

21. Immuno-hematologic disorders

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Immuno-hematologic disorders are a broad group of entities in which hematologic diseases, usually cytopenias, are caused by immune reactions. These reactions lead to the development of hemolytic anemia, thrombocytopenia, or neutropenia, either separately or in combination. Common underlying mechanisms include immunodeficiency, systemic autoimmunity, and drug-induced reactions. Transplacental transfer of maternal alloantibodies can lead to fetal and neonatal cytopenias. Other immune reactions include antibodies to clotting factors, which result in both thrombosis and hemorrhage, and hemolytic and nonhemolytic reactions during transfusion of blood products. (J Allergy Clin Immunol 2003;111:S669-76.)

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Immuno-hematologic diseases occur in varying ways that affect different blood cell lineages. This article will include sections on red cells (autoimmune hemolytic anemia [AIHA], hemolytic disease of the fetus and newborn), platelets (ITP [immune thrombocytopenic purpura, neonatal alloimmune thrombocytopenia [AIT], post-transfusion purpura [PTP], thrombotic thrombocytopenic purpura [TTP]), and granulocytes (autoimmune and neonatal alloimmune neutropenia).

The predominant antibody-mediating immuno-hematologic disease is IgG. It opsonizes blood cells and results in their extravascular clearance by the mononuclear phagocyte system. This clearance is mediated by Fc receptors (FcR), predominantly in the spleen. Studies have demonstrated that the FcR system is composed of multiple types, including FcRI, FcRIIa and IIb, and FcRIIIa and IIIb. Clinically, this area has primarily been explored in ITP by studies with specific probes, which explored the roles of the different FcR.¹ The IgG subclasses have different abilities to bind to FcR and to fix complement and traverse the placenta from the maternal to the fetal circulation. These differences have not been well studied in clinical settings.

Complement may play a critical role in opsonophagocytosis, either alone or in combination with IgG.² Com-

Abbreviations used

AIHA:	Autoimmune hemolytic anemia
AIN:	Autoimmune neutropenia
AIT:	Alloimmune thrombocytopenia
APA:	Antiphospholipid antibody
CAS:	Cold agglutinin syndrome
CBC:	Complete blood count
CVI:	Common variable immunodeficiency
DAF:	Decay accelerating factor
DAT:	Direct antiglobulin test
DIC:	Disseminated intravascular coagulation
FcR:	Fc receptor
HDN:	Hemolytic disease of the fetus and newborn
HIT:	Heparin induced thrombocytopenia
HIT-T:	Heparin induced thrombocytopenia with thrombosis
HPA:	Human platelet antigen
HTR:	Hemolytic transfusion reactions
IAT:	Indirect antiglobulin test
ITP:	Immune thrombocytopenic purpura
IVIG:	Intravenous immunoglobulin
LDH:	Lactate dehydrogenase
MIRL:	Membrane inhibitor of reactive lysis
NAIN:	Neonatal alloimmune neutropenia
NHFTR:	Nonhemolytic febrile transfusion reaction
PCH:	Paroxysmal cold hemoglobinuria
PNH:	Paroxysmal nocturnal hemoglobinuria
PTP:	Posttransfusion purpura
RBC:	Red blood cell
TTP:	Thrombotic thrombocytopenic purpura
TRALI:	Transfusion-related acute lung injury
WBC:	White blood cell

plement activation by IgG requires a dimer of IgG molecules to bind to the cell surface approximately 300 angstroms apart. This will lead to formation of the C1-C2-C4 complex and initiate the classic pathway. If there is sufficient deposition of complement on the cell surface, there will be assembly of the C5-9 attack complex, creating holes in the cell membrane with intravascular lysis and destruction of the cell. If IgG and complement (ie, C3b) together opsonize the cell, then the efficiency of clearance of the doubly opsonized cell is increased by complement receptors. IgM is thought to bind to the cell in question in the "periphery," that is, near the skin, which is cooler than in the body core. Single IgM molecules fix complement, because it is pentavalent. The IgM then dissociates from the cell as the cell re-enters the core of the body and warms up, leaving the complement attached to the cell.

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TABLE I. Classification of immune hemolytic anemias³

Warm AIHA
Idiopathic or primary
Secondary (lymphoproliferative disorders, autoimmune disorders [ie, SLE], immunodeficiency [ie, HIV or CVI])
Cold immune hemolytic anemia
CAS
Idiopathic
Secondary
Acute, transient (infections)
Chronic (lymphoproliferative disorders)
PCH
Idiopathic
Secondary
Acute, transient (infections other than syphilis)
Chronic (syphilis)
Mixed-type AIHA
Idiopathic
Secondary (lymphoproliferative disorders, autoimmune disorders)
Drug-induced immune hemolytic anemia
PNH

AIHA, Autoimmune hemolytic anemia; SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; CVI, common variable immunodeficiency; CAS, cold agglutinin syndrome; PCH, paroxysmal cold hemoglobinuria; PNH, paroxysmal nocturnal hemoglobinuria.

RED CELL DISORDERS

AIHA is the prototypic immunohematologic entity for the serologist, because testing is by far the most useful of any of the cytopenias (Table I).³ Estimates of incidence are unreliable; they range from 1:100,000 to 300,000 of the general population. Clinical information is further limited, because many of the cases of AIHA are secondary to other diseases, such as chronic lymphocytic leukemia.

The diagnosis of AIHA should be considered when there is both anemia and evidence of hemolysis. Two criteria must be met to diagnose AIHA: (1) serologic evidence of red cell autoantibodies and (2) laboratory and/or clinical evidence of hemolysis. The former is provided by a positive direct antiglobulin test (DAT, direct Coombs test) or indirect antiglobulin test (IAT), the latter by anemia combined with reticulocytosis, history of jaundice or hyperbilirubinemia, decreased haptoglobin, or elevated lactic dehydrogenase (LDH).

Measurement of the DAT and IAT is a standard, reproducible test widely available at all times in academic and community hospitals. A DAT alone is not enough to characterize a case as AIHA, because a positive DAT may not cause hemolysis. In one series, as many as 5% to 10% of hospitalized adults had a positive DAT. "Cold active" antibodies are detected frequently at 4°C and 22°C but will not cause hemolysis, that is, cold agglutinin syndrome (CAS), unless they retain anti-red cell activity at 37°C. A positive DAT may be dissected by the use of "monospecific" antisera to identify IgG or complement, C3b, on the red cell surface. For unusual cases in which the DAT and IAT are negative but immune hemolysis is strongly suspected, additional reagents, such as polybrene

or anti-IgA, can be used and the aid of a reference laboratory sought. Warm antibodies are polyclonal IgG autoantibodies reactive at 37°C; elution of the antibody demonstrates a pan-agglutinin. Cold antibodies are either polyclonal or monoclonal and are almost always IgM. Mixed AIHA has a DAT positive for both IgG and C3; there may be a concomitant cold-active (IgM) anti-I antibody. Paroxysmal cold hemoglobinuria (PCH) has a biphasic IgG auto anti-red blood cell (RBC) antibody (Donath-Landsteiner antibody) that fixes complement at low temperatures but dissociates at higher temperatures. Paroxysmal nocturnal hemoglobinuria (PNH) cells have an inordinate sensitivity to complement-mediated lysis.

The hemoglobin and hematocrit are variable but are typically low. They may be near normal in compensated hemolysis, when the reticulocyte count is high. The platelet and white blood cell (WBC) counts are normal, unless hemolysis is associated with lymphoproliferative diseases (WBC) or Evans syndrome (platelets). Leukopenia may be seen early in PCH, and thrombocytopenia is very common in PNH. Reticulocytosis and an increased mean corpuscular volume (MCV) are common. Reticulocytopenia may be seen if anemia is of such recent onset that compensatory reticulocytosis has not yet had time to develop (first week), if there are very high levels of antibody, or if the antibody is directed against an antigen with increased expression on RBC progenitors, such as anti-Kell. The peripheral smear shows increased spherocytes, polychromasia, and macrocytes in warm AIHA. In CAS, red cell agglutination is common; the smear may be normal in both types of AIHA.

Other common features include hyperbilirubinemia, high LDH and low haptoglobin levels, and hemoglobinuria. Bone marrow examination often shows erythroid hyperplasia. Increased plasma cells in the marrow are consistent with autoimmune disease. Other findings may suggest a lymphoproliferative disorder and secondary AIHA. PCH may be associated with methemoglobinuria.

AIHA in children is almost always warm disease, occurring most commonly in those younger than age 4.³ Affected adults tend to be elderly and female and to have secondary causes.

The clinical presentation is highly variable. Patients with fulminant hemolysis present with the sudden onset of pallor, jaundice, edema, dark urine and, unlike ITP or autoimmune neutropenia (AIN), may have associated hepatosplenomegaly and lymphadenopathy. This is seen in children commonly and often associated with a viral infection; the jaundice may subside in 1 to 3 days. In this setting, other acute onset anemias need to be considered, such as glucose-6-phosphate deficiency (G6PD) deficiency and occult blood loss, but a positive DAT confirms the diagnosis of AIHA. There may also be an insidious onset with waxing and waning. Typical symptoms include weakness, dizziness, fatigue, pallor, and dyspnea on exertion. Other less specific symptoms include fever, bleeding, coughing, abdominal pain, and weight loss. Up to 50% of cases of AIHA in childhood and a higher percentage among adults will be chronic and persistent.

CAS is responsible for 16% to 32% of AIHA.^{4,5} Primary/idiopathic CAS is seen primarily in elderly females, with a peak incidence of 70 years of age. Infections may cause a transient acute hemolytic syndrome that is seen in adolescents and young adults. Symptoms appear 2 to 3 weeks after the infection starts (corresponding to a peaking cold agglutinin titer) and then resolve spontaneously after 2 to 3 more weeks. Agents include mycoplasma pneumonia, infectious mononucleosis, cytomegalovirus, adenovirus, influenza virus, *Escherichia coli*, varicella zoster virus, HIV, and listeria. CAS associated with lymphoproliferative disorders and with syphilis is often chronic. Hemolysis in CAS of any cause is precipitated or worsened by the cold. Therefore, external temperature and clothing, including gloves, are very important.

PCH is a very uncommon condition and is responsible for approximately 2% of cases of immune hemolytic anemia in childhood.⁶ Acute, transient PCH in children is often the result of infections and is characterized by signs of acute hemolysis, including black or red urine. Chronic PCH, often associated with late-occurring or congenital syphilis, is now very rare. Special testing may be required to detect the antibody to the red cell.

Drug-induced hemolysis is not rare. Direct tests comprising the mixing of drug and patient serum may, however, not be informative because the true reaction may involve a drug metabolite, not the actual medication, creating a falsely negative testing.⁷ Conversely, certain medications may cause a positive DAT but not cause hemolysis, that is, methyldopa or certain cephalosporins.

PNH is an acquired sensitivity to complement-mediated cell lysis as a result of the loss of the phosphatidyl-inositol-glycerol (PIG) linkage of a number of cell surface proteins to blood cells. Two of these missing glycoproteins are CD59 and CD55, (membrane inhibitor of reactive lysis [MIRL] and decay accelerating factor [DAF]), important inhibitors of complement-mediated lysis. PNH is characterized clinically by thrombosis, especially of the hepatic vein, as a result of platelet activation by complement. Presentation is often connected to development of or recovery from aplastic anemia. Diagnosis is based on the sugar water test, the Ham test, or by flow cytometry looking for CD59.

Many cases of both warm and cold AIHA are caused by diseases such as chronic lymphocytic leukemia, lymphoma, and HIV. Therefore a work-up for an underlying etiology of a newly presenting AIHA is important. Management options (Table II)⁸ include the use of anti-CD20 monoclonal antibody,⁹ intravenous immunoglobulin (IVIG),¹⁰ and plasmapheresis.¹¹

PCH is usually self-limited, and symptomatic treatment with warmth and avoiding exposure to the cold are often sufficient. If needed, transfusion of P antigen-negative RBCs with use of a blood-warming device is feasible. Plasmapheresis may be useful in life-threatening cases.¹¹ Steroids are not very effective.

Hemolytic disease of the fetus and newborn (HDN) can be divided into Rh disease, ABO incompatibility, and

TABLE II. Management of warm and cold hemolytic anemia

Warm hemolytic anemia
Corticosteroids
Splenectomy
Intravenous gamma globulin
Erythropoietin
Mycophenolate mofetil
Cyclophosphamide
Azathioprine
Vincristine
Danazol
Anti-CD-20
Cold agglutinin syndrome
Cold avoidance
Plasmapheresis
Azathioprine
Chlorambucil
Cyclophosphamide

other antigen incompatibilities. Rhesus antibody is still the most common, accounting for more than 50% of all cases of HDN with anti-D antibody accounting for almost 25% of all antibodies detected. Kell antibodies were the next most frequent (29%), followed by Duffy (7%), MNS (6%), Kidd, Lutheran, and anti-U.¹²

The relative frequency of incompatibility of "D" has changed over time. The institution of prophylaxis with anti-D is one of the great success stories of medicine. The incidence of RhD alloimmunization has decreased from 43.3 per 1000 samples in 1967 to 2.6 per 1000 in 1996.¹³

Pregnant women undergo antibody screening at the first prenatal visit. RhD⁻ women without evidence of alloimmunization receive 120 to 300 µg of rhesus immune globulin at 28 weeks gestation. This reduces antenatal alloimmunization from 2% to 0.1%. Additional indications for anti-D include spontaneous abortions, elective abortion, ectopic pregnancy, genetic amniocentesis, chorionic villous sampling, fetal blood sampling, or any other procedure or event that might result in fetomaternal hemorrhage. A second dose is given within 72 hours of delivery if the infant is RhD⁺.¹⁴

A further refinement is to perform a Kleihauer-Betke test on all deliveries of Rh⁻ women to detect the rare cases of substantial fetal maternal hemorrhage requiring more than the standard 300 µg of anti-D prophylaxis to prevent maternal sensitization. Once an Rh⁻ woman is sensitized, anti-D is no longer effective. In such cases, intensive maternal plasmapheresis combined with immunosuppression has been attempted to reduce the Rh antibody levels, but standard therapy is to assess the fetal risk and provide repeated in utero RBC transfusions as needed.

In 1950 to 1960, when 1% or more of all deliveries were affected, 50% of the affected patients would be mildly to moderately anemic and jaundiced after birth, 25% would be significantly anemic and jaundiced after birth, and 25% would be substantially affected in utero. The latter cases would result in fetal demise or premature

delivery. Premature infants were particularly vulnerable to developing kernicterus and brain damage as a result of the high bilirubin levels. The transfusion of red cells to the affected fetus every 3 weeks has become the standard of care for the now uncommon, severely affected fetus.¹⁵ Perinatal survival of more than 90% has been reported in a number of series with hydrops fetalis at presentation, reducing the chance for a viable neonate. Each subsequent pregnancy in a family with an Rh⁺ fetus will be at least as severely affected as the index case.

ABO antigen group is a common cause of hemolysis in the newborn. One in 10 pregnancies has the "set up," and virtually everyone has anti-A and anti-B antibodies, even without any exposure to blood products or previous pregnancies. No preventive measures are available. Mother is group O, and baby is A or B or AB. Both the direct and indirect Coombs tests are often positive, but the direct is only mildly positive in cord blood.

IMMUNE NEUTROPENIA

Primary AIN is seen predominantly in infants and toddlers between the ages of 6 and 24 months. Two hundred forty cases were reported in one series,¹⁶ and there are other series reporting more than 50 cases. The degree of neutropenia is typically severe, but AIN is virtually always a benign disorder. More than 80% of patients suffer only from recurrent, minor infections, such as skin abscesses, otitis media, and upper respiratory infections; at least 8% are diagnosed incidentally on a complete blood count (CBC) obtained for other reasons. Only 12% have pneumonia; sepsis and especially meningitis are extremely rare in AIN. To an even greater extent than with ITP in childhood, the long-term outcome of AIN is good. Spontaneous remission is seen in more than 90% of patients, usually within 7 to 24 months from diagnosis, that is, by the age of 2 to 4 years.

As with ITP and AIHA, AIN is caused by increased peripheral destruction of neutrophils by autoantibodies. CBC with differential usually reveals a selective, profound neutropenia with an otherwise normal CBC, often including a normal WBC. The platelet and red cell counts are normal, although monocytosis and/or lymphocytosis may be seen. What distinguishes AIN is that the percentage of neutrophils is virtually always less than 10%, and usually less than 5%. Testing in AIN is complicated, because relatively few laboratories are capable of the appropriate screening. One series recommended repeating neutrophil antibody testing, as many as three times, to detect antibodies in clinically suspected cases if the initial test results were negative.¹⁶ However, the diagnosis of AIN, as indicated above, remains clinically based. Laboratory testing, in addition to neutrophil antibodies, includes granulocyte colony stimulating factor levels, bone marrow examination, and even response to IVIG.¹⁷

Treatment beyond antibiotics is not frequently required. Symptomatic treatment for acute infections with antibiotics is sufficient in more than 70% of cases. One option is to perform a bone marrow examination and then

proceed with granulocyte colony stimulating factor, adjusting the dose as needed to maintain the absolute neutrophil count (ANC) more than 1000/ μ l, for whatever period is required (usually not indefinitely, as infrequent patients require chronic support of their neutrophil count). Another option is to infuse 1 to 2 g/kg of IVIG over 1 to 2 days (or 1 g/kg with 30 mg/kg of IV methylprednisolone) without the bone marrow examination. If the neutrophil count rises substantially to more than 1000/ μ l, the response confirms the diagnosis of AIN and provides therapeutic benefit.

Neonatal alloimmune neutropenia (NAIN) is the neutrophil equivalent of HDN of red cells or AIT of platelets. Fetal neutrophil antigens, foreign to the mother and inherited from the father, provoke the formation of maternal IgG antibodies that cross the placenta and destroy the fetal neutrophils¹⁸; the mother's peripheral neutrophil count is normal. Estimates of frequency vary widely from 0.2% to 2%.^{19,20} NAIN is often associated with antibody to the neutrophil-specific antigens NA1 and NB1 and, less commonly, with NA2, NB2, and other antigens.²¹ It may also occur as a result of maternal FcRIIIb deficiency in neutrophils (FcRIII null), resulting in an anti-FcRIIIb antibody. Like AIT, but unlike HDN, firstborns are commonly affected. IVIG has been used to treat NAIN.²²

THROMBOCYTOPENIA

ITP is an autoimmune, antibody-mediated disease, similar to AIHA and AIN. Unlike these entities and unlike AIT, serologic testing is not of diagnostic or prognostic value and has no role in routine evaluation or management.²³ Diagnosis is clinical, based on isolated, usually severe thrombocytopenia combined with an otherwise normal CBC, including smear and a physical examination that is normal except for signs of bleeding. Patients typically present with petechiae and ecchymoses; more serious bleeding includes epistaxis, hematochezia, and hematuria with the most feared complication, intracranial hemorrhage. The above definition of ITP is very useful for pediatric outpatients who are otherwise completely well.²⁴ It is less applicable for complicated adults who are inpatients and who are on several medications for a number of medical conditions. Other diagnoses to consider include drug-induced PTP and TTP (see below), inherited thrombocytopenias, disseminated intravascular coagulation (DIC), and myelodysplasia.

There is a significant tendency in children for ITP to spontaneously improve within 1 year from diagnosis in approximately 80% of patients. Spontaneous improvement also appears to occur in adults, albeit more slowly and in a lesser percentage of patients. Therefore, treatments such as IVIG 0.5 to 1 g/kg, IV anti-D 50 to 75 μ g/kg, and prednisone 1 to 2 mg/kg, are administered as needed to transiently support the platelet count until spontaneous improvement is seen.²⁵ If/when the platelet count stabilizes at more than 20,000 to 30,000/ μ L, no further treatment is generally required. If this does not happen, the only treat-

ment proven to be curative is splenectomy, now performed laparoscopically in nearly all cases.²⁶ In adult patients, there is debate as to whether to perform splenectomy 1 to 3 months from diagnosis, if there is not a lasting response to steroids, or to wait for 1 year before deciding whether to proceed to surgery. In children, the consensus is to wait at least 1 year from diagnosis and until the child is older than age 5. In adults, the short-term cure rate is 85% and the 5 to 10 year cure rate is 60% to 70%; in children, the cure rate is thought to be higher, although long-term follow-up data are lacking. Treatment of patients who have undergone and failed to respond to splenectomy is controversial and utterly lacking controlled data.²⁷ The most promising, novel treatment is anti-CD20 monoclonal antibody, which transiently depletes normal B cells and has led to apparent cures in as many as 30% of refractory patients; further studies are required. Other treatments such as, IV cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporin, and danazol have been explored in pilot series. No treatment, other than anti-CD20 monoclonal antibody and, possibly, repeated IV cyclophosphamide has been demonstrated to have either a 50% or better response rate or a significant cure rate, that is, the platelets remain elevated even when the medication is discontinued. Experimental treatments with very preliminary data include autologous bone marrow transplantation and thrombopoietin-thrombopoietin agonists.

HIV-thrombocytopenic purpura has been a very common complication of HIV infection and is very similar to classic ITP. Highly active antiretroviral therapy of HIV has greatly reduced the incidence of HIV-thrombocytopenic purpura. By reducing the viral load, the thrombocytopenia is either prevented or treated in the majority of cases. Other cases respond well to IV anti-D (if Rh+) or splenectomy. Steroids may predispose to opportunistic infections.

A number of drugs can trigger an immune response that causes shortened platelet survival and thrombocytopenia. This can be difficult to distinguish from ITP.²⁸

The possible pathophysiologic mechanisms of drug-induced thrombocytopenia include drug adsorption onto the platelet surface, neoantigen formation, that is, a ligand-induced antigen, and autoimmune drug reaction.²⁹ Recent studies of quinidine/quinine-dependent antibodies have shown that the IgG Fab portion binds to drug-dependent antigen localized to glycoprotein IIb/IIIa and Ib/IX.³⁰ In heparin-induced thrombocytopenia (HIT), the Fab portion of the antibody binds to a complex, formed usually between heparin and circulating platelet factor 4.³¹ The Fc portion then binds to the platelet FcRIIa, triggering platelet activation and consumption. This may result in heparin-induced thrombocytopenia/thrombosis (HIT-T). HIT is relatively common and has been reported in up to 5% of patients treated with unfractionated (standard) heparin for periods of 5 to 14 days.³² Venous and arterial thrombosis was reported in 10% to 30% of patients.³³ Low-molecular-weight heparins have a lower incidence of HIT, but they have serologic cross-reactivity in approximately 20% of cases. Therefore, direct thrombin inhibitors, that is, a form

of hirudin, are the treatment of choice. HIT-T is by far the most serious, drug-induced thrombocytopenia, both because of its relatively high frequency and because the thrombosis may threaten an organ, limb, or life.

Other commonly offending drugs include sulfonamides, sulfonylureas, penicillin, cephalosporins, indinavir, atorvastatin, pentoxifylline, mesalamine, ticlopidine, gold, and acetazolamide.³⁴

PTP is a rare condition that usually develops 7 to 10 days after a red cell transfusion. It is seen especially in older women with a history of childbirth and manifests with the onset of bleeding signs and symptoms concomitant with severe thrombocytopenia. Almost all cases occur in PI^{A1-} women and are associated with the formation of PI^{A1} (human platelet antigen [HPA]-1a) antibodies. These antibodies destroy the transfused PI^{A1+} cells and the PI^{A1-} recipient's cells by an antibody-dependent mechanism that is poorly understood. There are reports of fatal bleeding in this self-limited disorder for which high-dose IVIG is the therapy of choice.³⁵

AIT is well studied and has a pathophysiology that mimics HDN and NAIN.³⁶ AIT is based on parental incompatibility of PI^{A1} (HPA1a) or one of at least 15 other "platelet-specific" antigens. The same antigens are involved as in PTP; these antigens are also infrequently involved in platelet transfusion refractoriness.

TTP has been shown in its acquired form to be an autoantibody-mediated disease, with the antibody target being the von Willebrand cleaving protease, ADAMTS13.³⁷ The diagnosis is suspected in a patient with thrombocytopenia and hemolytic anemia. The other parts of the pentad include neurologic changes, renal findings (especially hematuria), and fever; an LDH higher than 1000 is typical. Deficiency of the metalloproteinase results in platelet thrombi with microangiopathic hemolysis. Testing for levels of the protease is still restricted to research laboratories. Treatment involves plasmapheresis with plasma replacement; immunosuppression is being actively explored.

TRANSFUSION REACTIONS

Transfusion reactions may be divided into hemolytic and nonhemolytic. In turn, hemolytic transfusion reactions (HTR) can be divided into acute and delayed reactions.

Acute HTR are most commonly caused by transfusion of ABO-incompatible blood. The incidence is estimated at 1 in 33,000, with death reported in 1 in 600,000 transfusions—approximately 4% to 5%.³⁸ Conversely, in 50% of cases, the mismatched transfusion is completely asymptomatic. Reactions are the result of pre-existing isohemagglutinins, which form IgM antibody-RBC complexes that induce complement-mediated intravascular lysis and provoke DIC. A vasomotor response is also induced, leading to vasodilatation, increased capillary permeability, and hypotension. The systemic effects of Acute HTR are mediated by a number of proinflammatory cytokines, including IL-1, TNF- α and IL-6.³⁹ These substances mediate a shocklike state with fever, rigors, and capillary leakage. Laboratory findings include hemo-

globinemia, hemoglobinuria, and a positive DAT test. Complement is activated, DIC develops, and renal failure may ensue. Management includes stopping the transfusion immediately, restoring and maintaining blood pressure and urine output, and treating DIC, if present.

Delayed HTR is most commonly the result of an anamnestic response from exposure to minor RBC antigens, typically those belonging to the Rh, Kidd, Kell, or Duffy blood groups. These hemolytic reactions are often seen 5 to 10 days after transfusion. Clinical features include low-grade fever, jaundice, and falling hemoglobin. Laboratory features include extravascular hemolysis caused by IgG-sensitized RBC lysis, elevated indirect bilirubin and LDH, and a positive DAT test, until all of the RBCs have all been hemolyzed. The course is self-limited and the hemolysis is not fulminant, so the complications seen with an AHTR are very infrequent. Supportive care may include a "replacement" transfusion. Careful antibody identification to provide antigen-negative RBCs for all subsequent transfusions, including the replacement one if needed, is critical.

Nonhemolytic febrile transfusion reactions (NHFTR) are commonly seen after platelet transfusions, with an incidence of approximately 0.5%, rising to more than 10% in multitransfused patients.⁴⁰ It is the most common cause of fever caused by blood transfusions, especially in women due to pregnancy-related allosensitization. Clinical features include a rise in temperature of 1°C or more during or within several hours of transfusion, chills, rigors, flushing, headache, nausea, anxiety, dyspnea, or hypotension. Differential diagnosis includes a hemolytic transfusion reaction (with fever), microbial contamination causing sepsis, or coincident fever (in an often neutropenic host).

The most prevalent pathophysiology is a direct role for cytokines released from leukocytes during product storage especially tumor necrosis factor α and IL-1 β .⁴¹ The other proposed less common mechanism involves alloimmunization and formation of leukocyte antibodies that subsequently react with donor neutrophil or lymphocyte (HLA) antigens on transfused, contaminating WBC (or platelets). The least frequent but most serious form (see below) is microbial contamination.

Management is largely preventative. Removal of the contaminating leukocytes before storage limits cytokine accumulation and minimizes the leukocyte content of the platelets. The latter but not the former can be achieved by leuko-reduction (filtration) at the time of transfusion.⁴² Premedication with acetaminophen and diphenhydramine is also useful.

Microbial contamination of blood products primarily occurs with platelet transfusions. The exact incidence is unknown, although it appears to occur in at least 1:1000 platelet transfusions.

Allergic reactions are often caused by hypersensitivity to plasma proteins. The incidence is 1% to 3% and more commonly seen in recipients of plasma (including platelet transfusions).⁴³ The clinical features may include urticaria, pruritus, laryngeal edema, bronchospasm, and hypotension. If the reaction is severe, treatment is to stop

the transfusion and administer diphenhydramine, steroids, or both parenterally. Future blood products have to be washed to remove plasma before transfusion. Milder reactions can be stopped temporarily, antihistamines administered, and then the transfusion can usually be resumed. Recurrent urticaria is infrequent and can be handled by pretreatment with oral or parenteral antihistamines. Anaphylactic reactions are rare complications, reported in 1 per 20,000 to 50,000 transfusions.⁴⁴ They are seen typically in IgA-deficient patients with anti-IgA antibodies, but often a definite cause is not found. The clinical features may include acute generalized urticaria, pruritus, light-headedness, hypotension, shock, and cardiac arrest. Treatment is to stop the transfusion immediately. Epinephrine, IV fluids, vasopressors, antihistamines, or steroids may be required. In the future, for patients with known IgA deficiency, it is appropriate to use twice-washed or frozen-thawed-washed-deglycerolized RBCs and plasma components or to use blood products from known IgA-deficient donors.

Transfusion-related acute lung injury (TRALI) is a life-threatening complication of transfusion with plasma-containing blood products, which is reported in 1 in 5000 transfusion units.⁴⁵ TRALI and bacterial contamination of platelets are by far the least recognized transfusion reactions. Food and Drug Administration data suggest that TRALI is the third most common cause of transfusion-associated mortality (after mismatched RBC transfusion and anaphylaxis and before microbial contamination), comprising approximately 9% of reported transfusion related mortality. Clinical features are characterized by severe respiratory distress within 1 to 4 hours of transfusion. This is associated with cough, fever, cyanosis, and low blood pressures. Hypotension is often not responsive to fluids. Pulmonary edema and hypoxemia are seen. Patients with TRALI have normal central venous pressures and normal or low pulmonary wedge pressures, which help to distinguish them from cryptogenic pulmonary emboli.⁴⁶ Radiographic findings include basilar and perihilar infiltrates; severe cases appear as a "white out." Proposed mechanisms include complement-fixing donor leukocyte antibodies directed at recipient neutrophil antigens or HLA determinants. These can be tested for in specialized laboratories. If confirmed or strongly suspected, the donor is excluded from further donation. C5a, complement anaphylatoxin, is released, which contributes to pulmonary leukosequestration. Activation of neutrophils occurs with changes in vascular permeability and interstitial edema. Treatment includes intensive respiratory support as needed, including mechanical ventilation and steroid therapy rather than diuretics or adrenaline. If not fatal, TRALI often resolves in 24 to 48 hours.

Transfusion-associated graft-versus-host disease is a rare, highly lethal complication of transfusions after bone marrow transplantation. Donor T lymphocytes proliferate and react against host histoincompatible tissues. Target organs include skin, liver, gut, and bone marrow. The high fatality rate in transfusion-associated graft-versus-

host disease is often the result of marrow aplasia resulting in sepsis. This is seen in either significantly immunodeficient patients or immune-competent patients who are HLA heterozygous and receive blood products from a donor who is homozygous for one of the recipient's haplotypes.⁴⁷ Treatments are toxic and not very effective; prevention is the best approach. Gamma irradiation of all cellular blood products at a dose of 25 Gy is the recommended method of prevention. Leuko-reduction is insufficient by approved methodologies. Patients whose blood products require irradiation include those with hematopoietic malignancies, marrow and solid organ transplant recipients, congenital and acquired immunodeficiency, premature infants, intrauterine transfusions, and directed donations from blood relatives.⁴⁸ HIV infection in the recipient is not an indication.

ANTIBODIES AGAINST CLOTTING FACTORS

Antibodies against factor VIII are found in 15% to 25% of severe, factor VIII-deficient hemophilia patients; these are allo-antibodies.⁴⁹ Autoantibodies to factor VIII can also develop, especially in pregnant women and the elderly. Autoantibody patients traditionally have been treated with immunosuppression using steroids, cyclophosphamide, or both; anecdotal data exist with anti-CD20 monoclonal antibody.

Antibodies to other clotting factors are rare and even rarer in patients not congenitally deficient in clotting factor. Medications recognized as instigating antibody to factors in the past, that is, streptomycin for antibody to factor XIII, are not still widely used.

The lupus anticoagulant-antiphospholipid antibody (APA) is a relatively common coagulation abnormality, the significance of which is difficult to assess from testing only. The antibody prolongs clotting tests, such as the partial thromboplastin time, by binding to anionic phospholipids. In certain cases, this may predispose to thrombosis and less commonly, in others, it may predispose to hemorrhage. Other clinical features are also heterogeneous. APA syndrome, either primary or secondary to autoimmune diseases such as systemic lupus erythematosus, is associated with a high risk of thrombosis (30%-40%) and may have fulminant multiorgan involvement.⁵⁰ Alternatively, antibody may precipitate spontaneous abortions because of placental vascular thrombosis and infarctions, at any time during gestation but especially in the second trimester.⁵¹ APA formation may be associated with drugs such as phenothiazine, hydralazine, with infections such as HIV, and with upper respiratory tract infections especially in children. In these cases, it is not usually associated with thrombosis.⁵²

The lupus anticoagulant is suspected when there is unexplained prolongation of the activated partial thromboplastin time. Preliminary confirmation is if the partial thromboplastin time fails to correct to normal upon addition of normal plasma. More specific testing demonstrates an inhibitor to a phospholipid-dependent clotting reaction, not to a specific clotting factor. These tests include the tis-

sue thromboplastin inhibition assay, dilute Russell viper venom time, and platelet or phospholipid neutralization.

Management is complicated. If there is no history of thrombosis, anticoagulation therapy is not recommended except for short periods immediately after orthopedic surgery. If there is a history of thrombosis, long-term anticoagulation therapy to a high international normalized ration is recommended because of the estimated at least 50% chance of recurrence. In women with recurrent fetal loss, the optimal management is heparin-based anticoagulation with or without low-dose aspirin.⁵¹

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