Coagulation Cascade

**Primary Hemostasis**
- **Symptoms:** MUCOSAL BLEEDING
- Injured blood vessel releases tissue factor, causes platelet to "activate" → secrete granular contents → further hemostasis
- GpiIIb/IIIa in plt surface undergoes conformational change → binds fibrinogen, crosslinking platelets
- Platelet surface → makes phospholipid scaffold to facilitate secondary hemostasis.

**Secondary Hemostasis**
- **Symptoms:** Hemarthrosis/Hematomas
- Coagulation factors
- Begins when Tissue Factor (TF) → activates Factor VII
  - activated Factor VII → common pathway to convert Factor X → Xa
  - Thrombin (II) generated, activating Factor XI → also feeds into common coag pathway (through factors IX and VIII cofactors)
  - Eventually crosslinked fibrin
- Burst of thrombin → generating insoluble fibrin meshwork

Approach to Bleeding Disorders

- **Types:**
  - **Congenital:**
    - Hemophilia A: Factor VIII Deficiency
    - Hemophilia B: Factor IX Deficiency
    - von Willebrand's Disease (Types I, II, III)
  - **Acquired:**
    - Acquired Hemophilia A
    - DIC
    - Liver Disease Coagulopathy
    - Vitamin K Deficiency

**History/Physical**
- **History**
  - History of Bleeding:
• Bleeding during infancy/childhood (umbilical stump, circumcision)
• Bleeding during loss of teeth, trauma, surgeries.
• Easy bruising (poor sensitivity/specificity)
• **Surgical Bleeding**: ask about timing!
  ▪ Immediate
  ▪ Delayed
  ▪ Need for transfusion
• Gynecological
  ▪ **Secondary Hemostasis Disorders: Bleeding into muscles and joints.**
  ▪ **Primary Hemostasis** (Platelet Dysfunction, thrombocytopenia)
    ▪ Superficial bleeding: (Mucosal/Gums, menorrhagia)

  ▪ **Exam Findings:**
    ▪ Family History
    ▪ Medications/Herbals

  ▪ **Exam Findings:**
    ▪ Petechiae - Thrombocytopenia / Platelet Defect
    ▪ Ecchymosis
    ▪ Scurvy - Perifollicular Hemorrhage
    ▪ **HHS - Telangetasias (lips/fingertips)** (hereditary hemophilic telangiectasias)
    ▪ **Amyloidosis** - Enlarged tongue, carpal tunnel, periorbital purpura (acquired clotting protein deficiency, esp FX)
    ▪ **Ehlers-Danlos Syndrome** - Joint hypermobility, skin elasticity (Bleed b/c cannot constrict arterioles)
    ▪ **Severe AS** - Harsh systolic murmur (acquired Type II vWF disease)
    ▪ **Thrombocytopenia** - Splenomegaly.
    ▪ **Liver Disease** - coagulopathy

## Lab Tests

- **PT** - Prothrombin Time
  ▪ Prolonged PT:
    ▪ MOST common: Acquired deficiency of factor VII (Vitamin K, Liver disease, DIC, warfarin)
- **aPTT** - activated Partial Thromboplastin time
  ▪ MOST common: Lupus inhibitor
  ▪ Abnormalities in FVIII and IX
  ▪ (Adds nothing to preoperative evaluation of pt with no hx of abnormal bleeding)
- How they are done:
  ▪ Lab tests performed on citrated plasma, tests thrombin generation on phospholipid surface.
  ▪ Tubes MUST be adequately filled (otherwise too much or too little citrate that comes with the tube).
- **TT** - Thrombin Time
  ▪ Time for clot formation after thrombin added to citrated plasma.
  ▪ Indicated if PT or PTT prolonged or heparin contamination suspected.
  ▪ **Prolonged in any thrombin inhibitor (heparin, leparudin, argatroban).**
  ▪ Abnormal fibrinogen or dysfibrinogenemia = prolonged TT.

### Isolated PT Elevation

<table>
<thead>
<tr>
<th>Isolated PTT Elevation</th>
<th>PTT &amp; PT Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Vitamin K Deficiency</td>
<td>-Heparin</td>
</tr>
<tr>
<td>-Liver Disease</td>
<td>-Factor Deficiency/Inhibitor: Factor VIII</td>
</tr>
<tr>
<td>-Warfarin Therapy</td>
<td>Factor IX</td>
</tr>
<tr>
<td>-Factor VII Deficiency/Inhibitor</td>
<td>Factor XI</td>
</tr>
<tr>
<td></td>
<td>Factor XII</td>
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</tr>
</tbody>
</table>
Isolated PT Elevation | Isolated PTT Elevation | PTT & PT Elevation
---|---|---
-vWF Disease | Factor II | -
-Lupus Anticoagulant | Factor V | -
Factor X | Factor X | -Paraproteinemia
-A/Hypo/Dysfibrinogenemia

- **Mixing Studies**
  - Used when evaluating PT or PTT prolongation (and less commonly TT)
  - Distinguishes *clotting factor deficiency vs. inhibitor*
  - Mix normal plasma with patient’s:
    - **Corrects = deficiency of clotting factor** (even 50% of clotting factor is enough, 20-30% needed for normal PT/PTT)
    - **If NOT correct = inhibitor** (antibody produced that inhibits clotting factor). Tx w/ immunosuppression.
  - Most common inhibitors: Factor VIII (acquired hemophilia), Lupus anticoagulant etc..
- **Bethesda Assay**
  - Strength and titre of inhibitor directed against Factor VIII or IX
- **Factor Studies**:
  - **Factor VIII** - Hemophilia A
  - **Factor IX** - Hemophilia B
  - **Factor XI** - Hemophilia C (Ashkenazi Jews, not associated with bleeding problems)
  - **Factor V** - "Para-hemophilia"
  - **D-Dimer** - fibrin breakdown products
    - Deciding if stopping anticoagulation in pts with DVT

### Congenital Hemorrhagias

#### Hemophilia A & B
- Hemophilia A: Factor VIII Deficiency *(more common)*
- Hemophilia B: Factor IX Deficiency
- NOTE: Hemophilia C (Factor XII deficiency) is not associated with bleeding problems.
- **X-linked recessive disorders (Practically indistinguishable)**
  - Devoted into: Mild, Moderate, Severe (depends on activity level of the factor)
    - Mild: >5% of factor activity
    - Severe: <1% of factor activity
- **Clinical Features**:
  - **Recurrent Hemarthrosis --> eventually chronic crippling degenerative joint disease.**
    - MUST treat with factor replacement
  - **CNS hemorrhage** possible and fatal
  - Presentation based on type:
    - MILD: Presents in adulthood, post-traumatic or surgical bleeding.
- **Treatment**:
  - **Factor VIII or IX replacement with recombinant or plasma-derived.**
    - Can be taught to administer by IV at home.
  - Desmopressin - helps treat mild hemophilia A
    - (release of vWF and Factor VIII from endothelium)
  - ASA and NSAID use --> CONTRAINDIATED
Von Willebrands Disease (vWD)

- Function of von Willebrand's Factor:
  - Tethers platelets
  - Protects Factor VIII from circulation
  - Therefore, many vWD patients have low Factor VIII levels enough to raise aPTT.
- Von Willebrands Disease (vWD) - 1% of population.
  - Type I - MILD - Normal multimers of vWF, but lower levels of all.
  - Type II - mutations in vWF factor. (absence of high molecular weight vWF multimers).
  - Type III - SEVERE - Undetectable vWF levels. (Autosomal Recessive)
- Autosomal Disorder
  - Named after Von Willebrand who described it in patients on Olive Islands off Sweden.
  - DIFFERENT from hemophilia (because seen in women & men)
- Clinical Features:
  - Mucocutaneous bleeding (hemarthrosis rare)
  - Women: Menorrhagia, endometriosis, post-partum hemorrhage.
  - MILD vWD: may not be detected (Platelet function analyzer assay - PFA)
- Workup:
  - Platelet Function Analyzer (measure clotting time)
  - May be normal in Type I MILD disease.
  - To diagnose:
    - vWF antigen level
    - vWF activity
  - Caution: vWF levels fluctuate with stress, estrogen, exercise, bleeding etc.:
    - May need repeated assays. (Type O can have lower levels)
- Treatment:
  - Desmopressin causes release of vWF from endothelial cells.
  - use when they have symptoms of bleeding.
  - Once use DDAVP, all vWF released, so can't use continuously
  - vWF + Factor VIII concentrates (i.e.
    - If more severe bleeding or Type II and III vWD

Thromabasthenia (Glanzman's Syndrome) - plts > 400,000/cc with malfunction.

Acquired Hemophilias

Acquired Hemophilia A

- Acquired antibody to Factor VIII
  - Often occurs in women (post-partum, but many idiopathic)
- Clinical Features:
  - Bleeding with isolated PTT prolongation.
  - Can be severe and life-threatening
  - Bleeding is mucocutaneous & multifocal (hemarthrosis is rare) --> unlike Congenital Hemophilia!!!
- Labs:
  - Isolated PTT prolongation
  - Factor VIII level are barely detectable
  - Mixing study: Uncorrectable PTT (inhibitor)
  - Lupus inhibitor is NEGATIVE.
  - Further Workup:
    - Measure titre of antibody in Bethesda Assay
- Treatment
  - LOW Titre: Factor VIII high dose concentrates
  - HIGH Titre: Recombinant Factor VIIa or activated Prothrombin Complex Concentrates (aPCC)
    - (PCC: contain Factors II, VII, IX, X ---> all activate Factor X, secure hemostasis without VIII)
    - May require immunosuppression

Acquired Hemophilias
Liver Disease Coagulopathy
- Liver synthesizes all factors.
- Liver Failure --> Hemorrhagic condition.

Coagulopathy of Liver Failure
1. High PT, PTT, and TT.
2. Hypofibrinogenemia
3. Dysfibrinogenemia
4. Thrombocytopenia due to: (can be refractory to transfusions)
   - Splenic sequestration
   - D-Dimers Poorly cleared --> Accelerate fibrinolysis --> Consume platelets

- Clinical Features:
  - Present not anticoagulated with high INR.
  - Despite high INR, liver disease patients can be hypercoagulable (natural anticoagulants are deficient to)
- Treatment:
  - INR correction with FFP almost impossible. (short half-life of F VII of few hours).
    - Surgeons often ask for this, but very hard.
    - Can try with FFP, but also give Vitamin K to correct coagulopathy.

Disseminated Intravascular Coagulation
- See Platelets --> DIC

Vitamin K Deficiency
- Acquired for active forms of Factors II, VII, IX, X (gamma-carboxyllation of these factors)
- Vitamin K produced by GI flora, and present in green-leafy vegetables.
  - Deficiency common in:
    - Malnourished
    - Antibiotics
    - Fat Malabsorption (Vitamin K is fat soluble)
- Treatment:
  - Vitamin K 5-10mg/day
  - Anticoagulation with warfarin is challenging, small amounts can cause very high INR
    - Partial repletion of Vitamin K is needed (removes labile quality to INR) - often 200-300mcg/day.

Platelets
- See Platelet Disorders (click here)

Liver Failure Coagulopathy
- Liver synthesizes all coagulation factors
- Liver failure is a hemorrhagic condition
  - Elevates both PT and PTT
  - Nearly all clotting factors are usually low.
  - Thrombin time can be low too (not only from low fibrinogen, but low glycosylation of fibrinogen - causes functionally abnormal fibrinogen).
  - Splenomegaly in cirrhosis --> thrombocytopenia (platelet sequestration - can be refractory to transfused platelets).
• D-Dimers (breakdown of fibrin) not cleared in liver disease \(\rightarrow\) can accelerate fibrinolysis and platelet consumption
  - D-Dimer can be anticoagulant and fibrinolytic.

• Despite prolonged INR values, patients in liver disease can get VTE
  - Many of naturally occurring anticoagulants are also deficient.
  - Full correction of INR is difficult with FFP, almost impossible (short halflife of Factor VII - only few hours).
  - Surgeons often want correction of INR, which is hard.

• Main Effects:
  - Coagulopathy
  - Hypofibrinogenemia
  - Dysfibrinogenemia (D-Dimer effect)
  - Thrombocytopenia.

• Management:
  - FFP can be used to correct coagulopathy, but short half-life of Factor VII limits efficacy...
  - If going to correct coagulopathy, should also also give Vitamin K

**Immune Thrombocytopenic Purpura**

• Autoimmune condition.
  - Autoantibodies directed towards platelet surface proteins \(\rightarrow\) platelet destruction.
  - ALSO: Have decreased platelet production. (NEW!! was ignored in the past, but now can treat).

• ITP is common, more often in children.
  - Children: often self-limited in children from viral infections
  - Adults: seldom self-limited

• Clinical findings:
  - Often very asymptomatic (don't always bleed)

• Diagnosis:

<table>
<thead>
<tr>
<th>Diagnosis of ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diagnosis of exclusion</td>
</tr>
<tr>
<td>1. Otherwise normal CBC (or concomitant bleeding anemia)</td>
</tr>
<tr>
<td>2. Absence of organ dysfunction</td>
</tr>
<tr>
<td>3. Normal peripheral blood smear</td>
</tr>
</tbody>
</table>

• Various forms:
  - Drug-induced
  - Abnormal Immune Regulation (SLE, HIV, Lymphoproliferative malignancies like CLL)

• Pathology:
  - Platelets may be large (suggesting recently released from bone marrow)
  - They have advanced hemostatic function (accounts for less severe bleeding seen)

• Management:
  - Not all require therapy, monitor for further platelet declines or signs of bleeding.
  - 30,000-40,000 have less than 15% chance of further thrombocytopenia.. follow CBC qFew-Weeks.
  - If <30,000 or bleeding, sometimes need treatment
    - Sometimes need treatment.
    - **1st line**: prednisone or methylprednisolone (1-2 mg/kg/day)
      - Some hematologists use higher dose dexamethasone for higher response rate. (never been compared).
      - Response in 75-80% of pts, but relapse is common.
    - **2nd line** (if don’t respond to steroids, continue to bleed)
      - IVIG (if actively bleeding or anti-D (pregnant women to prevent hemolytic disease of newborn)
      - IVIG or anti-D also indicated for rapid increase in platelets (i.e. going to OR)
      - Also used: rituximab (not studied but used, anti-CD20) and mycophenolate mofetil.
    - In the past, splenectomy done for ITP, but post-splenectomy complications common. Now 2nd line b/c now have excellent drugs (rituximab), but 3/4 effective.

Immune Thrombocytopenic Purpura
• Also have agents for platelet production: (BOTH NEW!)
  ▪ Stimulate thrombopoietin receptor, induce platelet production.
    ▪ Romiplostim (IV)
    ▪ Eltrombopag (oral)
  ▪ **Both new agents approved for refractory ITP, work well.**

### Thrombophilic Syndromes

- Cannot be done on warfarin (Protein C and Protein S levels are low) or during acute VTE.

**Screening:**
- Prothrombin 22:10 mutation
- Activated Protein C resistance (including Factor V Leiden testing)
- APLA
- Lupus inhibitor
- Antithrombin Level
- Protein C
- Protein S

**Syndromes:**
- Factor V Leiden
- Prothrombin gene mutation
- Antithrombin III Deficiency
- Protein C Deficiency
- Protein S Deficiency

**Antiphospholipid Syndrome**

**Order lupus anticoagulant, Anti-Cardiolipin Antibody, and Anti-B2-glycoprotein I Antibody**

Not covered by OHIP: aPTT is a "poor-mans" test.

**Lupus Anticoagulant (LAC)**
- IgG, IgM or both that interferes with phospholipid-dependent tests of in-vitro coagulation. Misnomer because it increases thrombosis (not anticoagulates), and not usually associated with SLE.
- To diagnose: aPTT (common, insensitive, cannot be used in pregnancy), Kaolin clot time, dilute russel viper venom time (dRVVT) and plasma clot time (PCT).

**Antiphospholipid Antibodies (APA)**
- Acquired IgG, IgA, or IgM that are targeted against a phospholipids in cell membranes. These often cause placental thrombosis and infarction (unknown how). Prostacyclin normally vasodilates and inhibits platelet aggregation. Removal causes vasoconstriction and platelet aggregation occur causing thrombosis. Also inhibits protein C.

**Cardiolipin (ACA)**
- phospholipid in inner mitochondrial membrane. ACL (aka aCL, cardiolipin), IgG and IgM are important (IgA less important) (Fun fact: VDRL uses beef cardiolipin, and pts with ACA cause false positives).

### Approach to Abnormal PT/PTT

**Patients with Bleeding**

<table>
<thead>
<tr>
<th>Coagulation Test Result</th>
<th>Inherited or Acquired</th>
<th>Underlying Cause/Disorder</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑PT, normal aPTT</td>
<td>Congenital</td>
<td>Factor VII deficiency</td>
<td>FFP, recombinant factor VIIa</td>
</tr>
</tbody>
</table>
## Patients with Bleeding

<table>
<thead>
<tr>
<th></th>
<th>patients with bleeding</th>
<th>Treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired</td>
<td>DIC</td>
<td>Treat underlying cause, supportive transfusions (FFP, cryoprecipitate, platelets)</td>
</tr>
<tr>
<td>Acquired</td>
<td>Liver disease</td>
<td>FFP</td>
</tr>
<tr>
<td>Acquired</td>
<td>Vitamin K deficiency</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>Acquired</td>
<td>Vitamin K antagonists</td>
<td>Vitamin K, FFP, PCCs</td>
</tr>
<tr>
<td>Acquired</td>
<td>Certain paraproteins</td>
<td>No specific treatment for hemostasis. Treatment for paraproteinemia as otherwise indicated</td>
</tr>
<tr>
<td>Acquired</td>
<td>Certain dysfibrinogenemias</td>
<td>Cryoprecipitate</td>
</tr>
</tbody>
</table>

### Normal PT, ↑aPTT

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Hemophilia A (factor VIII deficiency)</th>
<th>Treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Factor VIII concentrates, desmopressin for mild cases</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Hemophilia B (factor IX deficiency)</th>
<th>Factor IX concentrates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Factor XI deficiency</td>
<td>FFP</td>
</tr>
<tr>
<td></td>
<td>vWD</td>
<td>Desmopressin or vWF-containing factor VIII concentrates</td>
</tr>
</tbody>
</table>

### Acquired

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Acquired hemophilia</th>
<th>Bypassing agents to treat bleeding Immunosuppressants to eradicate inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired</td>
<td>Acquired vWD</td>
<td>—</td>
</tr>
<tr>
<td>Acquired</td>
<td>Heparin</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>Acquired</td>
<td>Direct thrombin inhibitors</td>
<td>No antidote available</td>
</tr>
</tbody>
</table>

### ↑PT, ↑aPTT

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Factor V deficiency</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Factor X, factor II deficiency</td>
<td>PCCs</td>
</tr>
<tr>
<td>Patients with Bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>Hypofibrinogenemia or afibrinogenemia</td>
<td>Cryoprecipitate or fibrinogen concentrates</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>Combined deficiency of factor V and factor VIII</td>
<td>Factor VIII concentrates and FFP</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>Combined deficiency of factors II, VII, IX, and X</td>
<td>High-dose vitamin K, FFP, PCCs</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td>Fibrinolysis (tPA, urokinase, etc.)</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td>Factor V inhibitors</td>
<td>FFP, platelets, immunosuppression</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td>Lupus inhibitor-associated hypoprothrombinemia</td>
<td>FFP, PCCs</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td>Factor X deficiency from amyloidosis</td>
<td>PCCs, FFP</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td>Vitamin K deficiency</td>
<td>Vitamin K</td>
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<tr>
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<td><strong>Acquired</strong></td>
<td>Heparin</td>
<td>Protamine sulfate</td>
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<td>Direct thrombin inhibitors</td>
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<td><strong>Acquired</strong></td>
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<td>Treat underlying cause, supportive transfusions (FFP, cryoprecipitate, platelets)</td>
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<tr>
<td><strong>Acquired</strong></td>
<td>Liver disease</td>
<td>Supportive transfusions (FFP, cryoprecipitate)</td>
</tr>
<tr>
<td><strong>Normal PT and aPTT</strong></td>
<td><strong>Congenital</strong></td>
<td>vWD</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>Factor XIII deficiency</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
<td>Platelet deficiency or dysfunction</td>
<td>Platelets</td>
</tr>
</tbody>
</table>
### Patients with Bleeding

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Deficiencies of fibrinolytic inhibitors (PAI-1 or α2-antiplasmin)</td>
<td>ε-Aminocaproic acid</td>
</tr>
<tr>
<td>Congenital</td>
<td>Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)</td>
<td>ε-Aminocaproic acid</td>
</tr>
<tr>
<td>Congenital</td>
<td>Ehlers-Danlos syndrome</td>
<td>−</td>
</tr>
<tr>
<td>Acquired</td>
<td>Low-molecular-weight heparin and fondaparinux</td>
<td>No antidote. Protamine reverses ≤50% of enoxaparin activity at most</td>
</tr>
<tr>
<td>Acquired</td>
<td>Drugs and herbs causing platelet dysfunction</td>
<td>Desmopressin, platelet transfusion</td>
</tr>
<tr>
<td>Acquired</td>
<td>Uremia</td>
<td>Desmopressin, cryoprecipitate</td>
</tr>
<tr>
<td>Acquired</td>
<td>Scurvy</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Acquired</td>
<td>Myeloproliferative disorders</td>
<td>−</td>
</tr>
<tr>
<td>Acquired</td>
<td>Factor XIII inhibitors</td>
<td>−</td>
</tr>
</tbody>
</table>

### Patients without Bleeding

<table>
<thead>
<tr>
<th>Coagulation Test Result</th>
<th>Inheritance</th>
<th>Disorder</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal PT, ↑aPTT</td>
<td>Congenital</td>
<td>Deficiency of contact factors (HMWK, PK, factor XII)</td>
<td>−</td>
</tr>
<tr>
<td>Acquired</td>
<td></td>
<td>Lupus inhibitor</td>
<td>−</td>
</tr>
</tbody>
</table>