enzyme in the pentose phosphate pathway of glucose metabolism. Deficiency diminishes the reductive energy of the red cell and may result in hemolysis, the severity of which depends on the quantity and type of G6PD and the nature of the hemolytic agent .

Genetics

- 1. Sex-linked recessive mode of inheritance by a gene located on the X chromosome(similar to hemophilia).
- 2. Disease is fully expressed in hemizygous males and homozygous females.
- 3. Variable intermediate expression is shown by heterozygous females (due to random deletion of X chromosome, according to Lyon hypothesis).

The molecular basis of G6PD deficiency

- 1. Deletions of G6PD genes are incompatible with life
- 2. Point mutations are responsible for G6PD deficiencies. They result in:

  a. *Sporadic mutations:* Have no causal relationship with malarial selection. These patients manifest with chronic nonspherocytic hemolytic anemia (CNSHA WHO Class I).

  b. *Polymorphic mutations: These mutations have resulted from malaria selection;*hence, they correlate with specific geographic areas. They are usually WHO Class II or III and not Class I.

WHO Class	Variant	Magnitude of enzyme deficiency	Severity of hemolysis
I	Harilaou, Tokyo, Guadalajara, Stonybrook, Minnesota	2% of normal activity	Chronic nonspherocytic hemolytic anemia
II	Mediterranean	3% of normal activity	Intermittent hemolysis
III	A^-	10–60% of normal activity	Intermittent hemolysis usually associated with infections or drugs
IV	B (Normal)	100% of normal activity	No hemolysis

Pathogenesis

- 1. Diminished NADPH/NADP and GSH/GSSG ratios
- 2. Impaired elimination of oxidants (e.g., H2O2)
- 3. Oxidation of hemoglobin
- 4. Red cell integrity impaired, especially on exposure to oxidant drugs and chemicals

Clinical Features

- Episodes of hemolysis may be produced by:
  - Drugs
  - Fava bean
  - Infection (in more susceptible subjects).

1. Drug-induced hemolysis

- a. Typically in African Americans but also in Mediterranean types
- b. List of drugs
- c. Acute self-limiting hemolytic anemia with hemoglobinuria
- d. Heinz bodies in circulating red cells
- e. Blister cells, fragmented cells, and spherocytes
- f. Reticulocytosis
- g. Hemoglobin normal between episodes

Table 7-7. Agents Capable of Inducing Hemolysis in G6PD-Deficient Subjects[a]

Clinically significant hemolysis	Usually not clinically significant hemolysis
Analgesics and antipyretics	
Acetanilid	Acetophenetidin (phenacetin)
	Acetylsalicylic acid (large doses)
	Antipyrine[a,b]
	Aminopyrine[b]
	p-Aminosalicyclic acid
Antimalarial agents	
Pentaquine	Quinacrine (Atabrine)
Pamaquine	Quinine[b]
Primaquine	Chloroquine[c]
Quinocide	Pyrimethamine (Daraprim)
	Plasmoquine
Sulfonamides	
Sulfanilamide	Sulfadiazine
N-Acetylsulfanilamide	Sulfamerazine
Sulfapyridine	Sulfisoxazole (Gantrisin)[c]
Sulfamethoxypyridazine (Kynex)	Sulfathiazole
Salicylazosulfapyridine (Azulfidine)	Sulfacetamide
Nitrofurans	
Nitrofurazone (Furacin)	
Nitrofurantoin (Furadantin)	
Furaltadone (Altafur)	
Furazolidone (Furoxone)	
Sulfones	
Thiazolsulfone (Promizole)	
Diaminodiphenylsulfone (DDS, dapsone)	Sulfoxone sodium (Diasone)
Miscellaneous	
Naphthalene	
Phenylhydrazine	Menadione
Acetylphenylhydrazine	Dimercaprol (BAL)
Toluidine blue	Methylene blue
Nalidixic acid (NegGram)	Chloramphenicol[b]
Neoarsphenamine (Neosalvarsan)	Probenecid (Benemid)
Infections	Quinidine[b]
Diabetic acidosis	Fava beans[b]

2. Favism

- a. Acute life-threatening hemolysis, often leading to acute renal failure caused by ingestion of fava beans
- b. Associated with Mediterranean and Canton varieties
- c. Blood transfusion required

3. Neonatal jaundice

- a. Usually associated with Mediterranean and Canton varieties
- b. Infants may present with pallor, jaundice (can be severe and produce kernicterus*),

  and dark urine.
- In a majority of neonates, the jaundice is not

  hemolytic but hepatic in origin.

4. Chronic nonspherocytic hemolytic anemia

- a. Occurs mainly in people of northern European origin
- b. Hematologic picture
  - (1) Chronic nonspherocytic anemia
  - (2) Reticulocytosis
  - (3) Shortened red cell survival
  - (4) Slight jaundice
  - (5) Mild splenomegaly.

Treatment

- 1. Avoidance of agents that are deleterious in G6PD deficiency
- 2. Indication for transfusion:
  a. Hemoglobin (Hb) level below 7 g/dL
  b. Persistent hemoglobinuria and Hb below 9 g/dL
- 3. Chronic nonspherocytic hemolytic anemia (NSHA):
  a. In patients with severe chronic anemia: transfuse red blood cells to maintain Hb level 8–10 g/dL and iron chelation, when needed
  b. Indications for splenectomy
    (1) Hypersplenism
    (2) Severe chronic anemia
    (3) Splenomegaly causing physical impediment

Hemophilia

- Hemophilia A (factor VlIl deficiency) and hemophilia B (factorIX deficiency) are the most common and serious congenital coagulation factor deficiencies.

Clinical Course of Hemophilia

- Hemophilia should be suspected when unusual bleeding is encountered in a male patient. Clinical presentations of hemophilia A and hemophilia B are indistinguishable.
- The frequency and severity of bleeding in hemophilia are usually related to the plasma levels of factor VIII or IX .
- The median age for first bleeding episode is 10 months, corresponding to the age at which the infant becomes mobile.

CLINICAL MANIFESTATIONS

Neither factor VIII nor factor IX crosses the placenta; Only approximately 2% of neonates with hemophilia sustain intracranial hemorrhages and 30% of male infants with hemophilia bleed with circumcision.

CLINICAL MANIFESTATIONS

- Even in patients with severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age.
- the hallmark of hemophilia is hemarthrosis.

Table 11-11. Relationship of Factor Levels to Severity of Clinical Manifestations of Hemophilia A and B

Type	Percentage factor VIII/IX	Type of hemorrhage
Severe	<1	Spontaneous; hemarthroses and deep soft 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	Variable	Gynecologic and obstetric hemorrhage common, other symptoms depend on plasma factor level.

Table 11-12. Common Sites of Hemorrhage in Hemophilia

- Hemarthrosis
- Intramuscular hematoma
- Hematuria
- Mucous membrane hemorrhage
  - Mouth
  - Dental
  - Epistaxis
  - Gastrointestinal
- High-risk hemorrhage
  - Central nervous system
    - Intracranial
    - Intraspinal
  - Retropharyngeal
  - Retroperitoneal
  - Hemorrhage causing compartment syndrome/nerve compression
    - Femoral (iliopsoas muscle)
    - Sciatic (buttock)
    - Tibial (calf muscle)
    - Perineal (anterior compartment of leg)
    - Median and ulnar nerve (flexor muscles of forearm)

Table 11-13. Incidence of Severity and Clinical Manifestations of Hemophilia

Severity	Severe	Moderate	Mild
Incidence			
Hemophilia A	70%	15%	15%
Hemophilia B	50%	30%	20%
Bleeding manifestations			
Age of onset	≤1 year	1–2 years	2 years–adult
Neonatal hemorrhages			
Following circumcision	Common	Common	None
Intracranial	Occasionally	Rare	Rare
Muscle/joint hemorrhage	Spontaneous	Following minor trauma	Following trauma
CNS hemorrhage	High risk	Moderate risk	Rare[a]
Postsurgical hemorrhage	Common	Common	Rare[a]
Oral hemorrhage[b]	Common	Common	Rare[a]

[a]FVIII, >25; FIX, >15.

[b]Following trauma or tooth extraction.

Treatment

- Factor replacement therapy is the mainstay of hemophilia treatment. The degree of factor correction required to achieve hemostasis is largely determined by the site and nature of the particular bleeding episode.
- Strategies for hemophilia care include on demand treatment of acute bleeding episodes or, for severe hemophilia patients, prophylactic administration of clotting factor concentrate to maintain trough factor levels >1% augmented with on-demand treatment of breakthrough bleeding episodes.

Ancillary Therapy

- DDAVP
- In hemophilia A patients (DDAVP) increases plasma FVIII levels 2.5- to 6-fold. It is commonly used to treat selected hemorrhagic episodes in mild hemophilia A patients. When used intravenously the dose is 0.3 µg/kg administered in 25–50 mL normal saline over 15–20 minutes. Subcutaneous DDAVP is as effective as intravenous DDAVP, facilitating treatment of very young patients with limited venous access.
- Concentrated intranasal DDAVP (Stimate), available as a 1.5-mg/mL preparation,has approximately two thirds the effect of intravenous DDAVP.

Table 11-15. Treatment of Bleeding Episodes

Type of hemorrhage	Hemostatic factor level	Hemophilia A	Hemophilia B	Comment/ adjuncts
Hemarthrosis	30–50% minimum	FVIII 20–40 U/kg q12–24h as needed; if joint still painful after 24 h, treat for further 2 days	FIX 30–40 U/kg q24h as needed; if joint still painful after 24 h, treat for further 2 days	Rest, immobilization, cold compress, elevation.
Muscle	40–50% minimum, for iliopsoas or compartment syndrome, 100%, then 50–100% × 2–4 days	20–40 U/kg q12–24h as needed For iliopsoas or compartment syndrome, initial dose is 50 U/kg	40–60 U/kg q24h as needed For iliopsoas or compartment syndrome, initial dose is 60–80 U/kg	Calf/forearm bleeds can be limb threatening. Significant blood loss can occur with femoral-retroperitoneal bleed.
Oral mucosa	Initially 50%, then EACA at 50 mg/kg q6h × 7 days usually suffices	25 U/kg	50 U/kg	Antifibrinolytic therapy is critical. Do not use with PCC or APCC.
Epistaxis	Initially 30–40%, use of EACA 50 mg/kg q6h until healing occurs may be helpful	15–20 U/kg	30–40 U/kg	Local measures: pressure, packing.
Gastrointestinal	Initially 100%, then 50% until healing occurs	FVIII 50 U/kg, then 25 U/kg q12h	FIX 100 U/kg, then 50 U/kg q day	Lesion is usually found, endoscopy is recommended, antifibrinolytic therapy may be helpful.

Table 11-15. (*Continued*)

Type of hemorrhage	Hemostatic factor level	Hemophilia A	Hemophilia B	Comment/ adjuncts
Hematuria	Painless hematuria can be treated with complete bed rest and vigorous hydration for 48 hrs. For pain or persistent hematuria 100%	FVIII 50 units/kg; if not resolved, 30–40 U/kg q day until resolved	FIX 80–100 units/kg; if not resolved, then 30–40 U/kg q day until resolved	Evaluate for stones or urinary tract infection. Lesion may not be found. Prednisone 1–2 mg/kg/d × 5–7 days may be helpful. Avoid antifibrinolytics.
Central nervous system	Initially 100%, then 50–100% for 14 days	50 U/kg, then 25 U/kg q12h	80–100 U/kg, then 50 U/kg q24h	Treat presumptively before evaluating, hospitalize. Lumbar puncture requires prophylactic factor coverage.
Retroperitoneal retropharyngeal	Initially 80–100%, then 50–100% until complete resolution	FVIII 50 units/kg, then 25 U/kg q12h until resolved	FIX 100 U/kg, then 50 U/kg q24h until resolved	Hospitalize.
Trauma or surgery	Initially 100%, then 50% until wound healing is complete	50 U/kg, then 25 U/kg q12h	100 U/kg, then 50 U/kg q24h	Evaluate for inhibitor prior to elective surgery.

Ancillary Therapy

- Antifibrinolytic Therapy
- Antifibrinolytic drugs inhibit fibrinolysis by preventing activation of the proenzyme plasminogen to plasmin.
- Tranexamic acid (Cyklokapron):
- 20–25 mg/kg (maximum, 1.5 g) orally or
- 10 mg/kg(maximum, 1.0 g) intravenously every 8 hours.

THANK YOU