Approach to Patients with Hemorrhagic Disorders

Whereas many healthy people consider their bleeding and bruising excessive, patients with underlying von Willebrand disease, the most common hereditary bleeding disorder, often fail to identify their bleeding symptoms. Therefore, it is necessary to ask for specific information from patients about bleeding and bruising (Is the patient easily bruised? What is the size of the bruises? If the patient has had surgery, were blood transfusions needed?). If the patient had a wisdom tooth extracted, were return visits required for packing, suturing, or transfusion? The patient should be questioned about drug use (including intravenous drug abuse), sexual activity, anemia, transfusions, recurrent infections, connective tissue diseases, malignancies, and immunocompromised states.

The type of bleeding is informative. Active bleeding can be caused by a localized anatomic lesion or an underlying bleeding diathesis. Mucosal bleeding, with recurrent epistaxis, gum bleeding, ecchymoses, and menorrhagia, is suggestive of von Willebrand disease or other platelet disorders. Deep-tissue bleeding (e.g., hemorrhagic and painful muscle hematomas) is more commonly seen in hemophilia and clotting factor deficiencies. Patients with clotting factor deficiencies may have delayed bleeding, presumably because the initial platelet thrombus provides immediate hemostasis but is not properly stabilized by the fibrin clot.

Aspirin can partially impair platelet function and trigger bleeding symptoms in a patient with mild underlying von Willebrand disease. Because several hundred drug formulations contain aspirin (often with no indication of aspirin content in the product name), identification of aspirin as the cause of a hemorrhagic disorder can be difficult.

Thrombocytopenia

Thrombocytopenia, a decreased platelet count, may be caused by abnormal platelet production, accelerated platelet removal resulting from immunologic or nonimmunologic mechanisms, sequestration of platelets in the spleen, or combinations of these disorders.

The hallmark of thrombocytopenia is nonpalpable petechiae, which reflect bleeding probably from capillaries or postcapillary venules. Petechiae usually are only a few millimeters in diameter and occur at sites of increased intravascular pressure, such as over the lower extremities and on the oral mucosa, and at sites constricted by certain types of clothing, such as brassiere straps. Purpura, more extensive subcutaneous bleeding, may occur with a confluence of petechial lesions. Palpable purpura indicates an additional component of vascular inflammation and suggests underlying systemic vasculitis, such as cryoglobulinemia. Thrombocytopenia also leads to mucosal bleeding; deep-tissue bleeding is less common.

There is no clearly demarcated level of platelets above which patients can be considered safe. In general, a platelet count greater than 20,000/µl is considered safe; platelet counts of 10,000/µl or below may be tolerated in nonsurgical patients [see 5:X Transfusion Therapy]. Patients with idiopathic thrombocytopenic purpura bleed less at a given platelet level than patients with aplastic anemia. Presumably, the larger, younger platelets are more effective in hemostasis. The risk of intracranial hemorrhage usually directs therapy.

Elderly patients and patients with coexistent illnesses bleed more than young patients and patients with thrombocytopenia alone. An associated disorder, such as liver dysfunction or connective tissue disease, increases the risk of serious bleeding.

In the initial laboratory evaluation, the complete blood count will establish whether the thrombocytopenia is an isolated finding or associated with anemia or leukopenia. If thrombocytopenia is an isolated finding, the physician should confirm the platelet count by repeating the complete blood count. A falsely low platelet count can be the result of in vitro platelet clumping caused by the presence of cold-dependent or ethylenediaminetetraacetic acid–dependent agglutinins. Examination of the blood smear and a repeat platelet count in a citrated or heparin-anticoagulated blood sample will resolve this problem.

The peripheral smear may reveal morphologic abnormalities in platelets and indicate the presence of polychromatophilia, neutropenia, lymphopenia, spherocytosis, blasts, or fragmented microangiopathic erythrocytes. The mean platelet volume, as determined by automated blood cell counters, may provide an additional clue to the cause of the thrombocytopenia. Low platelet volumes (< 6.4 femtoliters) suggest poor production, whereas larger volumes suggest rapid platelet regeneration or dysplastic platelet production.

PLATELET PRODUCTION DEFECTS

Diagnosis

A marrow aspiration with biopsy is critical for diagnosis of thrombocytopenia. The finding of a hypoplastic marrow in which the total cellularity is reduced with a concomitant decrease in megakaryocytes implies aplastic or hypoplastic anemia. The first presumption of a cause in these cases is drug toxicity. A marrow that is fibrosed or infiltrated with leukemic or other malignant cells represents the syndrome of pancytopenia from infiltrated marrow.

A marrow aspirate and biopsy sample showing normal cellularity and normal maturation of the erythroid and myeloid precursors, with decreased numbers of apparently normal megakaryocytes, suggests that the patient has ingested a drug, such as ethanol, that specifically affects the megakaryocytic progenitor cells. Ethanol also produces ineffective megakaryopoiesis. In vitamin B12 deficiency and folate deficiency, all three marrow cell lines are affected. The marrow smear shows many large hyperlobated megakaryocytes. Some myeloproliferative disorders are characterized by ineffective megakaryopoiesis with bizarre binucleate megakaryocytes.

When accelerated removal appears to be the cause of the patient’s thrombocytopenia, a rapid differential diagnosis should be made [see Table 1]. A bone marrow aspirate and biopsy will be very helpful. Usually, thrombocytopenia with an abundance of normal megakaryocytes in the marrow is the result of accelerated platelet removal. Normally, platelets survive for 10 days and have a half-life of about 4 days; in accelerated-removal states, such as idiopathic thrombocytopenic purpura, the platelet half-life may be as short as 30 to 60 minutes. The platelet count will then reflect the balance between accelerated platelet removal and compensatory megakaryopoiesis.

Platelet survival studies are not generally available and are not usually necessary to determine whether accelerated platelet
removal is occurring. Infusion of random-donor platelets can be used as a diagnostic and therapeutic procedure. When accelerated platelet removal is responsible for the thrombocytopenia, transfusion with six platelet packs only slightly elevates the platelet count, which then returns to baseline values in less than 24 hours. This therapeutic test becomes unreliable, however, if the patient has been previously alloimmunized by blood or platelet transfusions or by multiple pregnancies.

**Treatment**

If a drug is the suspected cause of the thrombocytopenia, it should be discontinued. Specific replacement is required for deficiencies of vitamin B₁₂ and folate. When the thrombocytopenia is causing significant bleeding, platelet transfusion will be required until the situation resolves [see 5X Transfusion Therapy].

Recombinant thrombopoietin is in clinical trials. Interleukin-11 (IL-11), which plays a contributory role in megakaryopoiesis, has been shown to be efficacious in reducing the need for platelet transfusion after chemotherapy and has approval by the Food and Drug Administration for secondary prophylaxis of ITP. Interleukin-11 has been shown to be efficacious in reducing the need for platelet transfusion after chemotherapy and has approval by the Food and Drug Administration for secondary prophylaxis of ITP.

**ACCCELERATED PLATELET REMOVAL DUE TO IMMUNE DESTRUCTION**

**Idiopathic Thrombocytopenic Purpura**

**Pathophysiology** Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by rapid platelet destruction; antibodies against the patient’s own platelets are present. These autoantibodies bind to specific proteins on the platelet surface, and the antibody-coated platelets are removed by the reticuloendothelial system, especially in the spleen. The immunoglobulin on the platelet membrane is usually IgG (most commonly of the subclass IgG₁). This immunoglobulin is frequently directed against the platelet glycoprotein (GP) IIb-IIIa, the receptor complex that mediates fibrinogen binding and platelet aggregation. Less frequently, the immunoglobulin is directed against the GP Ib complex. The marrow may respond to the thrombocytopenia by increasing platelet production. In some cases, the marrow response is suboptimal probably because the antiplatelet antibodies also react with megakaryocyte cell surface antigens. The platelets produced in ITP are usually large and functional, which may account for the clinical observation that most patients with ITP do not have significant clinical bleeding.

**Clinical features** ITP typically appears in young women, but in some communities, the prevalence of ITP in young women has been superseded by its occurrence in men who are seropositive for HIV infection. Predisposing diseases and contributing factors may also include infectious mononucleosis and other acute viral illnesses, Graves disease, and Hashimoto thyroiditis, as well as antiphospholipid antibody syndrome and antiphospholipid antibody syndrome. For ITP patients who have antiphospholipid antibody, the outcomes, courses, and response to therapy do not differ from those of other ITP patients.

The onset of ITP is usually insidious. History and physical examination are usually negative except for the presence of petechiae, most commonly in the lower extremities. Clinical bleeding is usually mild, consisting of purpura, epistaxis, gingival bleeding, and menorrhagia. Blood blisters (wet purpura) in the mouth indicate the presence of severe thrombocytopenia. Retinal hemorrhages are uncommon. The spleen is usually not palpable. The presence of a palpable spleen raises the possibility of systemic lupus erythematosus (SLE), lymphoma, infectious mononucleosis, or hypersplenism from underlying chronic liver disease.

**Laboratory evaluation** The peripheral smear is usually normal; the few platelets that are present are large and well granulated. The presence of hypochromia suggests iron deficiency from chronic blood loss; spherocytes raise the possibility of associated autoimmune hemolysis (Evans syndrome); and red blood cell fragments (schistocytes) suggest a disease such as disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), or hemolytic-uremic syndrome (HUS). The marrow shows abundant megakaryocytes, many of which are small, erythroid, and megakaryoid precursors remain normal. Re-

### Table 1 Causes of Thrombocytopenia

<table>
<thead>
<tr>
<th>Type</th>
<th>Disorder</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet production defect</td>
<td>Marrow aplasia or hypoplasia,</td>
<td>Radiation, cytotoxic drugs, idiopathic</td>
</tr>
<tr>
<td></td>
<td>pancytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marrow infiltration, pancytopenia</td>
<td>Cancer (leukemia, lymphoma), fibrosis</td>
</tr>
<tr>
<td></td>
<td>Selective impairment of platelet</td>
<td>Drugs (ethanol, gold, trimethoprim-sulfamethoxazole, sulfonamides, thiazides, phenylbutazone); infections (childhood rubella, HIV)</td>
</tr>
<tr>
<td></td>
<td>production</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ineffective megakaryopoiesis</td>
<td>Vitamin B₁₂ deficiency, folic acid deficiency, myelodysplastic syndrome, alcohol abuse</td>
</tr>
<tr>
<td>Accelerated platelet removal</td>
<td>Immune destruction</td>
<td>Autoantibodies (idiopathic thrombocytopenic purpura, systemic lupus erythematosus, lymphoproliferative disease); proven drug antibodies (quinidine, quinine, heparin, GPIIb-IIIa antagonists); infections (infectious mononucleosis, HIV, gram-negative septicemia, malaria); suspected drug antibodies (thiazide diuretics, acetaminophen, cimetidine, aminosalicylic acid); posttransfusion purpura</td>
</tr>
<tr>
<td></td>
<td>Nonimmunologic removal</td>
<td>Disseminated intravascular coagulation, preeclampsia, vasculitis, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, HELLP syndrome, severe bleeding, platelet washout after massive transfusion, giant hemangioma, gram-negative septicemia</td>
</tr>
<tr>
<td></td>
<td>Hypersplenism</td>
<td>Enlarged spleen from various causes</td>
</tr>
</tbody>
</table>

HELLP—hemolysis, elevated liver enzymes, low platelet count
results of tests for SLE are negative. Platelet-associated IgG (PA-IgG) levels are elevated; however, because platelets normally contain IgG in their \(\alpha\)-granules, PA-IgG does not distinguish between antiplatelet antibodies, immune complexes deposited on platelet surface, and antibodies released from the platelet granules and bound on its surface. Therefore, tests for PA-IgG are not useful in the diagnosis of ITP.

**Differential diagnosis** The differential diagnosis of ITP includes a falsely low platelet count resulting from ethylenediaminetetraacetic acid–dependent or cold-dependent agglutinins that cause in vitro platelet clumping (diagnosed by reexamination of the platelet count in citrated or heparin-anticoagulated blood sample); the gestational thrombocytopenia of pregnancy (usually a mild problem that is not associated with increased bleeding risk); myelodysplastic syndrome (usually associated with anemia and leukopenia); and underlying lymphoproliferative disease.

**Course and prognosis** ITP is a relatively benign disorder that has a mortality of approximately 1% to 5%; most deaths in adult cases result from intracranial bleeding. Acute ITP is usually confined to children and young adults and is frequently preceded by a viral illness. Permanent spontaneous remission occurs in less than 3 months. Chronic ITP, the usual adult variety, refers to disease that persists for more than 3 months. Although spontaneous remissions and relapses do occur in chronic ITP, long-term spontaneous remissions are uncommon. On the other hand, the long-term prognosis of ITP is benign, even in refractory cases, when these patients are managed properly.

**Treatment** The treatment of ITP depends on the age of the patient; disease severity; whether petechiae are present alone or with moderate or severe mucosal or central nervous system bleeding; and whether the patient is pregnant.

The American Society of Hematology has released an evidence-based practice guideline for the management of ITP, which can be summarized as follows:

1. Patients with platelet counts above 50,000/\(\mu\)l do not routinely require treatment.
2. Treatment is indicated in patients with platelet counts below 20,000 to 30,000/\(\mu\)l and in patients with platelet counts below 50,000/\(\mu\)l and significant mucosal bleeding or risk factors for bleeding (e.g., hypertension, peptic ulcer disease, or a vigorous lifestyle).
3. Patients with platelet counts below 20,000/\(\mu\)l need not be hospitalized if they are asymptomatic or if they have only mild purpura.

Patients with asymptomatic mild or moderate thrombocytopenia (i.e., platelet count > 50,000/\(\mu\)l) do not require active therapy. They may be followed and simply alerted to report any mucosal bleeding or crops of new petechiae. Avoidance of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is strongly advised.

For patients with moderate mucosal bleeding, therapy is begun with prednisone at a dosage of 60 to 100 mg/day in divided doses. Corticosteroids interfere with the macrophage attack on platelets and eventually reduce the amount of antiplatelet antibody produced by splenic and marrow lymphoid cells. Unless bleeding is severe, the patient need not be hospitalized. Heavy physical activity, particularly any activity that involves the Val-
salva maneuver, should be avoided so as not to increase intracranial pressure. The avoidance of aspirin and other NSAIDs should be emphasized. If required, red blood cell transfusions can be given; however, it is rarely necessary to transfuse platelets in such cases.

The platelet count usually rises several days to 2 to 3 weeks after the start of therapy. When the platelet count reaches normal levels, the prednisone dose can be tapered over a 3- to 4-week period. Although complete long-term remissions with prednisone alone have been reported, sustained complete response after therapy occurs in fewer than 10% of patients.

Splenectomy is indicated if platelet counts remain below 30,000/\(\mu\)l after 4 to 6 weeks of steroid therapy or when the platelet count begins to fall again after the tapering of steroid. The procedure produces long-standing remission in about 65% of patients with ITP. It is best to resume oral corticosteroid therapy before splenectomy so that the patient will have a platelet count of at least 30,000 to 50,000/\(\mu\)l at the time of surgery. Alternatively, if the patient is not responsive to steroid therapy, intravenous immune globulin (IVIG) may be administered at a dosage of 1g/kg/day for 2 days or 0.4 g/kg/day for 5 days a few days before surgery. IVIG will produce a transient increase in the platelet count in the majority of patients, but it is a very expensive therapy. The platelet count usually begins to rise on the first postoperative day, often overshooting normal values by the second week. Pneumococcal, *Haemophilus influenzae*, and meningococcal vaccines should be administered 1 to 2 weeks before surgery.

If the patient is elderly or frail and hence may not survive splenectomy, the disease may be controlled by administration of the minimum amount of corticosteroids required to raise the platelet count to 30,000 to 50,000/\(\mu\)l, a level above which severe bleeding rarely occurs. Because patients with ITP who are classified as therapeutic failures generally do well clinically, the role of such potentially dangerous agents as cyclophosphamide and azathioprine in the management of such cases should be evaluated on a case-by-case basis.

Severe mucosal or CNS bleeding is a true medical emergency requiring hospitalization. Red cells are transfused as required, and prednisone is administered immediately, beginning with a 100 mg dose and then continuing at a level of 25 mg every 6 hours. IVIG should be administered at a dosage of 0.4 g/kg/day for 5 days or 1 g/kg/day for 2 days, and transfusion with 8 to 10 U of random-donor platelets should be carried out when the infusion of the first dose of IVIG, usually given over approximately 60 minutes, is complete. The platelet transfusion after the infusion of IVIG produces a greater and more durable increase in the platelet count. Side effects include generalized aches, headache, flushing, fever, and chills. When severe uterine bleeding occurs, a single 25 mg dose of conjugated estrogen can be administered intravenously to control the hemorrhage. It should be emphasized that the benefit of IVIG is usually transitory and lasts only a few days. Plans for splenectomy should follow this emergency therapy.

The mechanism of action of IVIG is not completely understood. It may produce reticuloendothelial blockade by blocking the IgG-Fc sites on the monocyte-macrophages. Highly specific anti-idiotypic antibodies may also block the binding of platelet autoantibodies to the platelet GPIb-IIIa antigen.

Studies indicate that the catalytic rate of IgG is mediated by a new receptor for the Fc component of IgG, termed FcRn (neonatal Fc receptor, so named because it was initially identified in neonatal intestinal epithelium), on the vascular endothelial cells. Normally, IgG, but not IgM, that enters the cell through the process of pinocytosis is
protected from catabolic breakdown by binding to the FcRn. After the administration of high-dose IVIG, this receptor is presumably saturated, permitting the degradation of the pathologic antibody to occur in proportion to its concentration in plasma.\(^{13}\)

**Refractory Idiopathic Thrombocytopenic Purpura**

A patient who remains severely thrombocytopenic after splenectomy and corticosteroid therapy or who goes into remission but later experiences a relapse and fails to respond to high doses of prednisone is said to have refractory ITP. Because serious hemorrhage is uncommon with platelet counts above 30,000/µl, it is often prudent to accept an incomplete response and not proceed to more toxic forms of management. Immunosuppressive agents are generally the mainstay of therapy at this stage. However, it should be emphasized that there are no large randomized studies to address this difficult problem and that generally these patients should be referred to a hematologist.

There are several major treatment alternatives for refractory patients. Azathioprine (100 to 150 mg/day orally) or, alternatively, cyclophosphamide (100 to 150 mg/day orally) plus prednisone (40 to 60 mg/day orally), can be given, with weekly monitoring of complete blood count and platelet count. Prednisone may be tapered and azathioprine or cyclophosphamide adjusted to avoid severe leukopenia. A frequent mistake is to discontinue the therapeutic trial prematurely. Both azathioprine and cyclophosphamide are myelosuppressive and should be given in sufficient dosages to cause a mild leukopenia, with a white blood cell count of approximately 3,000/µl, and both have been associated with development of myelodysplastic syndrome and acute myeloid leukemia. After 1 month, alternate-day prednisone therapy should be considered to avoid steroid side effects.

Another alternative is antibody therapy with intermittent courses of IVIG at the dosage schedules described above. The cost of this therapy and the usual short-lived response to it make it an unattractive choice. Anti-D antibody has been administered to Rh\(^{(D)}\) patients with ITP on the theory that the antibody-coated red blood cells would block Fc receptors on macrophages and prevent the accelerated removal of platelets. Other therapeutic options include vincristine, vinblastine,\(^{14}\) danazol,\(^{15}\) high-dose dexamethasone, cyclosporine, interferon alfa, and plasmapheresis.

In the refractory splenectomized patient, it is important to check for the continued presence of Howell-Jolly bodies and the possibility of an accessory spleen. The disappearance of Howell-Jolly bodies suggests the presence of a remaining accessory spleen or a regenerated spleen.

Patients with clinically significant thrombocytopenic bleeding can also benefit from fibrinolysis inhibitor e-aminoacaproyl acid (EACA). EACA can be given at 2 to 3 g orally four times daily until hemostasis is achieved.

**HIV-Related Idiopathic Thrombocytopenic Purpura**

GPIIIa, a linear peptide in the platelet membrane, has been identified as a major antigenic determinant for anti-GPIIIa antiplatelet antibody in HIV-1–related ITP.\(^{16}\) In patients with HIV infection, platelets also contain increased amounts of IgG, IgM, complement, and immune complexes. Platelet survival is moderately short and platelet production is impaired, especially at the later stage of the disease.\(^{17}\)

The use of immunosuppressive agents in HIV-infected patients is hazardous. If the drop in the platelet count is modest, no therapy is needed. When the thrombocytopenia is severe, a short course of prednisone can be administered, followed by splenectomy.

Acute thrombocytopenic hemorrhage in HIV-associated ITP may be managed by the administration of high-dose IVIG, similar to management in other ITPs. Chronic HIV-associated ITP may respond to oral zidovudine (AZT) or other antiviral therapies [see 7:XXXIII HIV and AIDS]. Anti-D antibody, dapsone, and interferon have also been used with some success.\(^{18-20}\) Patients who refuse splenectomy or who are thought to be poor surgical candidates may respond to low-dose splenic irradiation.\(^{21}\)

**Idiopathic Thrombocytopenic Purpura in Pregnancy**

Platelet counts as low as 70,000/µl occur in 5% of healthy pregnant women. When thrombocytopenia is observed for the first time during pregnancy, the differential diagnosis must include preeclampsia [see Table 1]. If other diagnoses can be excluded, the diagnosis is gestational thrombocytopenia, or incidental thrombocytopenia of pregnancy, and requires no management.\(^{22}\) If the diagnosis of ITP is made, however, the therapeutic choices are limited because splenectomy may cause spontaneous abortion and immunosuppressive agents may damage the developing fetus. Therefore, therapy is usually limited to corticosteroids or IVIG. Corticosteroids increase the risk of preeclampsia and gestational diabetes. In cases of severe thrombocytopenic hemorrhage, however, all of the available therapies should be used to protect the life and well-being of the mother.

Because the antiplatelet autoantibody in ITP has broad specificity and is almost always an IgG, it can cross the placenta and produce thrombocytopenia in the fetus. During a vaginal delivery, the pressure applied to the head of a thrombocytopenic fetus may induce an intracranial hemorrhage. Concern about this occurrence had led many experts to recommend early cesarean sections in women with a history of ITP or active disease. Although cesarean sections may help minimize fetal morbidity, they can cause significant bleeding in the thrombocytopenic mother. No area of hematology has produced more differences of opinion than the management of ITP during delivery, because of the potential danger to the fetus as well as to the mother.

A large prospective surveillance study has shown that measurement of maternal antiplatelet antibody is of no clinical utility. A mother with a history of ITP who has a normal platelet count can deliver a thrombocytopenic neonate (two of 15 births, or 13%). The overall incidence of thrombocytopenic neonates in women with ITP is quite low (four of 46 births, or 9%).\(^{23}\) No intracranial hemorrhages were observed in the study. In the six most severely thrombocytopenic neonates (platelet counts below 20,000/µl), the disorder was caused not by ITP in pregnancy but by the syndrome of neonatal alloimmune thrombocytopenia.\(^{24}\) Nevertheless, this issue remains highly charged, with some experienced investigators recommending percutaneous umbilical blood sampling in women with platelet counts below 70,000/µl and cesarean section if the fetal platelet count is below 50,000/µl.

**Thrombocytopenic Purpura with Lymphomas and Systemic Lupus Erythematosus**

Patients with SLE, Hodgkin disease, or non-Hodgkin lymphoma can present with a clinical picture identical to that seen in ITP. The diagnostic approach and therapy are the same as in ITP. Splenomegaly with splenic sequestration, marrow infiltration with malignant cells, and recent antinuclear or immunosuppressive therapy should be excluded. Patients with SLE or lymphoma may have Evans syndrome, in which ITP is associated with autoimmune hemolytic anemia. The management of Evans syndrome is the same as that of ITP and autoimmune hemolytic anemia.
Posttransfusion Purpura

Posttransfusion purpura (PTP) is characterized by acute onset of severe thrombocytopenia, often below 10,000/µl, accompanied by clinical bleeding. It may occur from 2 to 10 days after a transfusion of whole blood, packed red blood cells, or platelet-containing components. Almost all of the affected patients are multiparous women. Such disorders as septic thrombocytopenia, DIC, and heparin-induced thrombocytopenia must be considered in the differential diagnosis. The thrombocytopenia usually lasts for about 4 weeks. Because platelet transfusions are usually futile and sometimes precipitate severe systemic responses, they should be avoided if possible.

The pathophysiology of PTP is not completely understood. In most cases, the patient has been exposed to platelet alloantigens during pregnancy or as a result of a transfusion. Most patients with this disorder have antibodies to the platelet antigen PLA-1 (also termed HPA-1a), an antigen that is present on GPIIa on the platelet surface. In the United States, approximately 98% of the white population, 99% of the African-American population, and 99% of the Asian-American population are homozygous for PLA-1. Patients in whom PTP develops are usually PLA-1 negative and PLA-2 (HPA-1b) positive. The patient has been sensitized to the PLA-1 antigen, most frequently during pregnancy, and reexposure to PLA-1 platelets during red cell transfusion leads to an anamnestic response and the destruction of the foreign platelets. It is an apparent paradox that alloantibody directed against an antigen present on foreign platelets results in destruction of the patient’s autologous platelets, which do not express the PLA-1 antigen. There is evidence suggesting that the PLA-1 antigen becomes soluble and attaches to the PLA-1 negative platelets. Alternatively, exposure to foreign platelets may induce the formation of a true autoantibody against the endogenous platelets. The PLA-1/PLA-2 polymorphism accounts for 80% to 90% of PTP.

Confirmation of the diagnosis requires serologic studies demonstrating the presence of anti–PLA-1 antibody and a homozygous PLA-2 genotype. Several rapid platelet genotyping techniques based on the polymerase chain reaction have been developed.

There are no controlled clinical trials evaluating therapy for PTP because of the limited number of cases. Reports indicate that IVIG, used at doses similar to those used in the treatment of ITP, is efficacious in about 80% of cases. Another option is plasmapheresis, which appears to be as efficacious as IVIG but more cumbersome. High doses of corticosteroid is also effective, although this treatment is not as consistently effective as IVIG.

Drug-Induced Immune Platelet Destruction

Drug-induced immune platelet destruction is indistinguishable from ITP. The bone marrow shows abundant megakaryocytes, and special laboratories can detect the presence of antithrombin antibodies.

Quinidine and quinine purpura The pathogenic antibodies in cases of quinidine and quinine purpura develop as early as 12 days after exposure to the offending agent. In most cases, drug-dependent antibodies to platelet surface GPIb-IX have been identified in patients’ sera. The antibodies are drug dependent because they bind to the platelets only in the presence of quinine or quinidine. Presumably, the binding of the drugs to these platelet surface glycoproteins induces new antigenic sites on the proteins that are recognized by the antibodies.

The agent (quinidine or quinine) should be withdrawn in such cases. Neither corticosteroid therapy nor emergency splenectomy is of documented benefit in purpura induced by these agents. Plasmapheresis to remove the drug and antibodies would appear to be a logical treatment, but there are no systematic studies of its effectiveness. Transfused platelets are removed as rapidly as the recipient’s own platelets. Nevertheless, platelet transfusion may be attempted to control life-threatening bleeding. Treatment with prednisone and IVIG in a dose similar to that used in ITP is recommended.

A quinine-induced thrombocytopenia that is closely followed by the development of HUS has been recognized. Quininedependent antibodies to platelets, as well as to endothelial cells, have been found in patients’ sera. Even the small amount of quinine in tonic water seems to be sufficient to trigger recurrent bouts of the syndrome. Other drugs that may occasionally produce drug-dependent thrombocytopenia include dipyriramole and trimethoprim-sulfamethoxazole.

Heparin-induced thrombocytopenia Heparin-induced thrombocytopenia (HIT) is a frequent cause of drug-induced thrombocytopenia in hospitalized patients. Despite the presence of modest to moderate thrombocytopenia, HIT is rarely associated with bleeding but is associated with significant and sometimes fatal thrombosis [see 5.XIV Thrombotic Disorders].

Gold-induced thrombocytopenia Gold salt therapy for rheumatoid arthritis produces thrombocytopenia in 1% to 3% of patients. There is no evidence of a drug-antidrug antibody reaction as exists for quinidine and quinine thrombocytopenia. The condition is characterized by increased narrow megakaryocytes, shortened platelet survival, and, infrequently, antiplatelet antibodies. Most patients respond to therapy with 60 mg of prednisone daily. The usefulness of dimercaprol as a gold-chelating agent has not been established. Patients who are not responding to corticosteroid therapy appear to benefit from splenectomy.

Cocaine-associated thrombocytopenia An ITP-like syndrome has been reported in intravenous cocaine users. These individuals responded to an approach similar to that employed in ITP.

Thrombocytopenia caused by platelet glycoprotein IIb-IIIa receptor antagonists Three parenteral GPIIb-IIIa antagonists—abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat)—have been approved for use in the treatment of acute coronary syndrome and as adjunctive therapy in coronary angioplasty. Meta-analysis of clinical trials with GPIIb-IIIa antagonists suggests that the parenteral administration of a GPIIb-IIIa antagonist increases the likelihood of thrombocytopenia (platelet count below 100,000/µl) by approximately 50% (overall risk, 1.48), as compared with placebo, with an incidence of approximately one to two cases per 100 patients treated. The inclusion of heparin had no apparent additive effect. The development of thrombocytopenia can be acute (i.e., within 24 hours of exposure to the drug) or delayed (i.e., up to 14 days after the initiation of long-term therapy). Acute profound thrombocytopenia, with platelet counts below 20,000/µl, has been observed in 0.3% to 0.7% of patients receiving abciximab.

The most likely mechanism of thrombocytopenia appears to be autoimmune mediated. Presumably, preexisting anti–GPIIb-IIIa autoantibodies are present in these patients, and after the administration of the anti–GPIIb-IIIa antagonist, the binding of the

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drug to GPIIb-IIIa induces conformational changes in GPIIb-IIIa such that new epitopes are exposed that are recognized by the autoantibodies. These actions would explain the acute onset of profound thrombocytopenia. The incidence of anti–GPIIb-IIIa antibodies that will bind to autologous platelets in the presence of GPIIb-IIIa antagonists has been estimated to be approximately 1% in selected patient populations.37

When thrombocytopenia develops, with platelet count below 100,000/µl, the GPIIb-IIIa antagonist and any other potential offending medications (e.g., heparin) should be discontinued immediately. Depending on the platelet count, it may not be advisable to discontinue antiplatelet agents such as aspirin, ticlopidine, or clopidogrel (Plavix), because patients with this disorder are at high risk for acute coronary artery or stent thrombosis. If the platelet count drops below 10,000/µl, strong consideration should be given to platelet transfusion. In general, only one single-platelet transfusion is sufficient. There are anecdotal reports of acute coronary thrombosis associated with platelet transfusion in this setting when the platelet count climbs over 50,000/µl and the patient is off all antiplatelet agents. Thus, antiplatelet agents may need to be re instituted. In most cases, the platelet count returns to normal within 4 days, although it may take up to 2 weeks in the case of abciximab. It is recommended that a platelet count be obtained in all patients within 2 to 4 hours after the initiation of an intravenous GPIIb-IIIa antagonist and within 24 hours of ingestion of an oral GPIIb-IIIa inhibitor.

**Thrombocytopenia caused by metabolites of naproxen and acetaminophen** Five patients experienced thrombocytopenia after taking naproxen and acetaminophen. In each case, antibodies that reacted with normal platelets in the presence of a known drug metabolite of naproxen or acetaminophen were identified.32 Therefore, the sensitizing agents are drug metabolites that formed in vivo.

### ACCELERATED REMOVAL OF PLATELETS BY NONIMMUNLOGIC MECHANISMS

There are several nonimmunologic causes for thrombocytopenia. Blood vessel wall injury with increased thrombin generation and increased platelet activation and consumption occurs in several of these conditions.

**Thrombotic Thrombocytopenic Purpura and Adult Hemolytic-Uremic Syndrome**

TTP and HUS encompass a group of clinical syndromes in which a primary event damages the endothelia of small vessels, leading to widespread platelet-fibrin thrombi deposition in the small arteries and arterioles and capillaries. Thrombotic microangiopathy is a distinct feature of both TTP and HUS.

### Clinical features and diagnosis

The five major manifestations (pentad) of TTP are (1) severe microangiopathic hemolytic anemia associated with a very high serum lactic dehydrogenase (LDH) level and a blood smear showing the characteristic schistocytes and helmet cells; (2) moderate to severe thrombocytopenia with increased marrow megakaryocytes, which indicates intravascular platelet activation and consumption; (3) fever, which is occasionally quite high; (4) CNS signs and symptoms that can be quite mild initially with transient agitation, headache, and disorientation but sometimes progress explosively to hemiparesis, aphasia, seizures, focal deficits, coma, and death; and (5) renal disease, which is usually mild and produces moderate elevations of serum creatinine and urine protein. It should be emphasized that many patients do not present with all these signs and symptoms.

The adult form of HUS is a similar condition. Common features of TTP and HUS include microangiopathic hemolytic anemia, thrombocytopenia, and the presence of platelet fibrin thrombi in the small vessels. Renal involvement is uniformly severe in HUS, whereas CNS disease is less prominent than in TTP. There is a distinct form of HUS that occurs in approximately 15% of children after gastrointestinal infection with *Escherichia coli*, usually serotype 0157:H7. These patients present with bloody diarrhea and hemorrhagic colitis. *E. coli* 0157:H7 or other strains elaborate verotoxins (also called Shiga toxins) that bind to specific receptors on the endothelial surface, causing cell damage and even cell death.33 Studies show that verotoxin-1 (VT-1) can induce the upregulation of various prothrombotic and proinflammatory adhesive molecules on endothelial cells.34 The microvascular endothelial cells are particularly susceptible because they have a high expression of VT-1 receptors, which may explain the propensity for thrombosis in the microcirculation. Antibiotic treatment of children with *E. coli* 0157:H7 infection increases rather than decreases the risk of HUS, presumably because it causes the release of verotoxins from injured bacteria in the intestine, making the toxins more available for absorption. Thus, routine treatment with antibiotics is not recommended.36

### Differential diagnosis

Both TTP and HUS must be differentiated from SLE and from Evans syndrome. Microangiopathic hemolysis, neutrophilic leukocytosis, and a negative direct Coombs test (direct antiglobulin test) strongly suggest TTP or HUS. Coagulation tests usually reveal no significant abnormalities (i.e., no evidence of DIC); serum LDH is usually elevated. A marrow biopsy is generally not required but may show the characteristic, but not pathognomonic, platelet-fibrin hyaline thrombi in small arteries and arterioles.

### Etiology

TTP/HUS occurs spontaneously and is also associated with pregnancy, cancer, bone marrow transplantation, autoimmune diseases, and various drugs. In pregnancy, it resembles severe preeclampsia. In the postpartum period, the CNS manifestations may initially be confused with postpartum depression, with tragic results. Cases have been reported after a normal delivery and with abruptio placentae and preeclampsia.

Several drugs appear to cause TTP/HUS. These include chemotherapeutic drugs (e.g., mitomycin C, bleomycin, and cisplatin), immunosuppressive agents (e.g., cyclosporine and FK506), the antiplatelet agent ticlopidine, oral contraceptives, and quinine. For ticlopidine, the incidence is very low (0.02%) and the majority of cases occur after 2 to 4 weeks of therapy. However, the condition is difficult to predict. In one study, overall mortality in ticlopidine-induced TTP/HUS was 21%, with all deaths occurring in patients not treated with plasmapheresis.34 Such findings underscore the importance of a high index of suspicion and the prompt institution of plasmapheresis. Anecdotal cases of TTP/HUS associated with clopidogrel, which is related to ticlopidine, have also been reported.37

### Pathophysiology

Two mechanisms have been proposed to account for TTP/HUS. One hypothesis postulates the presence of a circulating platelet activating factor that stimulates platelets causing extensive intravascular platelet aggregation. The second hypothesis suggests that the primary insult is extensive arteriolar endothelial damage. Platelet activation, adherence,
occlusion, and fibrin strand formation then lead to thrombocytopenia and microangiopathic hemolysis. There are data to support both hypotheses.

Many investigators have observed that abnormally large multimers of von Willebrand factor (vWF) are present in patients with chronic relapsing TTP.38-40 These abnormal vWF multimers may have enhanced binding affinity to platelets and may contribute to the development of microvascular thrombosis. They accumulate because of a defect in the normal processing of vWF multimers, thus predisposing the patient to thrombosis. In support of this hypothesis, the vWF-cleaving protease has been purified.41 This enzyme is a new member of the ADAMTS (a disintegrin and metalloprotease with thrombospondin type 1 motif) family of metalloprotease that binds to zinc and calcium and is synthesized in the liver as a proenzyme (zymogen). It is then activated by proteolytic cleavage. There are multiple variants of this enzyme generated by alternative splicing of the messenger RNA, which may be of physiologic significance.42

A decrease in the vWF-cleaving protease activity in chronic relapsing TTP was initially described by two groups.43,44 This decrease has been confirmed and extended.45-46 In a prospective study of 111 adult patients with thrombotic microangiopathies, a decrease in vWF-cleaving protease activity was found in 59 of 66 TTP patients (89%) and in 6 of 45 HUS patients (13%).47 In this study, the TTP/HUS was considered either idiopathic or secondary, associated with clinical factors that include neoplasia, immunologic disorders, bacterial or viral infections, bone marrow transplantation, and drugs. In a second study, reduced protease activity was found in only 9 of 20 patients with TTP.48 Furthermore, a deficiency or decrease in the vWF-cleaving protease activity is not specific for TTP, because it was also found in patients with other thrombotic microangiopathic disorders, including some patients with ITP, DIC, SLE, and leukemia, many of whom did not have evidence of microangiopathy.48

The two groups who originally reported the decrease in vWF-cleaving protease activity in chronic relapsing TTP described the isolation of inhibitory antibodies from the patient plasma.49-50 This development has also been confirmed in the recent prospective study.51 A protease inhibitor was found in 47% of the TTP patients but not in the HUS patients. In the majority of cases, the inhibitor was not detectable when the patients were in remission.

Thus, evidence strongly suggests that a deficiency or decrease in the vWF-cleaving metalloprotease plays a major role in the pathogenesis of TTP but not HUS, suggesting that these two clinical entities may differ in pathophysiology. In the acquired form of TTP, this difference may be related to the presence of an inhibitory antibody. In the much rarer familial form, it may be the result of a constitutive enzyme deficiency. Plasma exchange could remove the abnormally large vWF multimers and the inhibitory antibodies in the patient's plasma, as well as replenish the protease.

However, it should be noted that normal vWF-cleaving protease activity is also observed in some patients with TTP. There is no apparent relation between protease activity and disease severity.46 It is also likely that the abnormally large vWF multimers are not sufficient to account for the pathogenesis of TTP. Large multimers can be detected in the plasma of patients with relapsing TTP when these patients enter clinical remission.49 In one well-studied case of chronic relapsing TTP, normalization of the abnormal vWF multimers failed to increase the platelet count and induce clinical remission.49 Extensive damage or activation of endothelial cells, perhaps in the setting of infection, pregnancy, or exposure to certain drugs, causes them to release the largest vWF multimers, which, as a result of defective processing, may cause platelet aggregation and microvascular thrombosis. With the identification of the vWF-cleaving metalloprotease, specific assays for this enzyme should be available to help clarify these issues.

**Treatment** Prompt institution of plasma exchange with fresh frozen plasma is the treatment of choice for TTP/HUS. In a large randomized trial by the Canadian Apheresis Group, intensive plasma exchange was more effective than plasma infusion in terms of patient survival (78% versus 63%).44 In that study, 1.5 times the calculated plasma volume was removed and replaced with fresh frozen plasma during each of the first 3 days of therapy and then one plasma volume a day thereafter for a minimum of 7 days. Some investigators obtained good results with a daily single-volume exchange instead of 1.5-volume exchange.45 It is reasonable to start with a daily single-volume exchange if the patient is clinically relatively stable, with moderate thrombocytopenia and no significant neurologic impairment. However, if the clinical situation worsens, more intensive double-volume plasma exchange (5,000 to 6,000 ml/day, or approximately 80 ml/kg/day) is indicated. Because vWF multimers are present in cryoprecipitate, cryosupernatant (i.e., fresh frozen plasma from which cryoprecipitate has been removed) can be substituted as replacement fluid when a patient is not responding to routine plasma exchange. One uncontrolled study showed increased benefit from this preparation as compared with fresh frozen plasma.46 Once therapeutic benefit has been achieved (as measured by restoration of normal CNS function, by rising platelet counts, and by falling LDH levels), the intensity and frequency of plasma exchange can be reduced to single-volume exchanges, first three times weekly and then twice weekly.

Although the importance of prompt plasma exchange has been established, the use of corticosteroids,49 aspirin, and dipyridamole has not been tested in prospective clinical trials. Because pheresis tends to lower the platelet count in a patient who is already thrombocytopenic, the problem of platelet transfusion arises. Some investigators have observed that platelet infusion may lead to exacerbation of TTP,46 whereas others use platelet transfusions as required.

Microangiopathy may persist for weeks or months after all other evidence of disease has subsided. In a large follow-up study of TTP patients, about one third of those who entered remission relapsed during a 10-year period, and about one in 10 experienced other serious medical problems. Therefore, careful follow-up is required.50

Splenectomy has been highly recommended by several experienced clinicians,51 and I have had some success with this approach. However, there have also been several failures that were complicated by the effects of splenectomy in an already difficult clinical situation. Thus, I do not routinely employ splenectomy in patients with TTP. The same modalities employed in TTP have also been used in HUS, along with hemodialysis for renal failure and medical management for hypertension.

**Thrombocytopenia Induced by Infection**

Severe viral, bacterial, fungal, and parasitic infection can produce DIC and, consequently, thrombocytopenia [see 5 XIV Throm-
PA-IgG has been found to be elevated. The IgG antibody appears to correlate with the severity of the thrombocytopenia. The elevation of liver enzymes, and a low platelet count. It probably represents an extremely severe form of preeclampsia. At some point between the 23rd and 39th week of pregnancy, affected patients present with thrombocytopenia marked by a platelet count of less than 100,000/µl, microangiopathic hemolysis, abnormal liver function tests, and, occasionally, hypertension. The results of the standard coagulation tests for DIC are normal, although there may be some elevation in the level of fibrin degradation products and depression of the antithrombin III (AT-III) levels. Patients with the HELLP syndrome are often severely ill, with circulatory, respiratory, and renal failure; postpartum hemorrhage; intrahepatic hemorrhage; and seizures. The disorder is treated by terminating the pregnancy, usually by delivery, and by providing meticulous supportive care. In a large series of patients with HELLP, the nadir of thrombocytopenia occurs 1 to 2 days after delivery. Persistent thrombocytopenia with microangiopathy, or the presence of organ failure, suggests postpartum TTP/HUS, and plasma exchange therapy should be considered.

**Thrombocytopenia in Hypothermia**

Thrombocytopenia caused by the hypothermia induced during cardiac surgery can occasionally occur. Hypothermia in elderly persons apparently can also cause thrombocytopenia; platelet levels as low as 30,000/µl have been reported. The mechanisms proposed to account for the thrombocytopenia include DIC and hepatic and splenic sequestration. After the patient's body temperature has been restored to normal, the platelet count spontaneously returns to normal levels over a period of 1 to 2 weeks.

**Platelet Washout and Vascular Bed Abnormalities**

Perioperative platelet washout formerly was a frequent cause of nonimmune thrombocytopenia. Patients who have brisk bleeding during surgery and are then transfused with more than 10 U of stored whole blood experience thrombocytopenia. In effect, the patients have undergone an exchange transfusion with blood that contained nonviable platelets. The platelet count is low; the prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time (TT) are normal. Therefore, the platelet count should be monitored in patients who are receiving massive transfusions (e.g., 10 U of red blood cells or whole blood). If the level falls below 100,000/µl and the patient is undergoing surgery or another hemostatic challenge, platelets should be administered.

Platelets may also be removed by an abnormal vascular bed. In giant hemangiomas, there is sluggish blood flow through improperly endothelialized channels. These surfaces may produce low-grade DIC.

**Platelet Sequestration**

The third major mechanism of thrombocytopenia is platelet sequestration. Platelet counts of 40,000 to 80,000/µl are common in patients with marked splenomegaly. Clinically significant hemorrhage rarely occurs unless a coexistent hemorrhagic disorder is present. Management is directed toward the primary disease. Splenectomy is rarely necessary.

**Platelet Function Disorders**

The clue to the existence of a platelet function defect is the finding of clinical hemorrhage in the presence of a prolonged bleeding time and a platelet count higher than 100,000/µl. Petechiae are rare. Platelet morphology and tests of platelet function may be abnormal [see Table 2].
Platelet Membrane Disorders

Bernard-Soulier syndrome is a rare autosomal recessive disease characterized by giant platelets, a prolonged bleeding time, moderate thrombocytopenia, and risk of fatal hemorrhage. The defect, an absence of platelet GPIb-IX-V complex (the major vWF binding site of the platelet), causes impaired platelet adhesion to wound surfaces. Ristocetin-induced platelet agglutination is abnormal and not corrected by the addition of normal plasma containing vWF. Acute hemorrhage is treated by platelet transfusions.

Glanzmann thrombasthenia is a rare autosomal recessive disorder in which platelet morphology and the platelet count are normal but the bleeding time is long. Because the critically important GPIIb-IIIa complex that forms the platelet binding site for fibrinogen is absent, the platelets do not undergo aggregation after stimulation by adenosine diphosphate (ADP), thrombin, or collagen. Ristocetin-induced agglutination, however, is normal. Treatment is platelet transfusions when necessary.

Platelet Granule Disorders

Patients with the gray platelet syndrome, a rare disorder, have mucosal bleeding, ecchymoses, and petechiae. Moderate thrombocytopenia is present, and the bleeding time is prolonged. The platelets are larger than normal and appear agranular because of the absence of α-granules. Because the α-granule contents are severely reduced, platelet adhesion and platelet-supported coagulation are deficient. Platelet aggregation with collagen is normal. Bleeding episodes should be treated by infusion of normal platelets.

Another rare disorder, the dense granule deficiency syndrome, is characterized by mucosal bleeding associated with a normal platelet count, normal platelet morphology, and variable prolongation of the bleeding time. Platelet aggregation with ADP and collagen are abnormal. The decrease in the dense granular contents of ADP impairs ADP-mediated events. Hemorrhage is treated by platelet transfusion.

1-Desamino-8-D-arginine vasopressin (DDAVP or desmopressin) is an alternative therapy for patients with primary platelet disorders requiring surgery.

ACQUIRED ABNORMALITIES OF PLATELET FUNCTION

Myeloproliferative Diseases and Associated Platelet Abnormalities

Platelet function abnormalities occur in the myeloproliferative diseases: chronic myeloid leukemia, polycythemia vera, essential thrombocytosis, and acute leukemia. The platelet count in chronic myeloproliferative disorders is often very high, but the bleeding time may be prolonged, and clinical bleeding may appear as mucosal hemorrhage and hematomas. The abnormality resembles an acquired storage-pool defect. Megakaryocytes are often abnormal with separated nuclei; the peripheral blood platelets are large and may be degranulated. Management of acute hemorrhage consists of transfusion of normal platelets to bring the level of normal platelets up to 50,000/µl. Aspirin and other NSAIDs should be avoided.

Uremia and Associated Platelet Abnormalities

A prolonged bleeding time associated with clinical bleeding despite a normal platelet count has been well documented in uremia. The identity of the inhibitory substance in uremic plasma that causes this thrombocytopenia is still unclear. DDAVP (0.3 µg/kg in 50 ml of saline over a 30-minute period) is effective in controlling uremic bleeding for about 4 to 6 hours. DDAVP infusion produces an increase in plasma vWF activity and particularly in the larger multimers of vWF, which may enhance platelet adhesion.

The hematocrit should be maintained above 30% in bleeding uremic patients because the bleeding time is prolonged when the hematocrit falls below 26%. Bleeding may also be controlled by the use of conjugated estrogens. Conjugated estrogen (Premarin) given orally (50 mg/day) or intravenously (0.6 mg/kg/day) for 4 to 5 days shortens the bleeding time by approximately 50% for about 2 weeks. The advantage of conjugated estrogens over DDAVP is the longer duration of their beneficial effect on platelet function, but they have a more delayed onset of action. The two drugs can be used concomitantly.

Liver Disease and Associated Platelet Abnormalities

In addition to hypersplenism and defective procoagulant synthesis, there is evidence that low-grade DIC occurs continually in severe liver disease. Impaired clearance of fibrin degradation products may further contribute to high plasma levels of fibrinogen degradation products. These products interfere with platelet function and fibrin polymerization, and their level correlates with clinical hemorrhage in severe hepatic cirrhosis. Therapy for this condition must be directed against the primary disease.

Effects of Macroglobulinemia and Other Dysproteinemias on Platelet Function

The presence of high concentrations of viscous proteins produces complicated effects on the entire hemostatic mechanism.

### Table 2 Classification of Platelet Function Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristic</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital</strong></td>
<td>Membrane abnormalities</td>
<td>Bernard-Soulier disease (GPIb-IX-V defect, impaired adhesion); Glanzmann thrombasthenia (GPIIb-IIIa defect, impaired aggregation)</td>
</tr>
<tr>
<td></td>
<td>Granule abnormalities</td>
<td>Gray platelet syndrome (absent or impaired α-granule release, impaired aggregation); dense granule deficiency (absent or impaired dense granule release, impaired aggregation)</td>
</tr>
<tr>
<td></td>
<td>Deficiency of a plasma factor</td>
<td>von Willebrand disease (deficiency or abnormality of von Willebrand factor; impaired adhesion); afibrinogenemia (deficiency of fibrinogen; impaired aggregation)</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td>Production of abnormal platelets</td>
<td>Myeloproliferative disease (essential thrombocytopenia, chronic myelogenous leukemia, polycythemia vera, myelofibrosis, acute myelogenous leukemia); myelodyplasia</td>
</tr>
<tr>
<td></td>
<td>Dysfunction of normal platelets</td>
<td>Systemic disease (uremia, liver disease, paraproteinemias, disseminated intravascular coagulation); drugs (aspirin and other nonsteroidal anti-inflammatory drugs, ticlopidine, clopidogrel, GPIIIb-IIIa antagonists, dextran, antibiotics [penicillin, carbenicillin, moxalactam], psychotropic drugs)</td>
</tr>
</tbody>
</table>
The proteins appear to coat platelets and interfere with adhesion and perhaps with aggregation. Management is directed at the primary disease, but if hyperviscosity and bleeding are significant, prompt plasmapheresis may be required to lower the level of abnormal protein and to correct the bleeding disorder.

**Drug-Induced Platelet Disorders**

**Aspirin and other nonsteroidal anti-inflammatory drugs**

In normal persons, ingestion of 0.6 g of aspirin prolongs the template bleeding time by 2 to 3 minutes. The platelets are irreversibly affected. Thromboxane A2 (TXA2) is a potent inducer of platelet release and aggregation [see 5.XII Hemostasis and Its Regulation]. Aspirin acetylates and irreversibly inhibits cyclooxygenase-1 (COX-1) and blocks the subsequent generation of thromboxane. Some apparently normal persons display marked sensitivity to the action of aspirin, so that their bleeding times are very much prolonged and they have clinically significant bleeding, particularly during or after surgery or trauma. These patients may have a mild form of von Willebrand disease or storage pool disease, often as much as 15 minutes, in uremic patients. The combination of alcohol and aspirin is also dangerous because of aspirin's antiplatelet effect.

Uremic patients are especially sensitive to bleeding induced by aspirin. A small dose of aspirin does not prolong the bleeding time of normal persons but produces a significant prolongation, often as much as 15 minutes, in uremic patients. The combination of alcohol and aspirin is also dangerous because of aspirin's ability to prolong the bleeding time.

Aspirin-induced bleeding is diagnosed by determining the existence of an acquired platelet function defect (a platelet count above 100,000/µl, abnormal platelet aggregation test results, and no prior bleeding history) and finding evidence of aspirin ingestion. Because some 300 compounds on the market contain aspirin, a negative history should be supplemented either by determining a serum salicylate level or by detecting an abnormal collagen aggregation pattern that reverts to normal in 7 days (the typical pattern of aspirin ingestion).

If bleeding is significant, it can be managed by platelet transfusion. Because inhibition of platelet COX-1 by aspirin is irreversible, the hemostatic compromise may last for 4 to 5 days after the aspirin has been discontinued. If the patient needs analgesia, acetaminophen or codeine can be used because neither affects platelet function. If the patient requires anti-inflammatory drugs, as in the therapy of rheumatoid arthritis, cyclooxygenase-2 (COX-2) inhibitors, which do not affect platelet function, can be used.

**Alcohol**

In addition to producing thrombocytopenia by suppressing platelet production, alcohol consumption can cause platelet function defects. In vitro studies have shown that alcohol impairs platelet aggregation and TXA2 release. Platelet function returns to normal after 2 to 3 weeks of abstinence.

**Dextran**

The 40,000-molecular-weight form of dextran is readily excreted, but 70,000-molecular-weight dextran may persist in the circulation for 3 days and interfere with platelet

### Table 3  Selected Platelet-Modifying Agents

<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>Antibiotics (β-lactam)</th>
<th>Anticoagulants</th>
<th>Antiplatelet agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Cephalosporins</td>
<td>Nitrofurantoin</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Local</td>
<td>Cefazolin</td>
<td>Nitroglycerin</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td>Nitroprusside</td>
<td>Abciximab</td>
</tr>
<tr>
<td></td>
<td>Cefoxitin</td>
<td>Propranolol</td>
<td>Clofibrate</td>
</tr>
<tr>
<td></td>
<td>Cephalothin</td>
<td>Quinidine</td>
<td>Clopindylate</td>
</tr>
<tr>
<td></td>
<td>Meoxalactam</td>
<td>Verapamil</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Amoxicillin</td>
<td>Quinolines</td>
<td>Miscellaneous agents</td>
</tr>
<tr>
<td></td>
<td>Apalachin</td>
<td>Drugs that increase platelet</td>
<td>Clofibrate</td>
</tr>
<tr>
<td></td>
<td>Azlocillin</td>
<td>cAMP concentration</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>Carbenicillic</td>
<td>Dipryridamole*</td>
<td>Ketanserin</td>
</tr>
<tr>
<td></td>
<td>Methicillin</td>
<td>Iloprost</td>
<td>Radiographic contrast agents</td>
</tr>
<tr>
<td></td>
<td>Mezlocillin</td>
<td>Prostacyclin</td>
<td>Conray-60</td>
</tr>
<tr>
<td></td>
<td>Naflolilin</td>
<td>Fibrinolytic agents</td>
<td>Renografin-76</td>
</tr>
<tr>
<td></td>
<td>Penicill G</td>
<td>Foods and food additives</td>
<td>Renovist II</td>
</tr>
<tr>
<td></td>
<td>Piperacillin</td>
<td>Ajoene</td>
<td>Ticlopidine*</td>
</tr>
<tr>
<td></td>
<td>Sulbenicillin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Used as a therapeutic antithrombotic agent.
BCNU—bischloronitrosourea (carmustine) cAMP—cyclic adenosine monophosphate
surface action. Management involves support until the dextran is excreted. Transfused platelets are affected by the dextran in plasma.

Antibiotics Carbenicillin and ticarcillin can inhibit platelet aggregation and contribute to a bleeding disorder, as can massive doses of penicillin. Massive doses of penicillin impair collagen-induced and ristocetin-induced platelet aggregation. Moxalactam, a third-generation cephalosporin, also causes a platelet function disorder. The clinical situation is most important when an acquired platelet function defect develops in a pancytopenic patient being treated for septicemia. Changing the antibiotics usually corrects this problem.

Miscellaneous agents A wide variety of other agents can modify platelet function [see Table 3].

Thrombocytosis and Thrombocythemia

DIAGNOSIS

A platelet count higher than 500,000/µl is referred to as reactive thrombocytosis. In reactive thrombocytosis, tests of platelet function (including platelet aggregation studies) are generally normal, and patients do not experience increased incidence of hemorrhage or thromboembolism even when the platelet count exceeds 1 million/µl.

Elevated platelet counts (often 1 million to 3 million/µl or more) also occur in chronic myeloid leukemia, agnogenic myeloid metaplasia with myelofibrosis, polycythemia vera, and essential thrombocythemia. In the diagnosis of essential thrombocythemia, the platelet count is higher than 600,000/µl and other causes of thrombocytosis (e.g., another myeloproliferative disorder or reactive thrombocytosis) have been excluded.

In myeloproliferative disorders, tests of platelet function are frequently abnormal [see Platelet Function Disorders, above]. Some patients with myeloproliferative disorders appear to show an enhanced propensity for hemorrhage and thromboembolism. Neither platelet number nor measurements of platelet function predict the degree of thrombosis or hemorrhage.

Clinically, the hemorrhagic signs include mucosal (particularly gastrointestinal) bleeding, hematomas, and ecchymoses. There may be splenic vein thrombosis, portal or mesenteric vein thrombosis, and recurrent deep vein thrombosis with or without pulmonary embolism. Arterial thrombosis is less common.

TREATMENT

Patients with essential thrombocythemia and polycythemia vera may have debilitating erythromelalgia (burning and itching of the fingers and toes) that can progress to ischemic acrocyanosis. This symptom complex appears to be caused by occlusion and inflammation of arterioles by platelet aggregates. Aspirin or indomethacin produces relief within hours. Aspirin given at a dosage of 325 mg daily can produce lasting benefit.

Hemorrhage and thrombosis are uncommon events even with platelet counts of 1 million/µl. In a patient with essential thrombocythemia who has clinically significant hemorrhage or thrombosis, good control of the platelet count can be achieved with oral hydroxyurea (15 mg/kg/day) with adjustments in the dosage as needed to lower the platelet count. Hydroxyurea therapy requires careful monitoring of the blood count; thus far, hydroxyurea therapy does not appear to increase the risk of a second malignant disorder. Newer therapies for thrombocythemia include the use of anagrelide, a powerful platelet-lowering agent.

Vascular Purpuras

Vascular purpuras are a heterogeneous group of disorders [see Table 4] that are characterized by cutaneous hemorrhage, occasionally associated with mucosal bleeding. The leakage occurs from terminal arterioles, capillaries, and postcapillary venules. The results of tests of platelet number and function and tests of procoagulant function are normal.

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Hereditary hemorrhagic telangiectasia (HHT) is transmitted as an autosomal dominant trait and is manifested most commonly as epistaxis or gastrointestinal bleeding. Recent linkage analyses have identified at least three HHT loci, including the genes for endoglin and activinlike receptor kinase. Both proteins are expressed on vascular endothelial cells and may function as receptors for transforming growth factor-β (TGF-β). TGF-β plays a complex role in coordinating responses between endothelial cells and the extracellular matrix, and mutations in the genes for endoglin and activinlike receptor kinase lead to the development of abnormal blood vessels and arteriovenous channels.

Physical examination reveals telangiectasias on finger pads, buccal mucosa, the tongue, and lip borders. Coagulation tests are generally normal. The pulmonary arteriovenous malformations that occur in some patients may produce dyspnea, hemoptysis, low arterial oxygen tension (P_{O_2}), and secondary erythremia. The diagnosis can be confirmed by pulmonary angiography. If the shunts are large and clinically significant, they can be treated by balloon embolotherapy. Paradoxical embolus with stroke can...
occur in patients with HHT who have pulmonary arteriovenous shunts and malformations.

Management of recurrent epistaxis often involves devising methods for obtaining nasal tamponade. Gastrointestinal bleeding is managed by the use of iron preparations when possible.

**SCURVY**

Vitamin C is required for the normal metabolism of collagen, folate, and perhaps iron. The patient with scurvy suffers primarily from impaired collagen synthesis. The lack of proper collagen support for the microvasculature leads to perifollicular hemor-riage, bleeding gums, and even deep tissue hematomas. Presumably, similar collagen defects lead to the so-called corkscrew hair and hyperkeratosis associated with this disorder.8 The characteristic clinical picture in a malnourished person suggests the diagnosis. Plasma or buffy coat levels of ascorbic acid are low, and other vitamin deficiencies are usually present as well. Effective therapy consists of 1 g of ascorbic acid daily in divided doses.

**CORTICOSTEROID EXCESS**

Corticosteroid excess, whether from endogenous or exogenous causes, produces cutaneous hemorrhages, probably because of corticosteroid-induced catabolism of protein in vascular supportive tissues.

**AMYLOIDOSIS**

Amyloidosis can present with subcutaneous ecchymoses that have a predilection for the neck and upper chest. Biopsy of the site shows the amyloid, which by its infiltration may weaken the vessel walls or interfere with surface activation of platelets, procoagulants, or both. In patients with primary systemic amyloidosis, especially when accompanied by a huge amyloid spleen, the amyloid can in very rare instances adsorb enough factor X to cause profound factor X deficiency and clinical bleeding.

**LEUKOCYTOCLASTIC VASCULITIS**

The purpuric lesions in patients with leukocytoclastic vasculitis may be raised (palpable purpura). On biopsy, these lesions may show mast cell degranulation and, when stained appropriately, immune complex deposition. Presumably, the immune complexes provide the chemotactic stimulation that leads to the congregation of neutrophils. Damage to the microvasculature is caused by the complement attack complex and by the release of the contents of the neutrophil granules. This inflammatory component produces the palpable purpura.

**SENILE PURPURA**

Patients with senile purpura have cutaneous hemorrhages on the dorsum of the hand, the wrist, and the upper arms and occasionally on the calves. Serious bleeding does not occur; no treatment is required. Presumably, this condition represents an age-dependent deterioration of the vascular supportive tissue.

**DAMAGE TO THE MICROVASCULATURE DUE TO EMBOLI**

DIC and TTP can cause localized vaso-occlusions leading to microvascular damage and leakage of red blood cells. Similar damage can be caused by emboli that arise from infected heart valves. Fat embolism may complicate fractures of the long bones and pelvis. The syndrome consists of fever, confusion, and petechiae or purpura, or both, over the neck, chest, face, and axillae. Cholesterol embolism can also cause petechiae, usually over the lower extremities. It typically occurs in a patient with severe atherosclerosis who has recently undergone an invasive procedure involving the abdominal aorta or renal arteries. Biopsy of the purpura shows cholesterol crystals when an appropriate stain is used.

**Hereditary Coagulation Disorders**

The coagulation disorders appear clinically as either spontaneous hemorrhage or excessive hemorrhage after trauma or surgery. The history usually indicates whether the disorder is congenital or acquired. The hereditary disorders are characterized by appearance in early life and by the presence of a single abnormality that can account for the entire clinical picture.

**VON WILLEBRAND DISEASE**

**Pathophysiology**

Von Willebrand disease, the most common hereditary bleeding disorder, is caused by a deficient or defective plasma vWF. The gene encoding vWF is on chromosome 12. vWF has specific domains for binding clotting factor VIII, heparin, collagen, platelet GPIb, and platelet GPIIb-IIIa. These domains relate directly to the following functions of vWF: (1) its action as a carrier molecule for factor VIII, in which it protects the clotting factor from proteolysis and substantially prolongs its plasma half-life; (2) its promotion of primary platelet adhesion at high wall shear rates by linking platelets via their GPIb-IX-V receptor to subendothelial tissues at the wound site; and (3) its support of platelet aggregation by linking platelets via their GPIIb-IIIa receptors.67 The vWF circulates as multimers that range in size from 0.5 million daltons (the dimer) to 20 million daltons. Even larger noncirculating multimers are present in endothelial cells, where they are stored in the Weibel-Palade bodies. The vWF is released either into the circulation or abluminally, where it attaches to subendothelial collagen. Platelet α-granules also contain vWF, which is released when platelets are activated. The vWF multimers that are 12 million daltons or larger are probably the most effective in supporting platelet adhesion.

**Laboratory Evaluation**

The many variant forms of von Willebrand disease differ in their clinical manifestations, laboratory abnormalities, and required therapies. Therefore, specific tests are needed to identify the type of disease and its severity. Testing begins with an activated PT (aPTT) and a platelet count [see 5.XII Hemostasis and Its Regulation]. Because vWF is a carrier protein for factor VIII, the aPTT is prolonged when the vWF level is low. The platelet count is usually, but not invariably, normal. Bleeding time is generally prolonged but not sufficiently reliable to be used for diagnosis. The diagnosis depends then on necessary factor VIII and vWF levels. There are two caveats concerning the tests for von Willebrand disease: (1) laboratory testing is notoriously variable and (2) the patient’s blood group affects the vWF level—that is, patients with blood group O have lower vWF levels than those with blood group A, B, or AB, by as much as 30%.68

The vWF level is measured by immunologic methods. The result is usually reported as a percentage of normal vWF antigen (factor VIII:Ag). Because vWF circulates in physiologically important multimeric forms, it is sometimes helpful to determine the multimeric composition of the vWF in the patient’s plasma. The functional capabilities of vWF are tested by the ris-
tocetin-induced platelet aggregation test. Ristocetin is added to a patient’s platelet-rich plasma, where it causes vWF to bind to platelets via the GPIb-IX-V receptor, leading to platelet activation and aggregation. In some laboratories, formalin-fixed platelets are used and agglutination of fixed platelets after the addition of ristocetin is measured. A new automated platelet function test utilizing a platelet function analyzer (PFA-100) has been developed. Citrated whole blood is aspirated through a capillary tube under high shear onto a membrane coated with collagen in which a central aperture is made. Platelets are activated by either ADP or epinephrine. The closure time is a function of vWF antigen, factor VIII, and ristocetin cofactor. In type 2A, the largest multimers are absent. In type 2B, multimers bind excessively to platelets because of a gain-of-function mutation. In type 2M, the abnormal vWF does not bind to GPIb-IX-V; in type 2N, the binding site of vWF for factor VIII is mutated.

**Pseudo–von Willebrand disease** A platelet form of von Willebrand disease, which is termed pseudo–von Willebrand disease, has been described in which an abnormal GPIb is present on platelets, causing excessive binding of normal plasma vWF to unstimulated platelets.

**Treatment**

**Mild or moderate types 1 and 2** DDAVP is effective in the management of traumatic bleeding and before surgery in some patients with mild or moderate type 1 and type 2A von Willebrand disease. The intravenous administration of DDAVP at a dosage of 0.3 mg/kg over a 15- to 30-minute period causes the release of vWF from endothelial cell stores. The peak response usually occurs in 30 to 60 minutes and persists for up to 4 to 6 hours. Subcutaneous administration of DDAVP has also been reported to be effective. Repeated DDAVP administrations over a 24-hour period are ineffective; tachyphylaxis follows depletion of the endothelial vWF store. A nasal DDAVP spray (300 µg) can be used in the ambulatory treatment of patients with von Willebrand disease, both for the management of bleeding episodes and as preparation for minor surgery. The side effects of intravenous DDAVP are generally mild, including significant water retention and, rarely, thrombosis. Myocardial infarction has been reported. Because of the variability of response to DDAVP, a patient should be given a trial infusion of DDAVP before undergoing a planned procedure to determine whether the patient has an adequate response. EACA, 3 g four times daily orally for 3 to 7 days, is also useful for dental procedures and minor bleeding events. Aspirin must be avoided.

**Moderate and severe types 2 and 3** Patients with type 3 von Willebrand disease and with types 2A and 2B, which are more se-

### Table 5 Classification and Differentiation of von Willebrand Disease

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Type 1</th>
<th>Type 2A</th>
<th>Type 2B</th>
<th>Type 2M</th>
<th>Type 2N</th>
<th>Type 3</th>
<th>Pseudo–von Willebrand Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>~75%</td>
<td>~20%</td>
<td>~5%</td>
<td>Rare</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cause</td>
<td>Deficiency of normal vWF</td>
<td>Abnormal vWF</td>
<td>Abnormal vWF</td>
<td>Abnormal vWF</td>
<td>Abnormal vWF</td>
<td>Severe deficiency of vWF</td>
<td>Abnormal platelet membrane</td>
</tr>
<tr>
<td>Template bleeding time</td>
<td>↓‡</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>N or ‡</td>
<td>N or ‡</td>
</tr>
<tr>
<td>Factor VIII assay</td>
<td>↓</td>
<td>N or ↓</td>
<td>N or ↓</td>
<td>N or ↓</td>
<td>↓</td>
<td>↓</td>
<td>N or ↓</td>
</tr>
<tr>
<td>vWF antigen</td>
<td>↓</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>N</td>
<td>↓↓</td>
<td>Variable</td>
</tr>
<tr>
<td>Ristocetin cofactor (RIPA)</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>↓↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

N=normal ↓=decreased ↑=increased vWF=von Willebrand factor

**Clinical Variants**

The current classification scheme for variants of von Willebrand disease comprises three major groups: type 1 is a partial quantitative deficiency of vWF, type 2 is a qualitative abnormality of vWF, and type 3 is a severe and virtually total quantitative deficiency of vWF [see Table 5].

**Type 1** Type 1 von Willebrand disease is the most common form (75% of cases). It is generally an autosomal dominant trait that usually appears in the heterozygous form. Patients with classic type 1 von Willebrand disease have a lifelong history of mild to moderate bleeding, typically from mucosal surfaces. They may be unaware of a bleeding disorder until they undergo surgery or experience trauma, when bleeding may be severe. vWF antigen, factor VIII, and the ristocetin cofactor levels are all decreased. The rare homozygous or double heterozygous form (type 3 von Willebrand disease) is characterized by severe hemorrhage, a long PTT, and factor VIII levels of less than 5%.

**Type 2** Type 2 von Willebrand disease is characterized by qualitative abnormalities of vWF and a variable decrease in vWF antigen, factor VIII, and ristocetin cofactor. In type 2A, the largest multimers are absent. In type 2B, multimers bind excessively to platelets because of a gain-of-function mutation. In type 2M, the abnormal vWF does not bind to GPIb-IX-V; in type 2N, the binding site of vWF for factor VIII is mutated.

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vere than type 3, generally require replacement therapy with Hu-
mate-P, a pasteurized intermediate-purity factor VIII concentrate
that has a substantial amount of large vWF multimers, or with
cryoprecipitate infusion containing vWF, factor VIII, and fibrino-
gen. Cryoprecipitate is generally not recommended unless the
risk of viral contamination can be avoided by testing or treat-
ment. Transfusion of normal platelets can also be attempted on
the grounds that platelet vWF can be hemostatically effective.73

**Treatment during pregnancy** Treatment is generally not
needed during pregnancy in women with von Willebrand dis-
ease. The plasma vWF level rises during the second and third
trimesters but falls rapidly after delivery. Late hemorrhage may
occur 2 to 3 weeks post partum.74 DDAVP is not used before de-

delivery because of the concern that it may initiate contractions.
Patients with type 2B von Willebrand disease may have worsening
thrombocytopenia during pregnancy because of the increase of
abnormal vWF in plasma.75

**Hemophilia A**

Hemophilia A affects one in 10,000 males and is characterized
by a deficient or defective clotting factor VIII. The factor VIII gene,
which is located on chromosome X at Xq28, is among the largest
known human genes, spanning 186 kb and containing 26 exons.
It encodes a protein of about 300,000 daltons, which circulates in
plasma at very low concentrations, and is normally bound to and
protected by vWF. The primary source of factor VIII production
is unknown, but the liver must be a significant source because hem-
ophilia A can be corrected by liver transplantation.

Because the gene for factor VIII coagulant activity is carried on
the X chromosome, the disease is manifested in hemizygous
males. All of the daughters of a hemophilic male will be carri-
ers, whereas half of the sons of a mother who carries the hem-
ophilia trait will be hemophiliacs and half of her daughters will be
carriers. Families appear to be affected to varying degrees, de-
pending on the specific nature of the genetic defect.

The clinical severity of hemophilia A correlates well with the
measured levels of factor VIII coagulant activity. In general, factor
VIII levels below 1% are associated with severe hemor-
rhagic symptoms, levels between 1% and 5% with moderate
hemophilia, and levels between 5% and 25% with mild hem-
ophilia [see Table 6].

Approximately one third of hemophilia A patients represent
new mutations and have a negative family history. More than 300
abnormal factor VIII genes have been found. The abnormalities,
which include point mutations, gene insertions, and gene
deletions, result in either deficient factor VIII production or the
generation of a functionally defective factor VIII. Interestingly,
an inversion within intron 22 of the factor VIII gene, which re-
sults in a truncated and unstable factor VIII protein, is found in
approximately 45% of all severely affected hemophilia A pa-
tients (factor VIII levels below 1%).76

**Diagnosis**

Diagnosis is made on the basis of the clinical picture, family
history (positive in two thirds of cases), and the factor VIII coag-
ulant activity level. In most cases, the type of bleeding history
and a classic family history rule out von Willebrand disease
(which, unlike hemophilia A, is autosomally transmitted). Accu-
rate DNA analysis for the common intron 22 inversion is now available in DNA testing laboratories. This test provides molecu-
lar diagnosis in approximately 45% of patients with severe he-
mophilia. However, it should not be ordered in patients with
mild or moderate hemophilia.

**Treatment**

**General principles** The psychosocial aspects of hemophilia
are complex. A child is often absent from school, is prone to crip-
pling deformities, and runs a risk of drug addiction because of
severe pain. Parents are understandably deeply concerned and
sometimes troubled by guilt. Treatment should address these is-

issues as well as the specific coagulation problem.

**Factor VIII replacement** Factor VIII concentrates are effec-
tive in controlling spontaneous and traumatic hemorrhage. Cryo-
precipitate, tested or treated to prevent hepatitis viruses and HIV,
remains the mainstay of care. The potential of contamination has
stimulated efforts to develop concentrated, virus-free prepara-
tions. A number of such preparations are now available, and the
problem is to balance cost against presumed benefit. Highly pure
factor VIII preparations (e.g., Monoclate-P and Hemofil M) are
made by using monoclonal antibodies and affinity chromatogra-
phy. Factor VIII gene has been cloned, and two forms of full-
length recombinant factor VIII (Recombinate and Kogenate) have
been on the market for several years; formal studies as well as ex-
tensive clinical experience indicate that they are safe and effica-
cious.77 A second-generation, B-domain–deleted recombinant
factor VIII has also been developed, and it was found to be effec-
tive and well tolerated in an open-label, multicenter trial.78 The
new recombinant factor VIII has the advantage of considerably
higher specific activity, and the final formulation is stable without
added human serum albumin, thus further reducing the poten-
tial risk of transmission of human infectious agents.

Dental prophylaxis is critically important to reduce the need
for dental surgery. Aspirin must be avoided. Revaccination
against hepatitis B virus also should be considered.

Genetic counseling should be part of the management pro-
gram. Because of the difficult life severe hemophiliacs lead, a
woman may opt to terminate pregnancy if she is certain of her
carrier status or if she knows that her fetus is affected. There are
several strategies for detecting carriers. In women who are carri-
ers, factor VIII levels are typically about half of normal, whereas
vWF levels are normal. The ratio of factor VIII to vWF for carri-
ers is thus 0.5; however, the error rate for this test is 10% to 17%.
A more accurate genetic diagnosis for carriers can be made by a
linkage approach. This approach is based on restriction fragment

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Table 6 Correlation of Factor VIII Coagulant Activity Level with Bleeding Patterns in Hemophilia

<table>
<thead>
<tr>
<th>Plasma Factor VIII Level</th>
<th>Bleeding Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1%</td>
<td>Severe, presentation in first year of life, bleeding with circumcision, spontaneous hemarthrosis and deep-tissue bleeding</td>
</tr>
<tr>
<td>1%–5%</td>
<td>Moderate, presentation in childhood, bleeding after trauma, spontaneous hemarthrosis rare</td>
</tr>
<tr>
<td>5%–25%</td>
<td>Mild; may be present in childhood; bleeding after trauma, surgery, or dental extraction</td>
</tr>
<tr>
<td>25%–50%</td>
<td>May be undetected, may present in adulthood with bleeding after major trauma or surgery</td>
</tr>
</tbody>
</table>
Management of acute hemorrhage  Deep tissue bleeding, hemorrhage, and hematuria are the common forms of clinical bleeding in hemophilia A. Acute threats to life are posed by retroperitoneal hemorrhage; bleeding of the mouth, tongue, or neck that impairs the airway; and intracranial hemorrhage. Both ultrasonography and computed tomography can be used to identify retroperitoneal and intramuscular hematomas.

Principles of replacement therapy  A plasma procoagulant level of 100% means that there is one unit of procoagulant per milliliter of plasma. Most persons have 40 ml of plasma per kilogram of body weight. Thus, from a determination of a patient’s plasma volume and procoagulant level, the required amount of factor VIII replacement can be calculated. For example, in the case of a 60 kg boy who has an uncomplicated hemarthrosis of the knee and a baseline factor VIII of less than 1%, raising the factor VIII level to about 25% (0.25 U/ml) for 2 to 3 days should suffice. This patient has a plasma volume of 60 kg × 40 ml/kg, or 2,400 ml; he will need 0.25 U/ml × 2,400 ml, or 600 U of factor VIII, as an initial bolus. Another method of estimation is based on the following effect: the infusion of 1 U of factor VIII per kg increases factor VIII levels by 2%. Thus, dividing the desired level of factor VIII increase by 2 will give the number of U/kg required. In the example cited, 25% of factor VIII will require 12.5 U/kg, or 750 U, of factor VIII replacement.

The biologic half-life of factor VIII is approximately 12 hours; the dose can be repeated every 12 to 24 hours as long as needed to control the hemorrhage. In patients with hemorrhosis, the factor VIII level should be maintained for 2 to 3 days.

Elective surgery and dental extraction  Dental work should be performed by a dentist who is experienced in the treatment of hemophiliacs. Before dental extraction, factor VIII is administered to raise the level to approximately 50%. The fibrinolytic inhibitor EACA is started the night before surgery at a loading dose of 3 g orally and continued at 2 to 3 g three to four times daily for 7 to 10 days after the dental work has been completed. Usually, further administration of factor VIII is not required. In the example cited, 25% of factor VIII will require 12.5 U/kg, or 750 U, of factor VIII replacement.

Before elective surgery, the factor VIII level should be raised to 50% to 100% (0.5 to 1.0 U/ml) and then maintained above 50% for the next 10 to 14 days. Maintaining a higher concentration of factor VIII does not reduce the frequency of hemorrhage. DDAVP can be used to treat acute traumatic hemorrhage in patients with mild to moderate hemophilia and even to prepare such patients for minor surgery. DDAVP, which causes the release of vWF from endothelial cell stores, cannot be used repeatedly over many days, because such stores become depleted. DDAVP is infused at a dosage of 0.5 μg/kg in 50 ml of saline over 15 to 30 minutes and produces a prompt increase in factor VIII. The biologic half-life of the released factor VIII is 11 to 12 hours.

Management of an inhibitor  Inhibitors tend to occur in more severely affected patients, who tend to receive the greatest number of factor VIII concentrates. In a recent single-center study of 431 patients over 3 decades, approximately 10% of patients with severe hemophilia A had an inhibitor (about a third were children younger than 10 years). Not all inhibitors produce clinical problems. Assays for factor VIII inhibitors should be performed at regular intervals in all patients who have severe hemophilia.

Hemorrhage in a patient with an inhibitor can be life threatening. In a patient who has an inhibitor titer of less than 5 Bethesda units and who is not a vigorous antibody responder, a large amount of factor VIII concentrate should be administered in an attempt to overwhelm the antibody. Alternative therapies are porcine factor VIII (HyateC), prothrombin complex concentrates (e.g., Konyne and Proplex) to circumvent the factor VIII deficiency, and activated prothrombin complex concentrates, such as Autoplex and FEIBA.

Recombinant activated factor VII (rFVIIa) has been found to be safe and efficacious in 70% to 85% of more than 1,500 bleeding episodes in hemophilia patients with inhibitors. Recombinant factor VIIa may compete against the normal plasma unactivated factor VII for tissue factor binding and thus enhance thrombin generation at the bleeding site. In addition, high-dose rFVIIa may bind to activated platelets and activate factors IX and X on the platelet surface in the absence of tissue factor.

High-dose intravenous IgG has been used to treat nonhemophiliacs with acquired factor VIII inhibitors, but it is usually not efficacious in hemophiliacs with inhibitors.

Other hereditary hemorrhagic disorders

Factor IX Deficiency (Hemophilia B)

Factor IX deficiency (hemophilia B, or Christmas disease) is an X-linked disorder that is clinically indistinguishable from hemophilia A. The factor IX gene is on the X chromosome and produces a protein of 56 kd that, like other vitamin K–dependent factors, has a region rich in γ-carboxylated glutamic acids. Presumably, calcium ion bridges link this region to the activated platelet cell surface, where factor IXa interacts with factor VIIIa to form a membrane-associated complex that efficiently converts factor X to factor Xa (intrinsic tenase) [see 5:XI Hemostasis and Its Regulation]. A large number of insertions, rearrangements, and deletions have been detected in the factor IX gene, and the hemophilia B syndrome is very heterogeneous.

Diagnosis  Diagnosis requires a factor IX assay. The management principles are the same as those for hemophilia A. Factor IX is replaced with fresh frozen plasma or with prothrombin complex concentrates. One of the newer factor IX concentrates (Mononine) has been sterilized and displays excellent specific activity and a desirable biologic half-life of 18 to 34 hours. Recombinant factor IX is also commercially available.

Treatment  The level of factor IX needed to control hemorrhage in patients with hemophilia B is somewhat lower than the level of factor VIII required for the treatment of hemophilia A—about 0.15 to 0.20 U/ml for the former and 0.30 to 0.50 U/ml for the latter. Factor IX is a smaller molecule than factor VIII and is distributed in the albumin space. In making replacement calculations, it is assumed that administration of 1 U/kg of factor IX will increase the plasma level by 1%, or by 0.01 U/ml. Factor IX has a biphasic half-life, and plasma levels of this factor can be

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maintained by infusing the concentrate every 24 hours during an acute bleeding episode in a patient with hemophilia B. Gene cloning techniques can now detect the factor IX deficiency carrier state and permit accurate genetic counseling.

Sustained correction of a bleeding disorder in hemophilia B mice has been demonstrated by the gene therapy approach, and clinical trials of factor IX in both hemophilia A and hemophilia B have been initiated. Different gene transfer approaches are used, including ex vivo transduction and transfection, retroviral vector, and adenovirus. The collective interim results indicate that the current approaches and doses are safe and that low levels of factor VIII and factor IX expression are detected.

Factor VII Deficiency

Occasionally, preoperative screening tests reveal that a patient has a mildly prolonged PT in the absence of liver disease, poor diet, or antibiotic administration. Some of these patients can be shown to be heterozygous for factor VII deficiency states, as confirmed by family testing and by measuring the factor VII antigen level in plasma. Therapy is not required unless major surgery is contemplated, in which case factor VII can be supplied in the form of fresh frozen plasma. Clinical bleeding in these patients is quite variable, ranging from nonexistent to severe. Less often, factor VII deficiency has been reported to be associated with thrombosis.

Fibrinolytic Abnormalities

Two uncommon congenital hemorrhagic disorders have been ascribed to abnormalities of fibrinolysis. Deficiency of α2-antiplasmin, the major plasmin inhibitor, has led to uncontrolled plasmin activity with consequent hemorrhage. Enhanced fibrinolytic activity with occasional clinical bleeding has also been linked to deficiency of plasminogen activator–1 (PAI-1), the physiologic inhibitor of tissue plasminogen activator (t-PA) and urokinase. Treatment of both types of fibrinolytic abnormalities consists of the antifibrinolytic agents, tranexamic acid, or EACA, which block the binding of plasminogen and plasmin with fibrin.

Acquired Hemorrhagic Disorders

In addition to the hereditary coagulation disorders, several acquired disorders have also been identified that can lead to generalized hemorrhage.

Vitamin K Deficiency

A vitamin K–dependent carboxylase in the liver synthesizes γ-carboxyglutamic acid, which is required for the biologic function of prothrombin and factors VII, IX, and X. In the absence of vitamin K, an abnormal prothrombin that lacks γ-carboxyglutamic residues is synthesized. Specific immunoassays performed in patients with vitamin K deficiency reveal a sharp decrease in normal prothrombin and a concomitant increase in the abnormal des-γ-carboxyprothrombin. The same molecular derangement occurs with factors VII, IX, and X.

Clinical Features and Diagnosis

Deficiency of vitamin K, which decreases prothrombin and factors VII, IX, and X, occurs in severe malnutrition, intestinal malabsorption, and obstructive jaundice. In obstructive jaundice, bile salts, which are necessary for the emulsification and absorption of the fat-soluble vitamins (vitamins A, D, E, and K), cannot enter the intestine. Chronic ingestion of oral antibiotics suppresses vitamin K production by intestinal organisms. The effect is especially marked in patients who, because of their illness, are unable to consume a full, nourishing diet. Nasal bleeding and ecchymoses occur if the procoagulant levels fall below 10% to 15% of normal.

Treatment

Therapy with phytonadione (10 to 25 mg/day orally) for 2 to 3 days, or parenteral phytonadione in obstructive jaundice, usually reverses the abnormality in about 6 to 24 hours. If there is severe bleeding, fresh frozen plasma (approximately 3 U) restores procoagulant levels rapidly [see Principles of Replacement Therapy, above].

Drug-Induced Hemorrhage

Warfarin-Induced Hemorrhage

Warfarin overdose or potentiation of its action by other drugs can cause very severe bleeding. The PT is prolonged, and mucosal bleeding, gastrointestinal bleeding, or ecchymosis is the usual pattern. If hemorrhage is significant, treatment to restore procoagulant levels to 30% of normal must be started with fresh frozen plasma. If there is no urgency, oral phytonadione may be given. Sudden onset of bleeding can be identified by a serum warfarin assay, which is available at special laboratories. It should be noted that some of the long-acting vitamin K antagonists that are used as rodenticides (superwarfarins) may lead to prolonged bleeding symptoms after factitious or accidental ingestion of these compounds. The synthesis of vitamin K–dependent clotting factors can be impaired for months after the initial exposure. Repeated administration of fresh frozen plasma, supplemented by massive doses of oral vitamin K1 (100 to 150 mg/day), may be required to control bleeding symptoms.

Heparin-Induced Hemorrhage

Heparin overdose may not be obvious. It causes subcutaneous hemorrhages and deep tissue hematomas. The PTT, PT, and TT are vastly prolonged, but the reptilase time (RT) is normal. Intra-venous protamine administration at a dosage of 1 mg/100 U of administered heparin terminates the disorder. Because the half-life of protamine is shorter than that of heparin, a heparin rebound may occur, necessitating a second administration of protamine. Low-molecular-weight heparin (LMWH) preparations cause much less bleeding than standard unfractionated heparin. The ability of protamine to reverse the actions of these LMWH preparations is highly specific for each compound. For example, protamine does not completely reverse the actions of enoxaparin.

Hemorrhage Caused by Thrombolytic Therapy

Thrombolytic therapy is now used for acute myocardial infarction and for some cases of pulmonary embolism. The complications of thrombolytic therapy are essentially all hemorrhagic. In general, bleeding has been confined to relatively trivial oozing at vascular union sites, but subdural hematomas, cerebral infarction, and intracranial bleeding have also occurred. The thrombolytic agents, even those designed to be relatively fibrin specific, occasionally cause a significant systemic lytic state, with low levels of fibrinogen, factor V, and factor VIII. Furthermore, the generation of fibrinogen degradation products in turn interferes with the formation of a firm clot and with platelet function.

If thrombolytic therapy is suspected as the cause of bleeding in a particular patient, blood should be drawn quickly for an aPTT, a TT, an RT, and a fibrinogen level. If thrombolytic thera-
Disseminated intravascular coagulation (DIC) is a syndrome characterized by widespread activation of the coagulation system, leading to the consumption of clotting factors and platelets, giving rise to a self-perpetuating coagulopathy and bleeding. DIC can be initiated by a variety of conditions, including infection, malignancy, inflammation, and trauma. The consequences of DIC depend on its cause and the rapidity with which the initiating event is propagated. If the activation occurs slowly, an excess of procoagulants is produced, predisposing to thrombosis. At the same time, as long as the liver can compensate for the consumption of clotting factors and the bone marrow can compensate for the consumption of platelets, the fibrinolytic system is relatively protected. However, if the activation occurs rapidly, fibrinolysis is greatly impaired and DIC can progress to an uncontrolled hemorrhage that may be difficult to stop.

The disorder is treated with cryoprecipitate (to raise the fibrinogen level to approximately 100 mg/dl), approximately 2 U of fresh frozen plasma (which can be increased to up to 6 U as needed to replace factor V and other procoagulants), and approximately 6 U of platelet concentrates. If these measures do not stop the bleeding, the use of a specific antifibrinolytic agent such as EACA should be considered. EACA is given as a 5 g bolus I.V. over 30 to 60 minutes and then in a dosage of 1 g/hr by continuous I.V. infusion.50

**Dysproteinemias**

The abnormal proteins associated with myeloma and macroglobulinemia can interfere with platelet function and cause clinical bleeding. These proteins can cause abnormalities in the coagulation tests as well. Both IgG and IgA myeloma proteins can cause prolonged TTs by interfering with the fibrin polymerization process. Less commonly, they may interact with specific clotting factors. Management is directed at the primary disease. Generally, these paraproteins do not cause clinically significant bleeding. If bleeding occurs, plasmapheresis rapidly corrects the defects by abruptly lowering the level of abnormal protein.

**Disseminated Intravascular Coagulation**

**Pathophysiology**

Many different circumstances can cause DIC [see Table 7]. In each case, massive activation of the clotting cascade overwhelms the natural antithrombotic mechanisms, giving rise to uncontrolled thrombin generation. This condition results in thromboses in the arterial and venous beds, leading to ischemic infarction and necrosis that intensify the damage, release tissue factor, and further activate the clotting cascade. Massive coagulation depletes clotting factors and platelets, giving rise to consumption coagulopathy and bleeding. Tissue damage and the deposition of fibrin result in the release and activation of plasminogen activators and the generation of plasmin in amounts that overwhelm its inhibitor, α2-antiplasmin. Plasmin degrades fibrinogen, prothrombin, and factors V and VIII and produces fibrin-fibrinogen degradation products. These substances interfere with normal fibrin polymerization and impair platelet function by binding to the platelet surface GPIIb-IIIa fibrinogen receptor. These fibrin-fibrinogen degradation products thus function as circulating anticoagulant and antiplatelet agents, exacerbating the consumption coagulopathy, and play a significant role in the bleeding diathesis [see Figure 1].

Endotoxin released during gram-negative septicemia enhances the expression of tissue factor, thereby accelerating procoagulant activation while suppressing thrombomodulin expression. These actions downregulate the protein C/protein S system, further promoting the tendency to DIC.56 In patients with solitary or multiple hemangiomas associated with thrombocytopenia (Kasabach-Merritt syndrome), DIC is presumably initiated by prolonged contact of abnormal endothelial surface with blood in areas of vascular stasis. Platelets and fibrinogen are consumed in these hemangiomas, where fibrinolysis appears to be enhanced,97 and such consumption can lead to hemorrhage. Certain snakebites can also produce DIC; several mechanisms have been identified. For example, Russell viper venom contains a protease that directly activates factor X and can produce almost instantaneous defibrination.

**Clinical Consequences**

The consequences of DIC depend on its cause and the rapidity with which the initiating event is propagated. If the activation occurs slowly, an excess of procoagulants is produced, predisposing to thrombosis. At the same time, as long as the liver can compensate for the consumption of clotting factors and the bone

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Table 7 Causes of Disseminated Intravascular Coagulation (DIC)

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<thead>
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<th>Events that initiate DIC</th>
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<td>Septicemia</td>
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<td>Cancer procoagulants (Trousseau syndrome)</td>
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<td>Acute promyelocytic leukemia</td>
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<td>Crush injury, complicated surgery</td>
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<td>Severe intracranial hemorrhage</td>
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<td>Retained conception products, abruptio placentae, amniotic fluid embolism</td>
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<td>Eclampsia, preeclampsia</td>
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<td>Major ABO blood mismatch, hemolytic transfusion reaction</td>
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<td>Burn injuries</td>
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<td>Heatstroke</td>
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<td>Malignant hypertension</td>
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<td>Extensive pump-oxygenation (repair of aortic aneurysm)</td>
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<td>Giant hemangioma (Kasabach-Merritt syndrome)</td>
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<td>Severe vasculitis</td>
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<td>Events that complicate and propagate DIC</td>
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<td>Shock</td>
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<td>Complement pathway activation</td>
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growth or emptying the uterus when complications of pregnancy have been the inciting cause. Hemodynamic support is essential. The use of antifibrinolytic agents such as EACA or aprotinin is contraindicated. Despite its bleeding complications, DIC is a severe hypercoagulable state, and these agents block the fibrinolytic system and may exacerbate its thrombotic complications. The administration of blood products, such as platelets, fresh frozen plasma, or cryoprecipitate, may add fuel to the fire and worsen the consumption coagulopathy. However, if clinical bleeding becomes significant, it is prudent to give vigorous blood product support.

The use of heparin in acute DIC is not established. Although heparin, by activating AT-III, is effective in inhibiting thrombin and therefore should be efficacious in the treatment of DIC, its use is generally limited to situations of chronic or compensated DIC. Heparin, given subcutaneously, is effective in the treatment of venous thrombosis in patients with Trousseau syndrome. Another situation in which heparin may be considered is at the beginning of induction chemotherapy, when an explosive release of thromboplastic materials associated with the lysis of the tumor cells is anticipated. For example, judicious use of heparin can ameliorate the marked exacerbation of DIC frequently associated with the use of chemotherapy in the treatment of acute promyelocytic leukemia. In this situation, if the patient presents with significant DIC even before chemotherapy, low-dose heparin (in the range of 300 U/hr by continuous infusion) may dampen the DIC as demonstrated by lowering the D-dimer and raising the plasma fibrinogen level. However, with the advent of all-trans retinoic acid in the initial treatment of acute promyelocytic leukemia, the use of heparin is generally not required. In the case of decompen-sated DIC, in which bleeding is the major clinical manifestation, heparin may significantly exacerbate the bleeding and its use is generally not indicated. Recently, the use of high-dose AT-III infusion has been advocated in this situation, but its efficacy has not been established by randomized studies.

Management of the DIC associated with solitary or multiple hemangiomas presents particular problems. When the hemagiomas are localized, they can be excised; occasionally, they show a good response to local irradiation. Attempts to control the DIC using heparin, corticosteroids, aspirin, sulfinpyrazone, estrogens, and dipyridamole have not been successful. The key to successful management of DIC associated with certain snakebites is identification of the snake and prompt administration of appropriate antivenin.

**ACQUIRED HEMOPHILIA AND OTHER DISORDERS OF CIRCULATING INHIBITORS**

In addition to the circulating alloantibody inhibitors seen in severe hemophilias A and B, clinical hemorrhage is occasionally caused by circulating inhibitors directed against specific clotting factors that seem to appear spontaneously. Because acquired autoantibody to factor VIII, which gives rise to the clinical picture of acquired hemophilia, is the most common of these circulating inhibitors, it will be described here in some detail, but many of the principles also apply to other inhibitors.

Autoantibodies to factor VIII are usually IgG4 and frequently IgG4 and thus do not fix complement. They are usually directed against the functionally important A2 and C2 domains on factor VIII. About half of the patients with an acquired factor VIII inhibitor have no identifiable associated disorder, but many different disease states have been identified in the remainder. Such associated conditions include autoimmune disorders such as...
SLE, lymphoproliferative disorders, plasma cell malignancies, drug reactions (e.g., reaction to penicillin), the postpartum state, and skin disorders.

Diagnosis

Patients with an acquired factor VIII inhibitor commonly present with new-onset mucosal hemorrhages, hematomas, and ecchymoses, along with a negative bleeding history. Typically, this disorder occurs in an elderly patient or in a young woman during pregnancy or in the postpartum period. The laboratory hallmark of an acquired inhibitor to a clotting factor is a prolonged clotting time that is not corrected by mixing equal parts of the patient’s plasma with normal plasma. In the case of factor VIII inhibitor, the PTT is prolonged and the PT and TT are normal. The antibody binds to factor VIII with complex kinetics such that the inhibitory effect becomes apparent only after prolonged incubation. Therefore, if an acquired factor VIII inhibitor is suspected, mixing studies should be performed after 5-minute and 60-minute incubations. The diagnosis can be confirmed by demonstration of a very low factor VIII level when other clotting factor levels are normal.

Treatment

The hemorrhage may be clinically life threatening. Attempts at replacement are usually not successful, because the inhibitor inactivates the exogenous factor VIII. Occasionally, if the inhibitor has a low titer, massive factor VIII replacement can overwhelm the inhibitor. However, this treatment may trigger a significant anamnestic response in the antibody level, which complicates further management. Immunosuppressive therapy with a combination of cyclophosphamide (given either as a monthly intravenous pulse therapy or orally on a daily basis) and prednisone has been successful in most cases. The inhibitor usually becomes undetectable after three to four monthly cycles of chemotherapy. In the case of severe or life-threatening hemorrhage in which there is not sufficient time to try to reduce the level of inhibitor, porcine factor VIII can be administered because the autoantibody usually displays low cross-reactivity.

The other alternative therapy for acute bleeding is the administration of procoagulant complexes, which may bypass the inhibitor block by providing large amounts of factor X and factor VII. Other therapeutic options include plasmapheresis and high-dose intravenous IgG, although the response rate for IVIG appears to be quite low. Recombinant activated factor VII (90 µg/kg given as an I.V. bolus every 2 to 3 hours) has been used successfully in patients with this condition.

ACQUIRED VON WILLEBRAND DISEASE

Diagnosis

Acquired von Willebrand disease is being recognized. Patients, generally in their 50s and 60s and without past history or family history of bleeding, present with mucocutaneous-type bleeding, and the workup is consistent with von Willebrand disease. It frequently occurs in the setting of underlying lymphoproliferative, myeloproliferative, or cardiovascular disease and is associated with a small monoclonal gammopathy on serum protein electrophoresis. The plasma antibody to vWF is functional in a minority of cases, as demonstrated by inhibition of vWF in a functional assay by mixing studies. However, most cases involve nonneutralizing antibodies to vWF, which can be demonstrated by enzyme-linked immunologic assay. Presumably, the antibody binds to vWF and causes its rapid clearance, leading to a low plasma vWF level. Nonimmune mechanisms (e.g., adsorption of vWF onto tumor cells) have also been described. Multimeric analysis of plasma vWF typically shows a decrease in the high-molecular-weight multimers.

Treatment

DDAVP is useful in correcting the bleeding diathesis in about one third of cases. High-dose intravenous IgG (1 g/kg I.V. daily for 1 to 2 days) generally gives a good temporary response, with an increase in the vWF level and a shortening of the PTT, lasting from a few days to 2 weeks. If the patient has a defined lymphoproliferative, myeloproliferative, or autoimmune disease, the underlying disease should be treated. However, the response to immunosuppressive therapy with cyclophosphamide and prednisone is generally not as favorable as the response in the case of acquired factor VIII inhibitor.

HEMORRHAGE CAUSED BY SEVERE LIVER DISEASE

Patients with severe liver disease may suffer life-threatening hemorrhages. The most frequent are esophageal and gastrointestinal hemorrhage related to varices, gastritis, or peptic ulcer. There may also be bleeding from biopsy sites and during and after surgery. Mucosal and soft tissue bleeding may occur but generally are not the dominant bleeding problem.

The coagulopathy of severe liver disease is complex and not well delineated. Because the liver is the major site of synthesis for all the clotting factors, decreased levels of multiple clotting factors are observed, including fibrinogen, prothrombin, factor V, and factor VII; factor VIII is excepted, presumably because it is an acute-phase reactant. An increased level of abnormal fibrinogen with reduced clotting capability is also observed in patients with cirrhosis. In addition, there is reduced clearance of activated clotting factors by the liver. DIC appears to occur commonly in patients with cirrhosis (presumably because of triggering of the clotting cascade by hepatic tissue damage), but its precise role in both acute fulminant hepatitis and chronic liver disease has not been firmly established. Platelet survival is shortened, and platelet splenic sequestration is increased, but platelet function is generally maintained. There is also evidence of hyperfibrinolysis, but its contribution to the overall hemostatic defect is uncertain. The liver also synthesizes most of the natural anticoagulant proteins. AT-III, protein C, and protein S levels are decreased. The best screening tests for this disorder include the PT, PTT, platelet count, fibrinogen level, and D-dimer level. Specific assays that may guide therapy include factor V, factor VII, and AT-III. Replacement for active bleeding is accomplished by administering fresh frozen plasma, cryoprecipitates, and platelets as required. Prothrombin-complex concentrates are not recommended, because they do not replenish all the deficient clotting factors and may exacerbate the DIC. In general, although the multiple hemostatic defects contribute to the bleeding diathesis in severe liver disease, hemodynamic and anatomic factors are the primary determinants in this situation.

PRIMARY FIBRINOLYSIS

Cases of generalized primary fibrinolysis are rare. Many of the early reports of primary fibrinolysis probably represented secondary fibrinolysis associated with DIC. Postprostatectomy hematuria may constitute a true example of hemorrhage caused...
by localized fibrinolysis. The high concentration of urokinase in the urine in this condition causes plasminogen to be converted to plasmin with resulting clot lysis. If other causes of persistent postoperative hemorrhagic states can be ruled out, the condition can be treated with oral or intravenous EACA. Local instillation of EACA by urethral catheter is also effective.

BLEEDING AFTER CARDIOPULMONARY BYPASS

Patients who undergo heart surgery with cardiopulmonary bypass sometimes experience intraoperative and postoperative bleeding in the absence of significant procoagulant consumption or heparin overdose. Thrombocytopenia may occur from heparin or platelet consumption during bypass. A significant acquired platelet function disorder may develop in some patients, perhaps caused by contact between the platelets and the oxygenator apparatus, but the exact nature of the defect remains controversial. In addition to the release of platelet α-granule contents, activation of fibrinolysis may occur together with modest clotting factor depletion. The hemorrhage in such cases generally responds to platelet transfusions. The use of DDAVP in this setting has been reported to reduce postoperative blood loss; however, a meta-analysis of 17 clinical trials showed only a modest beneficial effect.

The protease inhibitor aprotinin has also been tested in patients undergoing cardiopulmonary bypass on the basis that some of the bleeding is caused by enhanced proteolysis of clotting factors and platelet membrane proteins triggered by the procedure and the oxygenator. Aprotinin appears to be superior to EACA and DDAVP in reducing blood loss and blood transfusion requirement. Aprotinin should be reserved for patients who are likely to require blood transfusion, especially those undergoing second operations and those with preexisting hemostatic defects. Preoperative testing of hemostasis appears not to be useful.

During bypass surgery, patients are sometimes exposed to topical thrombin (fibrin glue), which is used for local hemostasis control. Generally, bovine thrombin and trace amounts of other clotting factors to which patients may develop antibodies are used in these preparations. The antibodies against bovine thrombin cause a prolongation of the TT but are innocuous in themselves. However, potentially serious complications arise when the antibodies cross-react with human thrombin. Some patients develop antibodies against bovine factor V that cross-react with human factor V and may lead to clinical bleeding. Mixing studies utilizing the patient’s plasma and normal plasma will reveal the presence of the inhibitors, and the measurement of the appropriate factor levels will allow the correct diagnosis to be made. Sometimes, plasmapheresis is required to control the acute bleeding.

EVALUATION OF POSTOPERATIVE BLEEDING

Serious hemorrhage during or after surgery is a complicated clinical problem requiring rapid diagnosis and prompt intervention. The first question is whether the bleeding has a local anatomic cause (e.g., unligated vessel) or is the result of a systemic hemostatic failure. If the patient is bleeding only in the operative area, it would suggest a local anatomic cause, such as an unligated bleeding vessel. The patient’s bleeding history, especially with the results of prior surgical procedures, is extremely useful, but the available history may be inadequate or incomplete. A revealing clue to a systemic malfunction is bleeding at multiple sites, particularly areas other than the surgical wound. Bleeding around a catheter, from venipuncture sites, and from venous cutdowns is highly indicative of a hemorrhagic disorder. Rapid assessment of the total clinical setting is imperative. The following questions should be addressed:

- Does the patient have underlying renal, hepatic, or malignant disease?
- Has the surgery required pump bypass techniques or the induction of hypothermia, or has the patient been in shock or been hypothermic?
- How many units of blood and blood products have been given and over what period of time?
- Were baseline screening procoagulant tests obtained before surgery, and is the patient’s frozen plasma still available?

The differential diagnosis of postoperative hemorrhage should include a number of bleeding disorders [see Table 8]. Prompt resolution requires a panel of coagulation tests—including PTT, PT, fibrinogen assay, and D-dimer—a platelet count, and a well-stained blood smear for evaluation of platelet morphology. This battery of tests should be performed immediately. More specialized studies can be obtained if there is evidence of a specific disorder.

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