Approach to bleeding disorders & treatment

by

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Approach to a patient of bleeding diathesis

1. Clinical evaluation: History,
   Clinical features

2. Laboratory approach: First line screening tests
   Second line specific tests
Clinical evaluation of bleeding patient

• History: Age at first manifestations
  - Family history
  - Spontaneous or after trauma
  - Time of manifestation after injury
  - Ease with which bleeding is controlled
  - Drug history

• Results of the clinical evaluation should lead to an efficient laboratory investigation
<table>
<thead>
<tr>
<th>INHERITED DISORDERS</th>
<th>ACQUIRED DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Early age of presentation</td>
<td>• Later age of presentation</td>
</tr>
<tr>
<td>• Family history positive</td>
<td>• Family history usually negative</td>
</tr>
<tr>
<td>• More severe</td>
<td>• Less severe</td>
</tr>
<tr>
<td>• Bleeding is the dominant feature</td>
<td>• Clinical picture is dominated by the underlying disorder e.g. DIC</td>
</tr>
<tr>
<td>• Single factor defect</td>
<td>• Multiple hemostatic defect</td>
</tr>
</tbody>
</table>
• Many infants with inherited coagulation disorders do not bleed significantly in the neonatal period.
• Hematomas may first be seen only when the child becomes active. Hemarthrosis commonly does not develop until a child is 3 or 4 years of age.
<table>
<thead>
<tr>
<th>Finding</th>
<th>Disorders of Coagulation</th>
<th>Disorders of Platelets or Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>Rare</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Deep dissecting hematomas</td>
<td>Characteristic</td>
<td>Rare</td>
</tr>
<tr>
<td>Superficial ecchymoses</td>
<td>Common; usually large and solitary</td>
<td>Characteristic; usually small and multiple</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>Characteristic</td>
<td>Rare</td>
</tr>
<tr>
<td>Delayed bleeding</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bleeding from superficial cuts and scratches</td>
<td>Minimal</td>
<td>Persistent; often profuse</td>
</tr>
<tr>
<td>Sex of patient</td>
<td>80%–90% of inherited forms occur only in male patients</td>
<td>Relatively more common in females</td>
</tr>
<tr>
<td>Positive family history</td>
<td>Common</td>
<td>Rare (except von Willebrand disease and hereditary hemorrhagic telangiectasia)</td>
</tr>
</tbody>
</table>
Clinical features of acquired bleeding disorders

• Bleeding manifestations usually are less severe than in the inherited forms.

• The clinical picture often is dominated by evidence of the underlying disorder rather than by bleeding alone.

• For example, DIC usually is associated with significant complications such as sepsis, hypoxia, acidosis.

• The physician should suspect sepsis or occult thrombosis in any sick neonate with unexplained thrombocytopenia.

• Multiple hemostatic defects commonly are present in patients with acquired hemorrhagic diseases, which often include thrombocytopenia and significant coagulation abnormalities.
FIGURE 45.1. Diffuse petechial rash induced by a tourniquet in a patient with chronic idiopathic thrombocytopenic purpura (platelet count = $40 \times 10^9/L$).
Clinical history of bleeding

Screening studies:
- CBC, Blood smear, PT, PTT
- Bleeding time/PFA

PT, PTT abnormal
- PTT only prolonged
  - FVIII, FIX, FXI
- PT only prolonged
  - FVII
- PT and PTT prolonged
  - FV, FX, prothrombin, fibrinogen
- Lupus anticoagulant screen
  - Mixing Study

Abnormal CBC, blood film, bleeding time/PFA
- vWD
  - vWF antigen
  - vWF:RCo
  - FVIII
  - vWF multimers
  - RIPA

Platelet Disorders:
- Congenital or Acquired
  - Platelet count
  - Morphology
  - Aggregometry
  - Electron microscopy
  - Review medications
  - Evaluate for other systemic disorders

No abnormalities
- FXIII assay
  - Consider rare fibrinolytic disorder
  - Evaluate for:
    - Connective tissue disorder
    - Child abuse
## Profiles of Hemostasis Screening Tests in Patients with Bleeding Disorders

<table>
<thead>
<tr>
<th>Prothrombin Time</th>
<th>Activated Partial Thromboplastin Time</th>
<th>Platelet Count</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>—</td>
<td>—</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acquired factor VII deficiency (early liver disease; early vitamin K deficiency; early warfarin therapy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Factor VII inhibitor; dysfibrinogenemia; some cases of DIC; inherited factor VII deficiency; certain factor X variants</td>
</tr>
<tr>
<td>—</td>
<td>↑</td>
<td>—</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Deficiency or inhibitor of factors VIII, IX, or XI; vWD; heparin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>—</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lupus inhibitor with qualitative platelet defect; certain factor X variants</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vitamin K deficiency; liver disease; warfarin; heparin; superwarfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓</td>
<td>Deficiency or inhibitor of factors X or V, prothrombin, or fibrinogen; lupus inhibitor with hypoprothrombinemia; DIC; dysfibrinogenemia; primary fibrinolysis</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DIC; liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>↓</td>
<td>Heparin therapy with associated thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>↑</td>
<td>Increased platelet destruction; decreased platelet production; hypersplenism; hemodilution</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td></td>
<td>Certain inherited platelet disorders (Wiskott-Aldrich syndrome, Bernard-Soulier syndrome)</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>↑</td>
<td>Myeloproliferative disorders</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td></td>
<td>Milder vWD; acquired qualitative platelet disorders (uremia, antiplatelet medications)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td></td>
<td>Inherited qualitative platelet disorders; vascular disorders; fibrinolytic disorders; factor XIII deficiency; autoimmune platelet sensitization; dysfibrinogenemia; mild factor deficiency (VIII, IX, XI); disorders of platelet procoagulant activity</td>
</tr>
</tbody>
</table>
Algorithm for Thrombocytopenia Evaluation

1. Platelet count < 150,000/µL
   - Hemoglobin and white blood count
     - Normal
       - Peripheral blood smear
         - Normal RBC morphology; platelets normal or increased in size
           - Consider:
             Drug-induced thrombocytopenia
             Infection-induced thrombocytopenia
             Idiopathic immune thrombocytopenia
             Congenital thrombocytopenia
     - Abnormal
       - Bone marrow examination
       - Platelets clumped: Redraw in sodium citrate or heparin
         - Microangiopathic hemolytic anemias (e.g., DIC, TTP)

2. Normal
   - Fragmented red blood cells
von Willebrand Disease

Mucocutaneous Bleeding
Platelet Count Normal

Assays for VIII_C, VWF_Ag,
Ristocetin Cofactor

Platelet Function Studies
Platelet Morphology
Tests of Aggregation and Release

Disorders of Platelet Function
FACTOR XIII DEFICIENCY
Also, consider mild deficiencies of factors VIII, IX, XI and dysfibrinogenemia

UREA CLOT SOLUBILITY TEST

ASSAY FOR FACTOR VII

DISORDER OF EXTRINSIC PATHWAY

ASSAYS FOR FACTORS VIII, IX, AND XI

BLEEDING PRESENT

ASSAYS FOR FACTOR XII, PREKALLIKREIN AND HMWK DEFICIENCY

BLEEDING ABSENT

DISORDER OF INTRINSIC PATHWAY

DISORDER OF COMMON PATHWAY

ASSAYS OF FACTORS X, V PROTHROMBIN, FIBRINOGEN, SPECIAL TESTS FOR DYSFIBRINOGENEMIA
BLEEDING DISORDERS IN WHICH THE RESULTS OF PRIMARY SCREENING TESTS MAY BE NORMAL

von Willebrand disease
Mild inherited coagulation disorders, particularly factor XI deficiency
Heterozygous carriers of inherited coagulation disorders
Factor XIII (fibrin-stabilizing factor) deficiency
Some forms of dysfibrinogenemia
Disordered platelet function, particularly deficient release reaction; Scott syndrome
Hereditary hemorrhagic telangiectasia
Allergic and other vascular purpuras
$\alpha_2$-Plasmin inhibitor deficiency
Elevated levels of plasminogen activator
### GUIDELINES FOR PREOPERATIVE HEMOSTASIS EVALUATION

<table>
<thead>
<tr>
<th>Level</th>
<th>Bleeding History</th>
<th>Surgical Procedure</th>
<th>Recommended Hemostasis Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Negative</td>
<td>Minor</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Negative</td>
<td>Major</td>
<td>Platelet count, PTT</td>
</tr>
<tr>
<td>III</td>
<td>Equivocal</td>
<td>Major, involving hemostatic impairment</td>
<td>PT, PTT, platelet count, factor XIII assay, euglobulin clot lysis time</td>
</tr>
<tr>
<td>IV</td>
<td>Positive</td>
<td>Major or minor</td>
<td>Level III tests; if negative, then factors VIII, IX, and XI assays, thrombin time, $\alpha_2$-antiplasmin assay; consider von Willebrand disease and platelet aggregation testing; consider specific tests for uncommon disorders listed in Table 45.3</td>
</tr>
</tbody>
</table>
ITP

IMMUNE THROMBOCYTOPENIA

Primary
Secondary
  Infections
  Collagen vascular diseases
  Lymphoproliferative disorders
  Solid tumors
  Drugs
  Miscellaneous
## ITP

### Features of Acute and Chronic Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age of incidence</td>
<td>Children, 2–6 y</td>
<td>Adults, 20–40 y</td>
</tr>
<tr>
<td>Sex predilection</td>
<td>None</td>
<td>3:1 female to male</td>
</tr>
<tr>
<td>Antecedent infection</td>
<td>Common 1–3 wk before</td>
<td>Unusual</td>
</tr>
<tr>
<td>Onset of bleeding</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Hemorrhagic bullae in mouth</td>
<td>Present in severe cases</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt;20,000/μL</td>
<td>30,000–80,000/μL</td>
</tr>
<tr>
<td>Eosinophilia and lymphocytosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Duration</td>
<td>2–6 wk; rarely longer</td>
<td>Months or years</td>
</tr>
<tr>
<td>Spontaneous remissions</td>
<td>Occur in 80% of cases</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
RECOMMENDATIONS FOR INITIAL TREATMENT OF IMMUNE THROMBOCYTOPENIA (IVIG) PATIENTS WITH PLATELET COUNTS <20,000–30,000/μl

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>None</td>
<td>Steroids (preferred) or IVIG</td>
</tr>
<tr>
<td>Minor purpura</td>
<td>None</td>
<td>Steroids (preferred) or IVIG</td>
</tr>
<tr>
<td>Mucosal membrane</td>
<td>IVIG or steroids</td>
<td>IVIG and/or steroids</td>
</tr>
<tr>
<td>bleeding that may</td>
<td></td>
<td></td>
</tr>
<tr>
<td>require clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe, life-threatening bleeding</td>
<td>Steroids and IVIG</td>
<td>Steroids and IVIG</td>
</tr>
<tr>
<td></td>
<td>Hospitalization</td>
<td>Hospitalization</td>
</tr>
<tr>
<td></td>
<td>Consider platelet transfusion</td>
<td>Consider platelet transfusion</td>
</tr>
<tr>
<td></td>
<td>and other measures</td>
<td>and other measures</td>
</tr>
</tbody>
</table>

*The current ASH guidelines recommend treatment for adults with platelet counts of <30,000/μl.*
ITP

1. **Emergency**
   - IV methylprednisolone 1g/d x 3 d
   - IVIG (1 g/kg/d x 1–2 d)
   - ± IV anti-D (50–75 μg/kg)
   - ± IV vincristine (1–2 mg)
   - ± Platelet transfusion
   - ± Factor VIII

2. **New diagnosis of ITP**

   **Platelet Count > 20–30,000/μl**
   - No treatment in the absence of special circumstances

3. **Initial treatment for platelet count < 20,000/μl**
   - Prednisone (1 mg/kg/d) or Dexamethasone (40 mg/d x 4 d)
   - ± IV anti-D (50–75 μg/kg)
   - ± IVIG (1 g/kg/d x 1–2 d)

4. **Treatment for refractory thrombocytopenia count < 20,000/μl**
   - Splenectomy
   - Thrombopoietin mimetics
     - Eltrombopag (50 mg/d)
     - Romiplostim (1–10 mcg/kg SC weekly)
     - Rituximab (375 mg/m² IV weekly x 4)

5. **Stable platelet count > 30–50,000/μl**
   - No therapy, observe

**FIGURE 47.5.** Therapy of adult immune thrombocytopenia (ITP). (1) Minimal emergency therapy includes intravenous (IV) methylprednisolone and intravenous
## THERAPEUTIC AGENTS AND THEIR DOSING SCHEDULES

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-D Immunoglobulin</td>
<td>50–75 µg/kg IV, repeated at 3-week intervals as indicated</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>150 mg daily for up to 8 wk</td>
</tr>
<tr>
<td>Colchicine</td>
<td>200 mg daily for up to 4 wk</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg daily for 4 d, repeated every 14 d for 4 cycles</td>
</tr>
<tr>
<td>Danazol</td>
<td>400 mg twice daily for 1 mo or longer</td>
</tr>
<tr>
<td>Eiltrombopag</td>
<td>50 mg daily. Must be continued indefinitely.</td>
</tr>
<tr>
<td>IVIG</td>
<td>1 g/kg IV for 1–2 d, repeated every 2 to 4 wk as indicated</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1 mg/kg daily for up to 28 d, then taper to lowest dose possible</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² IV weekly for 4 doses</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>1–10 mcg/kg subcutaneous injection weekly. Start at 1 mcg/kg and titrate based on platelet count. Must be continued indefinitely.</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2 mg at 5- to 7-day intervals for 2 or more doses</td>
</tr>
<tr>
<td>Vinblastin</td>
<td>7.5 mg at 5- to 7-day intervals for 3 or more doses</td>
</tr>
</tbody>
</table>

Modified from Narang et al.460
TTP&HUS

**Thrombocytopenia + MAHA**

- History & laboratory tests
  - ADAMTS13, complement studies
  - Stools for STEC, shigatoxins
  - Autoimmune serology
  - DIC panel
  - Blood cultures as indicated
  - Imaging studies and tissue biopsy as indicated

- Group III or IV (Table 48.1)

- Specific management

- Plasma exchange

- Severe ADAMTS13 deficiency
  - Inhibitor assay
  - Ab assay
  - Serial ADAMTS13
  - Familial study

- Genetic deficiency (hereditary TTP): Plasma infusion

- Autoimmune deficiency (acquired TTP):
  - Plasma exchange
  - Rituximab as indicated

- Genetic deficiency (hereditary TTP): Plasma infusion

- aHUS:
  - Eculizumab

- No severe ADAMTS13 deficiency
  - Cerebral edema
  - Pleural effusion
  - Pericardial effusion
  - Ascites
  - Tissue edema
  - Advanced renal failure
  - Hypertension

**FIGURE 48.11.** A scheme summarizing the current approach to patients presenting with thrombocytopenia and microangiopathic hemolytic anemia.
PRINCIPLES OF MANAGEMENT FOR THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- High index of suspicion is essential for patients presenting with thrombocytopenia or TIA/stroke.
  - Some patients may not have thrombocytopenia or microangiopathic hemolysis at presentation.
- Prompt treatment is critical to prevent serious complications and death.
- Daily plasma exchange is the therapy of choice for acquired TTP presenting with active thrombosis.
- Plasma infusion is used as an emergent substitute until plasma exchange is available.
- ADAMTS13 activity assay should be obtained before the patients receive any blood products.
- The diagnosis should be re-assessed during the course of therapy.
- Monitoring of ADAMTS13 during plasma therapy and remission may help clinical assessment.
  - For patients with persistent thrombocytopenia, ADAMTS13 >10% should suggest other causes of thrombocytopenia.
  - Monthly ADAMTS13 monitoring may detect impending relapses.
- Rituximab therapy should be considered for patients
  - Unable to wean off plasma exchange due to persistent and severe ADAMTS13 deficiency.
  - With persistent and severe ADAMTS13 deficiency during clinical remission.
  - Exhibiting a trend of declining ADAMTS13 levels.
- Hereditary TTP
  - Plasma infusion is effective for patients presenting with acute symptoms.
  - Plasma exchange is used if the patient has renal failure or fluid overload.
  - For most patients, plasma therapy every 2–3 wk prevents acute crisis, strokes, and renal failure.
PRINCIPLES OF MANAGEMENT OF ATYPICAL HEMOLYTIC-UREMIC SYNDROME (aHUS)

- Atypical HUS is a systemic disease
  - Gastrointestinal symptoms of nausea, vomiting, abdominal pain, diarrhea are common complaints.
  - Cardiopulmonary symptoms of chest pain and dyspnea may occur.
  - Neurologic abnormalities such as headache, somnolence, confusion, seizures, or visual defects may occur.
  - Advanced renal failure, hypertension or complications of abnormal vascular permeability favors the diagnosis of aHUS over TTP.
  - Renal failure may be minimal or mild in some cases.
- Atypical HUS is a diagnosis of exclusion
  - TTP should be excluded with ADAMTS13 assays.
  - Stx-HUS should be excluded with stool shiga toxin assays for patients with diarrhea.
  - Other causes of MAHA should be excluded with history, coagulation tests, autoimmune serology, microbiology, and/or tissue biopsy as indicated.
  - Acute presentation of atypical HUS may be triggered by a co-morbidity (Table 48.1).
- Plasma exchange is the initial choice of therapy until TTP is excluded
- Eculizumab is the treatment of choice for aHUS
  - Improvement in thrombocytopenia and mental status change is evident after one or two doses of eculizumab.
  - Recovery of renal function may occur slowly over many months.
  - Vaccination is critical for prevention of meningococcal sepsis.
- Long-term therapy with eculizumab should be considered for patients who
  - have more than minimal renal dysfunction, or
  - are predisposed to relapse with serious complications.
- If eculizumab is discontinued, close monitoring is indicated for early detection of relapse or organ injury. Follow-up evaluation should include
  - Symptoms, physical findings, blood pressure.
  - CBC, renal function and hemolysis markers.
Qualitative disorders of platelet function

- Therapeutic approaches include both general and specific treatment of bleeding.
- Patients should be warned to avoid trauma and antiplatelet medication, such as aspirin, and to maintain proper dental hygiene.
- Females may benefit from contraceptive therapy once they reach puberty.
- Treatment of bleeding or prophylaxis during surgical procedures usually requires blood or platelet transfusion with the associated risk of developing antiplatelet alloantibodies.
Desmopressin and rFVIIa administration have been shown to shorten the bleeding time in some patients.

In rare cases of life-threatening bleeding, a bone marrow or umbilical cord hematopoietic stem cell transplantation may be considered.

Responses to antifibrinolytic agents are more variable.

Administration of adrenal corticosteroids and splenectomy are usually ineffective.
VON WILLEBRAND DISEASE

- The mainstay of treatment for type 1 VWD is DDAVP (desmopressin), which results in release of VWF and FVIII from endothelial stores.
- DDAVP can be given intravenously or by a high-concentration intranasal spray (1.5 mg/mL). The peak activity when given intravenously is approximately 30 min, whereas it is 2 h when given intranasally.
- The usual dose is 0.3 μg/kg intravenously or two squirts (one in each nostril) for patients >50 kg (one squirt for those <50 kg).
- It is recommended that patients with VWD be tested with DDAVP to assess their response before using it. In patients who respond well (increase in laboratory values of two- to fourfold).
• It can be used for procedures with minor to moderate risk of bleeding. Depending on the procedure, additional doses may be needed; it is usually given every 12–24 h.
• Less frequent dosing may result in less tachyphylaxis, which occurs when synthesis cannot compensate for the released stores.
• The major side effect of DDAVP is hyponatremia due to decreased free water clearance.
• This occurs most commonly in the very young and the very old, but fluid restriction should be advised for all patients for the 24 h following each dose
• Type 3 disease, and for major procedures requiring longer periods of normal hemostasis, VWF replacement can be given.
• Virally inactivated VWF-containing factor concentrates are safer than cryoprecipitate as the replacement product.
• Antifibrinolytic therapy using either ε-aminocaproic acid or tranexamic acid is an important therapy, either alone or in an adjunctive therapy.
• In the case of a patient with major surgery or trauma, one recommendation is that clinicians attempt to bring the vWF (and factor VIII) level to near 100 IU/dl, and maintain it >40 to 50 IU/dl for the first 3 to 5 days, after which one recommended goal is to maintain the factor VIII level at >40 IU/dl for a total of 7 to 10 days or until healing is completed
TREATMENT OF INHERITED COAGULATION DISORDERS

- Replacement Therapy
  - Cryoprecipitate (factor VIII and Fibinogen)
  - Fresh Frozen Plasma
  - Prothrombin Complex Concentrates (Prothrombin, FVII, FIX, FX)
  - Recombinant FVIIa
  - Purified FVIII, FIX, FXI, FXIII

- Nontransfusion Therapy
  - DDAVP
  - Antifibrinolytic drugs
Haemophilia A

• DDAVP is effective in the treatment of minor bleeding manifestations in individuals with hemophilia A with baseline factor VIIIc levels >5 IU/dl,
• At least 24 hours should elapse before repeat administration of the drug in order for the endothelial cell stores of vWF to be replenished.
• Patients should be tested before surgery for their response to DDAVP by documenting adequate hemostatic levels of factor VIII levels 30 to 60 minutes after treatment
Haemophilia A&B

- Mild bleeds such as uncomplicated hemarthroses or superficial hematomas require initial therapy with factor levels of 30–50%.
- Large hematomas, or bleeds into deep muscles, require factor levels of 50% or even higher if the clinical symptoms do not improve, and factor replacement may be required for a period of 1 week or longer.
- The control of serious bleeds including those that affect the oropharyngeal spaces, CNS, and the retroperitoneum require sustained protein levels of 50–100% for 7–10 days.
- Prophylactic replacement for surgery is aimed at achieving normal factor levels (100%) for a period of 7–10 days.
• In order to prevent bleeds, especially the onset of hemarthroses.
• Hemophilic boys receiving regular infusions of FVIII (3 days/week) or FIX (2 days/week) can reach puberty without detectable joint abnormalities.
## Replacement Therapy in Hemophilia A and Hemophilia B

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Therapeutic Product</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
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<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A (factor VIII deficiency)</td>
<td>Cryoprecipitate&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Not required</td>
<td>1.25–1.75 bags/10 kg every 12 h for 1–3 d</td>
<td>3.5 bags/10 kg</td>
<td>1.75 bags/10 kg every 8 h for 1–2 d; every 12 h thereafter</td>
</tr>
<tr>
<td></td>
<td>Purified factor VIII&lt;sup&gt;4&lt;/sup&gt;</td>
<td>20–30 IU/kg</td>
<td>10–15 IU/kg every 12 h for 2–4 d</td>
<td>30–40 IU/kg</td>
<td>30–40 IU/kg every 12 h</td>
</tr>
<tr>
<td>Hemophilia B (factor IX deficiency)</td>
<td>Prothrombin complex&lt;sup&gt;6,7&lt;/sup&gt;</td>
<td>20–30 IU/kg</td>
<td>15 IU/kg every 24 h for 2–4 d</td>
<td>40–60 IU/kg</td>
<td>20–25 IU/kg every 24 h</td>
</tr>
<tr>
<td></td>
<td>Purified factor IX&lt;sup&gt;8,9&lt;/sup&gt;</td>
<td>20–30 IU/kg</td>
<td>15 IU/kg every 24 h for 2–4 d</td>
<td>60–70 IU/kg</td>
<td>20–40 IU/kg every 24 h</td>
</tr>
</tbody>
</table>
Factor XI deficiency

- The treatment of FXI deficiency is based on the infusion of FFP at doses of 15–20 mL/kg to maintain trough levels ranging from 10 to 20%.
- FXI has a half-life of 40–70 h, the replacement therapy can be given on alternate days.
- The use of antifibrinolytic drugs is beneficial to control bleeds, with the exception of hematuria or bleeds in the bladder.
- FXI inhibitor was observed in 10% of severely FXI-deficient patients who received replacement therapy.
- The use of PCC/aPCC or recombinant activated FVII has been effective in FXI inhibitor developed patients.
Factor XIII Deficiency Treatment

- The long half-life between 9 and 19 days.
- FFP and factor concentrates have been used successfully to prevent factor XIII–associated bleeding, and these remain the treatment of choice.
- A plasma-derived factor XIII preparation is available to treat congenital factor XIII deficiency.
- Recommended dosing is 40 IU/kg every 4 weeks with dose adjustments based on achieving a trough level of 5% to 20%.
- Recommended dosing for factor XIII concentrate is 10 to 20 IU/kg body weight every 4 to 6 weeks for prophylaxis against unprovoked bleeding.
Afibrinogenemia Treatment

• Replacement therapy is indicated for any episode of acute active bleeding, preoperatively, and in pregnant patients.
• Fibrinogen levels between 50 and 100 mg/dl are usually adequate for normal hemostasis.
• Each bag of cryoprecipitate contains 250 mg of fibrinogen, and one bag of cryoprecipitate typically raises plasma fibrinogen levels of an adult by 10 mg/dl.
• 5 to 10 bags of cryoprecipitate are usually sufficient in the average adult patient.
• There are plasma concentrates of fibrinogen now available that may provide advantages over the use of cryoprecipitate
The complications of replacement therapy in afibrinogenemia include allergic reactions, development of antifibrinogen antibodies, and anaphylaxis.

Thromboembolic complications following cryoprecipitate infusions include deep venous thrombosis and pulmonary emboli.

The risk of these complications may be increased when an inhibitor of fibrinolysis or oral contraceptive therapy is also administered.

Low-molecular-weight heparin in combination with fibrinogen replacement has been used to avoid these thromboembolic complications.
Dysfibrinogenemia Treatment

• The majority of patients with dysfibrinogenemia do not require any specific therapy.
• Any bleeding complications that develop can be managed with transfusion of either plasma or cryoprecipitate.
• In women with dysfibrinogenemia, recurrent miscarriages may be prevented using prophylactic cryoprecipitate, and successful pregnancy outcomes in such cases have been reported.
• Antifibrinolytic drugs have been used in some patients but should be especially avoided in patients who have thrombotic tendencies
Factor VII deficiency

• The minimum factor VII level required for surgical hemostasis is not known;
• Patients with levels <3 IU/dl are at high risk for bleeding, whereas patients with levels of 15 to 25 IU/dl are less likely to develop bleeding complications associated with surgery.
• Factor VII has a short half-life, possibly as short as 3.5 hours.
• Volume overload is likely, as plasma is commonly used as a source for factor replacement, and the safety profile of the various factor VII–containing products varies.
Factor VII deficiency

- Traditionally, FFP, PCCs, or plasma-derived factor VII concentrate has been used for factor VII replacement therapy.
- Recently, recombinant human activated factor VIIa has been the recommended product.
- In general, doses of between 15 and 30 mg/kg of rFVIIa were administered at intervals of 4 to 6 hours.
- The half-life of recombinant factor VIIa is between 2.5 and 3 hours, and the roles of continuous factor infusion and laboratory monitoring remain to be defined in treating factor VII-deficient patients.
## Acquired Coagulation Disorders

### Deficiencies of vitamin K–dependent coagulation factors
- Hemorrhagic disease of the newborn (vitamin K deficiency bleeding)
- Biliary obstruction (gallstone, strictures, fistulas)
- Malabsorption of vitamin K (sprue, idiopathic steatorrhea, celiac disease, ulcerative colitis, regional enteritis, gastrocolic fistulas, *Ascaris* infestation)
- Nutritional deficiency
- Drugs
  1. Pharmacologic antagonists of vitamin K (coumarins, indandiones, others)
  2. Those that alter gut flora (broad-spectrum antibiotics, sulfonamides)
  3. Miscellaneous (cholestryamine)

### Liver disease (see Table 54.3)

#### Accelerated destruction of coagulation factors
- Disseminated intravascular coagulation (see Table 54.4)
- Fibrinolysis (liver disease, thrombolytic agents, tumors, after surgery)

#### Inhibitors of coagulation
- Specific inhibitors (antibodies) (see Table 54.6)
- Antiphospholipid–protein antibodies (see Table 54.7)
- Miscellaneous (antithrombins, paraproteinemias)

#### Miscellaneous
- After massive transfusion
- After extracorporeal circulation
- Drugs (antibiotics, antineoplastic agents, others)
- Other disorders (polycythemia vera, congenital heart disease, amyloidosis, nephrotic syndrome, Sheehan syndrome, Gaucher disease, leukemia, others)
DIC

- Also called as defibrination syndrome, consumption coagulopathy.
- The pathophysiology of DIC is complex.
- The mechanisms that activate or “trigger” DIC act on processes that are involved in normal hemostasis,
- Platelet adhesion and aggregation
- Intrinsic and tissue factor–activated
- Extrinsic pathways of coagulation
FIGURE 54.2. Initiating mechanisms of disseminated intravascular coagulation (DIC). The solid arrows indicate normal hemostatic pathways, and dotted arrows indicate pathways by which certain disorders associated with DIC initiate or promote the coagulopathy of DIC. Initiation of coagulation by expression of tissue factor activity is probably the most important mechanism triggering DIC.
Treatment

- Heparin is a specific activator of the physiologic anti thrombin system and thereby inhibits a number of proteolytic enzymes, including factors IXa and Xa and thrombin.
- In patients with chronic DIC, the results of heparin therapy usually are favorable and may be dramatic.
- Heparin reduces the severity of bleeding and thromboembolic manifestations and produces parallel improvement in the abnormalities of laboratory test values.
- Elevated levels of d-dimer and FDPs drop rapidly, and accelerated fibrinolysis, disappears after the administration of heparin.
The major aim of replacement therapy with blood products in DIC is to replenish fibrinogen.

This goal is best accomplished by the administration of cryoprecipitate, each unit of which contains approximately 250 mg of fibrinogen.

The amount of cryoprecipitate given should be sufficient to elevate the plasma fibrinogen level to at least 100 to 150 mg/dl.

As a general guide, 3 g of fibrinogen can be expected to raise the plasma level of an adult patient approximately 100 mg/dl.
• Patients with DIC, bleeding, and platelet counts <50,000/ul should be considered platelet transfusion
• Due to acquired storage pool defect, as well as FDP inhibition of platelet function.
**Diagram 1** A strategy for management of factor VIII inhibitors in hemophilia and non-hemophilia patients. Key decisions are based on outcomes.
THANK U