Approach to Bleeding Diathesis

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Objectives
I. Clinical aspects of bleeding
II. Hematologic disorders causing bleeding
   • Coagulation factor disorders
   • Platelet disorders
III. Approach to acquired bleeding disorders
   • Hemostasis in liver disease
   • Surgical patients
   • Warfarin toxicity
IV. Approach to laboratory abnormalities
   • Diagnosis and management of thrombocytopenia
V. Drugs and blood products used for bleeding

Objectives - I
• Clinical aspects of bleeding

Clinical Features of Bleeding Disorders

<table>
<thead>
<tr>
<th>Site of bleeding</th>
<th>Platelet disorders</th>
<th>Coagulation factor disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin</td>
<td>Deep in soft tissues (joints, muscles)</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Mucous membranes (epistaxis, gum, vaginal, GI tract)</td>
<td></td>
</tr>
<tr>
<td>Ecchymoses (&quot;bruises&quot;)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hemarthrosis / muscle bleeding</td>
<td>Small, superficial</td>
<td>Large, deep</td>
</tr>
<tr>
<td>Bleeding after cuts &amp; scratches</td>
<td>Extremely rare</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding after surgery or trauma</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Immediate, usually mild</td>
<td>Delayed (1-2 days), often severe</td>
</tr>
</tbody>
</table>

Petechiae
(typical of platelet disorders)

Do not blanch with pressure (cf. angiomas)
Not palpable (cf. vasculitis)
Ecchymoses
(typical of coagulation factor disorders)

Objectives - II
- Hematologic disorders causing bleeding
  - Coagulation factor disorders
  - Platelet disorders
Coagulation factor disorders

- Inherited bleeding disorders
  - Hemophilia A and B
  - von Willebrand’s disease
  - Other factor deficiencies

- Acquired bleeding disorders
  - Liver disease
  - Vitamin K deficiency/warfarin overdose
  - DIC

Hemophilia A and B

<table>
<thead>
<tr>
<th>Coagulation factor deficiency</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>X-linked</td>
<td>X-linked</td>
</tr>
<tr>
<td>Incidence</td>
<td>1/10,000 males</td>
<td>1/50,000 males</td>
</tr>
<tr>
<td>Severity</td>
<td>Related to factor level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1% - Severe - spontaneous bleeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-5% - Moderate - bleeding with mild injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-25% - Mild - bleeding with surgery or trauma</td>
<td></td>
</tr>
</tbody>
</table>

Complications

- Soft tissue bleeding

Hemophilia

Clinical manifestations (hemophilia A & B are indistinguishable)

- Hemarthrosis (most common)
- Fixed joints
- Soft tissue hematomas (e.g., muscle)
- Muscle atrophy
- Shortened tendons
- Other sites of bleeding
  - Urinary tract
  - CNS, neck (may be life-threatening)
- Prolonged bleeding after surgery or dental extractions

Hemarthrosis (acute)

HISTORY

- Bleeding history
  - Forms the basis of the diagnosis and therapy of hemorrhagic disorders.
- Establishing symptoms
- A Lead to differential diagnosis
HISTORY

- Repeated visits to other physicians
- Previous need for transfusion of
  - Whole blood
  - Packed cells
  - Plasma
  - Platelets
- Documented anemia & prescription

DOCUMENTING HISTORY

- Epistaxis
- Gingival haemorrhage
- Petechae / bruise
- Tooth extractions
- Veni Puncture site bleeding

DOCUMENTING HISTORY Contd.,

- Bleeding from minor / major cuts
- Previous surgical procedure
  - Excessive bleeding
  - Needed transfusion
  - Re operation
  - Wound healing
- Bleeding at circumcision

- Hemoptysis
- Hematemesis
- Hematuria
- Hematochezia
- Melena

MENSTRUAL HISTORY

- CNS bleeding
- Ophthalmic bleeding
- Hemarthrosis

- Frequency
- Duration
- Compared to Peers
- Required transfusions
- Local causes
CHILD BIRTH
- Pregnancies
- Spontaneous / Induced abortions
- Estimated blood loss
- Documented anaemia
- Required
  - Transfusion
  - D & C
  - Hysterectomy
  - Iron therapy

Neonatal history
- Medicines
- Dietary history
- Family history / pedigree chart

EXAMINATION
- Age
- Sex
- General Examination
- Systemic examination

THROMBOCYTOPENIA
- Congenital
  - Is the history since birth
  - Is bleeding worse than count
  - Is there a family history
  - Are there any physical congenital abnormalities

THROMBOCYTOPENIA Contd.,
- Other differential diagnosis must be considered
  - Additional laboratory abnormalities
    - WBC - abnormal cells, neutropenia
    - RBC - Macrocytosis, Fragmentation
  - Are there additional clinical features
    - Lymphadenopathy, splenomegaly
    - Bone pain, Limping
    - Sick child
* In the presence of above findings consider marrow examination
- Underlying disorders
  - SLE
  - Auto antibody screen - ANF and ds DNA
- Anti-phospholipid syndrome
- HIV infection

- Intermediate purity plasma products
  - Virucidally treated
  - May contain von Willebrand factor
- High purity (monoclonal) plasma products
  - Virucidally treated
  - No functional von Willebrand factor
- Recombinant factor VIII
  - Virus free/No apparent risk
  - No functional von Willebrand factor

Dosing guidelines for hemophilia A

- Mild bleeding
  - Target: 30% dosing q8-12h; 1-2 days (15U/kg)
  - Hemarthrosis, ophthalmoplegia or dental, epistaxis, hematuria
- Major bleeding
  - Target: 80-100% q8-12h; 7-14 days (50U/kg)
  - CNS trauma, hemorrhage, lumbar puncture
  - Surgery
  - Retropitoneal hemorrhage
  - GI bleeding
- Adjunctive therapy
  - ε-aminocaproic acid (Amicar) or DDAVP (for mild disease only)

Complications of therapy

- Formation of inhibitors (antibodies)
  - 10-15% of severe hemophilia A patients
  - 1-2% of severe hemophilia B patients
- Viral infections
  - Hepatitis B
  - Hepatitis C
  - HIV
  - Human parvovirus
  - Hepatitis A
  - Other

Viral infections in hemophiliacs

<table>
<thead>
<tr>
<th>Hepatitis serology</th>
<th>HIV-positive (% positive)</th>
<th>HIV-negative (% positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>24</td>
<td>45</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>74</td>
<td>34</td>
</tr>
</tbody>
</table>

Blood 1993:81:412-418
Treatment of hemophilia B

- **Agent**
  - High purity factor IX
  - Recombinant human factor IX

- **Dose**
  - Initial dose: 100U/kg
  - Subsequent: 50U/kg every 24 hours

von Willebrand Disease: Clinical Features

- **von Willebrand factor**
  - Synthesis in endothelium and megakaryocytes
  - Forms large multimer
  - Carrier of factor VIII
  - Anchors platelets to subendothelium
  - Bridge between platelets

- **Inheritance**: autosomal dominant
- **Incidence**: 1/10,000
- **Clinical features**: mucocutaneous bleeding

Understanding of VWD

- **von Willebrand factor**
  - Synthesis in endothelium and megakaryocytes
  - Forms large multimer
  - Carrier of factor VIII
  - Anchors platelets to subendothelium
  - Bridge between platelets

- **Inheritance**: autosomal dominant
- **Incidence**: 1/10,000
- **Clinical features**: mucocutaneous bleeding

Laboratory evaluation of von Willebrand disease

- **Classification**
  - Type 1: Partial quantitative deficiency
  - Type 2: Qualitative deficiency
  - Type 3: Total quantitative deficiency

- **Diagnostic tests**

<table>
<thead>
<tr>
<th>Assay</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWF antigen</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
</tr>
<tr>
<td>vWF activity</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
</tr>
<tr>
<td>Multimer analysis</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Treatment of von Willebrand Disease

- **Cryoprecipitate**
  - Source of fibrinogen, factor VIII and VWF
  - Only plasma fraction that consistently contains VWF multimers

- **DDAVP** (deamino-8-arginine vasopressin)
  - ↑ plasma VWF levels by stimulating secretion from endothelium
  - Duration of response is variable
  - Not generally used in type 2 disease
  - Dosage: 0.3 µg/kg q 12 hr IV

- **Factor VIII concentrate (Intermediate purity)**
  - Virally inactivated product

Vitamin K deficiency

- **Source of vitamin K**
  - Green vegetables
  - Synthesized by intestinal flora

- **Required for synthesis**
  - Factors II, VII, IX, X
  - Protein C and S

- **Causes of deficiency**
  - Malnutrition
  - Biliary obstruction
  - Malabsorption
  - Antibiotic therapy

- **Treatment**
  - Vitamin K
  - Fresh frozen plasma
Common clinical conditions associated with Disseminated Intravascular Coagulation

Activation of both coagulation and fibrinolysis
Triggered by:
- Sepsis
- Trauma
  - Head injury
  - Fat embolism
- Malignancy
- Obstetrical complications
  - Amniotic fluid embolism
  - Abruptio placentae
- Vascular disorders
- Reaction to toxin (e.g. snake venom, drugs)
- Immunologic disorders
  - Severe allergic reaction
  - Transplant rejection

Disseminated Intravascular Coagulation (DIC) Mechanism

Systemic activation of coagulation

Intravascular deposition of fibrin

Depletion of platelets and coagulation factors

Thrombosis of small and midsize vessels with organ failure

Bleeding

Pathogenesis of DIC

Release of thromboplastic material into circulation

Fibrinogen

Fibrin

Thrombin

Consumption of coagulation factors;
presence of FDPs

↑ aPTT

↑ PT

↓ Fibrinogen

Presence of plasmin

↑ FDP

Intravascular clot

↓ Platelets

Schistocytes

Laboratory Evaluation of DIC

1. ASSESS DEPLETION OF COAGULATION FACTORS
2. ASSESS FIBRINOLYSIS
3. BLOOD FILM FOR MICRO-ANGIOPATHY

Laboratory Evaluation of DIC - I

• Assess Depletion Of Coagulation Factors
  • PLATELET COUNT
  • PROTHROMBIN TIME
  • PARTIAL THROMBOPLASTIN TIME
  • THROMBIN TIME
  • FIBRINOGEN
Laboratory Evaluation of DIC-II

Tests Of Fibrinolysis
- CLOT LYSIS
- EUGLOBIN LYSIS TIME
- FIBRIN PLATE LYSIS
- PARA-COAGULATION
- FDP
- D DIMER

Laboratory Evaluation of DIC-III

- Prothrombin activation peptide [F1.2]
- Thrombin anti-thrombin complexes
- AT III levels

These tests are not available for routine clinical management.

Disseminated Intravascular Coagulation Treatment approaches
- Treatment of underlying disorder
- Anticoagulation with heparin
- Platelet transfusion
- Fresh frozen plasma
- Coagulation inhibitor concentrate (ATIII)

Classification of platelet disorders

<table>
<thead>
<tr>
<th>Quantitative disorders</th>
<th>Qualitative disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal distribution</td>
<td>Inherited disorders (rare)</td>
</tr>
<tr>
<td>Dilution effect</td>
<td>Acquired disorders</td>
</tr>
<tr>
<td>Decreased production</td>
<td>Medications</td>
</tr>
<tr>
<td>Increased destruction</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td></td>
<td>Cardiopulmonary bypass</td>
</tr>
</tbody>
</table>

Thrombocytopenia

- Immune-mediated
  - Idiopathic
  - Drug-induced
  - Collagen vascular disease
  - Lymphoproliferative disease
  - Sarcoidosis
- Non-immune mediated
  - DIC
  - Microangiopathic hemolytic anemia

Approach to the thrombocytopenic patient
- History
  - Is the patient bleeding?
  - Are there symptoms of a secondary illness? (neoplasm, infection, autoimmune disease)
  - Is there a history of medications, alcohol use, or recent transfusion?
  - Are there risk factors for HIV infection?
  - Is there a family history of thrombocytopenia?
  - Do the sites of bleeding suggest a platelet defect?
- Assess the number and function of platelets
  - CBC with peripheral smear
  - Bleeding time or platelet aggregation study
Bleeding time and bleeding

- 5-10% of patients have a prolonged bleeding time
- Most of the prolonged bleeding times are due to aspirin or drug ingestion
- Prolonged bleeding time does not predict excess surgical blood loss
- Not recommended for routine testing in preoperative patients

Features of Acute and Chronic ITP

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age</td>
<td>Children (2-6 yrs)</td>
<td>Adults (20-40 yrs)</td>
</tr>
<tr>
<td>Female:male</td>
<td>1:1</td>
<td>3:1</td>
</tr>
<tr>
<td>Antecedent infection</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td>Abrupt</td>
<td>Abrupt-indolent</td>
</tr>
<tr>
<td>Platelet count at presentation</td>
<td>&lt;20,000</td>
<td>&lt;50,000</td>
</tr>
<tr>
<td>Duration</td>
<td>2-6 weeks</td>
<td>Long-term</td>
</tr>
<tr>
<td>Spontaneous remission</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Initial Treatment of ITP

<table>
<thead>
<tr>
<th>Platelet count (per µl)</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50,000</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>20-50,000</td>
<td>Not bleeding</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>IVIG</td>
</tr>
<tr>
<td>&lt;20,000</td>
<td>Not bleeding</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>Glucocorticoids IVIG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospitalization</td>
</tr>
</tbody>
</table>

Summary of case series with ITP

<table>
<thead>
<tr>
<th>Variable</th>
<th>No./total</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>370/1447</td>
<td>(26%)</td>
</tr>
<tr>
<td>With glucocorticoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With splenectomy</td>
<td>581/885</td>
<td>(66%)</td>
</tr>
<tr>
<td>Death from hemorrhage</td>
<td>78/1761</td>
<td>(4%)</td>
</tr>
<tr>
<td>Healthy at last observation</td>
<td>1027/1606</td>
<td>(64%)</td>
</tr>
</tbody>
</table>

Long-term morbidity and mortality in adults with ITP

- 134 patients with severe ITP studied for mean of 10.5 yrs
  - CR and PR patients (85%)
    - No increased mortality compared to control population
  - Non-responders/maintenance therapy
    - Increased morbidity due to ITP-related hospitalizations
    - Increased mortality related equally to bleeding and infection

George, JN. N Engl J Med: 1994;331; 1207
Portielje JE et al. Blood 2001;97:2549
Objectives - III

- Approach to acquired bleeding disorders
  - Hemostasis in liver disease
  - Surgical patients
  - Warfarin toxicity

Liver Disease and Hemostasis

1. Decreased synthesis of II, VII, IX, X, XI, and fibrinogen
2. Dietary Vitamin K deficiency (Inadequate intake or malabsorption)
3. Dysfibrinogenemia
4. Enhanced fibrinolysis (Decreased alpha-2-antiplasmin)
5. DIC
6. Thrombocytope尼亚 due to hypersplenism

Management of Hemostatic Defects in Liver Disease

- Treatment for prolonged PT/PTT
  - Vitamin K 10 mg SQ x 3 days - usually ineffective
  - Fresh-frozen plasma infusion
  - 25-30% of plasma volume (1200-1500 ml)
  - Immediate but temporary effect

- Treatment for low fibrinogen
  - Cryoprecipitate (1 unit/10kg body weight)

- Treatment for DIC (Elevated D-dimer, low factor VIII, thrombocytopenia
  - Replacement therapy

Vitamin K deficiency due to warfarin overdose

Managing high INR values

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR therapeutic-5</td>
<td>Lower or omit next dose; Resume therapy when INR is therapeutic</td>
</tr>
<tr>
<td>INR 5-9; no bleeding</td>
<td>Lower or omit next dose; Resume therapy when INR is therapeutic</td>
</tr>
<tr>
<td></td>
<td>Omit dose and give vitamin K (1-2.5 mg po)</td>
</tr>
<tr>
<td></td>
<td>Rapid reversal: vitamin K 2-4 mg po (repeat)</td>
</tr>
<tr>
<td>INR &gt;9; no bleeding</td>
<td>Omit dose; vitamin K 3-5 mg po; repeat as necessary</td>
</tr>
<tr>
<td></td>
<td>Resume therapy at lower dose when INR therapeutic</td>
</tr>
</tbody>
</table>

Any life-threatening bleeding

Omit warfarin
Vitamin K 10 mg slow IV infusion
PCC (or recombinant human factor VIIa)
Repeat vitamin K injections every 12 hrs as needed

Approach to Post-operative bleeding

1. Is the bleeding local or due to a hemostatic failure?
   1. Local: Single site of bleeding usually rapid with minimal coagulation test abnormalities
   2. Hemostatic failure: Multiple site or unusual pattern with abnormal coagulation tests

2. Evaluate for causes of peri-operative hemostatic failure
   1. Proximating abnormality
   2. Special cases (e.g. Cardiopulmonary bypass)

3. Diagnosis of hemostatic failure
   1. Review pre-operative testing
   2. Obtain updated testing
Objectives - IV

- Approach to laboratory abnormalities
  - Diagnosis and management of thrombocytopenia

Laboratory Evaluation of Bleeding

Overview

- CBC and smear
  - Platelet count
  - RBC and platelet morphology
- Coagulation
  - Prothrombin time
  - Partial thromboplastin time
  - Coagulation factor assays
  - 50:50 mix
  - Fibrinogen assay
  - Thrombin time
  - FDPs or D-dimer
- Platelet function
  - von Willebrand factor
  - Bleeding time
  - Platelet function analyzer (PFA)
  - Platelet function tests

Laboratory Evaluation of the Coagulation Pathways

Partial thromboplastin time (PTT)  Prothrombin time (PT)

Intrinsic pathway  Extrinsic pathway

Intrinsic system (surface contact)
- XIIa
- Xa
- XI
- IX
- VIIIa
- VIIa

Extrinsic system (tissue damage)
- Tissue factor
- X
- IXa
- VIIa
- VIII
- VII

Common pathway

Pre-analytic errors

- Problems with blue-top tube
  - Partial fill tubes
  - Vacuum leak and citrate evaporation
- Problems with phlebotomy
  - Heparin contamination
  - Wrong label
  - Slow fill
  - Underfill
  - Vigorous shaking
- Biological effects
  - Hct ≥55 or ≤15
  - Lipemia, hyperbilirubinemia, hemolysis
- Laboratory errors
  - Delay in testing
  - Prolonged incubation at 37°C
  - Freeze/thaw deterioration

Coagulation cascade

Blood Film
Initial Evaluation of a Bleeding Patient - 1

Normal PT  
Normal PTT  

- Urea solubility  
  Abnormal: Factor XIII deficiency  
  Normal:  

Consider evaluating for:  
- Mild factor deficiency  
- Abnormal fibrinolysis  
- Platelet disorder  
- Vascular disorder  

- Monoclonal gammopathy  

Initial Evaluation of a Bleeding Patient - 2

Normal PT  
Abnormal PTT  

- Repeat with 50:50 mix is abnormal  
- Test for inhibitor activity:  
  Specific: Factors VIII, IX, XI  
  Non-specific: anti-phospholipid Ab  

Initial Evaluation of a Bleeding Patient - 3

Abnormal PT  
Normal PTT  

- Repeat with 50:50 mix is abnormal  
  Test for inhibitor activity:  
  Specific: Factor VII (rare)  
  Non-specific: Anti-phospholipid (rare)  

- 50:50 mix is normal  
  Test for factor deficiency:  
  Isolated deficiency of factor VII (rare)  
  Multiple factor deficiencies (common)  

  (Liver disease, vitamin K deficiency, warfarin, DIC)  

Initial Evaluation of a Bleeding Patient - 4

Abnormal PT  
Abnormal PTT  

- Repeat with 50:50 mix is abnormal  
- Test for inhibitor activity:  
  Specific: Factors V, X, Prothrombin, Fibrinogen (rare)  
  Non-specific: anti-phospholipid (common)  

- 50:50 mix is normal  
- Test for factor deficiency:  
  Isolated deficiency in common pathway: Factors V, X, Prothrombin, Fibrinogen  
  Multiple factor deficiencies (common)  
  (Liver disease, vitamin K deficiency, warfarin, DIC)  

Coagulation factor deficiencies

Summary

Sex-linked recessive  
- Factors VIII and IX deficiencies cause bleeding  
  Prolonged PTT; PT normal  

Autosomal recessive (rare)  
- Factors II, V, VII, X, XI, fibrinogen deficiencies cause bleeding  
  Prolonged PT and/or PTT  
- Factor XIII deficiency is associated with bleeding and impaired wound healing  
  PT/PTT normal; clot solubility abnormal  
- Factor XII, prekallikrein, HMWK deficiencies do not cause bleeding  

Thrombin Time

- Bypasses factors II-XII  
- Measures rate of fibrinogen conversion to fibrin  

Procedure:  
- Add thrombin with patient plasma  
- Measure time to clot  

Variables:  
- Source and quantity of thrombin
Causes of prolonged Thrombin Time

- Heparin
- Hypofibrinogenemia
- Dysfibrinogenemia
- Elevated FDPs or paraprotein
- Thrombin inhibitors (Hirudin)
- Thrombin antibodies

Objectives - V

- Drugs and blood products used for bleeding

Treatment Approaches to the Bleeding Patient

- Red blood cells
- Platelet transfusions
- Fresh frozen plasma
- Cryoprecipitate
- Amicar
- DDAVP
- Recombinant Human factor VIIa

RBC transfusion therapy

Indications

- Improve oxygen carrying capacity of blood
  - Bleeding
  - Chronic anemia that is symptomatic
  - Peri-operative management

Red blood cell transfusions

Special preparation

<table>
<thead>
<tr>
<th>CMV-negative</th>
<th>CMV-negative patients</th>
<th>Prevent CMV transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irradiated RBCs</td>
<td>Immune deficient recipient</td>
<td>Prevent GVHD</td>
</tr>
<tr>
<td>Leukopenor</td>
<td>Previous non-hemolytic transfusion reaction</td>
<td>Prevents reaction</td>
</tr>
<tr>
<td>Washed RBC</td>
<td>PNH patients</td>
<td>Prevents hemolysis</td>
</tr>
</tbody>
</table>

Adverse reactions

Immunologic reactions

- Hemolysis: RBC incompatibility
- Anaphylaxis: Usually unknown; rarely against IgA
- Febrile reaction: Antibody to neutrophils
- Urticaria: Antibody to donor plasma proteins
- Non-cardiogenic pulmonary edema: Donor antibody to leukocytes

- Febrile reaction: Antibody to neutrophils
- Urticaria: Antibody to donor plasma proteins
- Non-cardiogenic pulmonary edema: Donor antibody to leukocytes
# Red blood cell transfusions

## Adverse reactions

<table>
<thead>
<tr>
<th>Non-immunologic reactions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>Volume overload</td>
</tr>
<tr>
<td>Fever and shock</td>
<td>Bacterial contamination</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Massive transfusion</td>
</tr>
</tbody>
</table>

## Transfusion-transmitted disease

<table>
<thead>
<tr>
<th>Infectious agent</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>~1/500,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1/600,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1/500,000</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>&lt;1/1,000,000</td>
</tr>
<tr>
<td>HTLV I/II</td>
<td>1/500,000</td>
</tr>
<tr>
<td>CMV</td>
<td>50% donors are sero-positive</td>
</tr>
<tr>
<td>Bacteria</td>
<td>1/250 in platelet transfusions</td>
</tr>
<tr>
<td>Creutzfeld-Jakob disease</td>
<td>Unknown</td>
</tr>
<tr>
<td>Others</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

## Platelet transfusions

- **Source**
  - Platelet concentrate (Random donor)
  - Pheresis platelets (Single donor)

- **Target level**
  - Bone marrow suppressed patient (>10-20,000/µl)
  - Bleeding/surgical patient (>50,000/µl)

## Platelet transfusions - complications

- **Transfusion reactions**
  - Higher incidence than in RBC transfusions
  - Related to length of storage/leukocytes/RBC mismatch
  - Bacterial contamination

- **Platelet transfusion refractoriness**
  - Alloimmune destruction of platelets (HLA antigens)
  - Non-immune refractoriness
  - Microangiopathic hemolytic anemia
  - Coagulopathy
  - Splenic sequestration
  - Fever and infection
  - Medications (Amphotericin, vancomycin, ATG, Interferons)

## Fresh frozen plasma

- **Content** - plasma (decreased factor V and VIII)
- **Indications**
  - Multiple coagulation deficiencies (liver disease, trauma)
  - DIC
  - Warfarin reversal
  - Coagulation deficiency (factor XI or VII)
- **Dose** (225 ml/unit)
  - 10-15 ml/kg
- **Note**
  - Viral screened product
  - ABO compatible

## Cryoprecipitate

- **Prepared from FFP**
- **Content**
  - Factor VIII, von Willebrand factor, fibrinogen
- **Indications**
  - Fibrinogen deficiency
  - Uremia
  - von Willebrand disease
- **Dose** (1 unit = 1 bag)
  - 1-2 units/10 kg body weight
Hemostatic drugs

**Aminocaproic acid (Amicar)**
- **Mechanism**
  - Prevent activation plasminogen -> plasmin
- **Dose**
  - 50mg/kg po or IV q 4 hr
- **Uses**
  - Primary menorrhagia
  - Oral bleeding
  - Bleeding in patients with thrombocytopenia
  - Blood loss during cardiac surgery
- **Side effects**
  - GI toxicity
  - Thrombus formation

**Desmopressin (DDAVP)**
- **Mechanism**
  - Increased release of VWF from endothelium
- **Dose**
  - 0.3µg/kg IV q12 hrs
  - 150mg intranasal q12hrs
- **Uses**
  - Most patients with von Willebrand disease
  - Mild hemophilia A
- **Side effects**
  - Facial flushing and headache
  - Water retention and hyponatremia

**Recombinant human factor VIIa (rhVIIa; Novoseven)**
- **Mechanism**
  - Direct activation of common pathway
- **Use**
  - Factor VIII inhibitors
  - Bleeding with other clotting disorders
  - Warfarin overdose with bleeding
  - CNS bleeding with or without warfarin
  - Dose
  - 90 µg/kg IV q 2 hr
  - "Adjust as clinically indicated"
- **Cost (70 kg person) - $1 per µg**
  - ~$5,000/dose or $60,000/day

**Screening Tests (APTT, PT, Platelet count)**
- **APTT prolonged, PT normal**
  - Probable hemophilia
  - Perform factor VIII and factor IX assay
- **PT prolonged, APTT normal**
  - Probable factor XI deficiency
  - Perform factor XI assay
  - Congenital factor XI deficiency
- **PT and APTT prolonged**
  - Suspect lack of cross-linking of fibrin clot by factor XII (factor XII deficiency)
  - Perform clot lysis test in 5 Mol/L urea
  - Suspect excessive clot lysis due to a deficiency of one of the major physiologic inhibitors of fibrinolysis
  - Measure α2-antiplasmin and plasminogen activator inhibitor -
Approach to bleeding disorders

Summary

Identify and correct any specific defect of hemostasis
- Laboratory testing is almost always needed to establish the cause of bleeding
- Screening tests (PT, PTT, platelet count) will often allow placement into one of the broad categories
- Specialized testing is usually necessary to establish a specific diagnosis

Use non-transfusional drugs whenever possible

RBC transfusions for surgical procedures or large blood loss

FUTURE

A. Endothelium - Major Regulatory Site
B. Cell Mediated
C. Adhesive molecules
D. Matrix metalloproteinases
E. Z-Protein

Thank You

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