22.6.12 Acquired haemolytic anaemia 5479 Amy Power

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22.6.12 Acquired haemolytic anaemia 5479 Uyoga S, et al. (2015). Glucose-6-phosphate dehydrogenase deficiency and the risk of malaria and other diseases in children on the coast of Kenya: a case-control and a cohort study. Lancet Haematol, 2, e437–44. 22.6.12 Acquired haemolytic anaemia Amy Powers and Leslie Silberstein ESSENTIALS Premature destruction of red cells occurs through two primary mechanisms: (1) decreased erythrocyte deformability that leads to red cell sequestration and extravascular haemolysis in the spleen and other components of the reticuloendothelial system—may be caused by membrane defects, metabolic abnormalities, exogenous oxidizing agents, or pathological antibodies; and (2) red cell mem- brane damage and intravascular haemolysis—may be caused by exposure to pathological antibodies, activated complement, mech- anical forces, chemicals, and infectious agents. Clinical features—general aspects These include (1) increased red cell production—manifestations in- clude reticulocytosis, polychromasia, macrocytosis, erythroid hyper- plasia, and bone changes; (2) increased red cell destruction—features include decreased haemoglobin levels, fragmented red cells, decreased haptoglobin levels, increased unconjugated bilirubin levels, increased plasma lactate dehydrogenase levels, haemoglobinaemia, haemo- globinuria, haemosiderinuria, and splenomegaly. Congenital haemolytic anaemias Congenital disorders resulting in a haemolytic anaemia include (1) dis- orders of the red cell membrane such as hereditary spherocytosis and hereditary elliptocytosis; (2) disorders of red cell enzymes such as glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency; and (3) disorders of globin structure. See also Chapters 22.6.7, 22.6.10, and 22.6.11 for further discussion. Acquired immune haemolytic anaemias Immune haemolysis may occur when IgG, IgM, or IgA antibodies and/or complement bind to the erythrocyte surface. The direct anti- globulin test (DAT) or direct Coombs’ test detects the presence of IgG antibody or complement on the red cell surface. IgM and IgA antibodies are not directly detectable with standard testing reagents. Autoimmune haemolytic anaemias—these are

best classified ac- cording to the temperature at which the antibody optimally binds to the erythrocyte: (1) warm autoimmune haemolytic anaemia— typically IgG; symptomatic patients present with anaemia, jaundice, and splenomegaly; often associated with lymphoid malignancies; first-line treatment is with corticosteroids. (2) Cold agglutinin- mediated autoimmune haemolytic anaemia—autoantibodies are typically IgM and are most active at low temperatures; seen in younger patients following infection with Mycoplasma pneumoniae or infectious mononucleosis and in older patients idiopathically or in association with lymphoproliferative diseases. (3) Paroxysmal cold haemoglobinuria. (4) Mixed type autoimmune haemolytic anaemia— both IgG and complement are present on the red cells; may be idio- pathic or secondary (often to systemic lupus erythematosus). Drug-induced haemolytic anaemia—haemolysis can be caused by drugs that induce a positive DAT. Drug-induced antibodies may be drug dependent or drug independent depending on whether the presence of the drug is required for their detection. Alloimmune haemolytic anaemias—these include (1) acute haemo- lytic transfusion reactions—may begin after the infusion of as little as 10 ml of incompatible blood, with symptoms and signs including chest or flank pain, nausea, vomiting, fever, chills, hypotension, re- spiratory distress, and haemoglobinuria. Despite immediate stopping of the transfusion and optimal supportive care, patients can develop renal failure, disseminated intravascular coagulation, and even die. (2) Other conditions—these include delayed haemolytic transfusion reactions, passenger lymphocyte haemolysis, and haemolytic dis- ease of the newborn (caused by RhD incompatibility, ABO incom- patibility, or other blood group incompatibility). Acquired nonimmune haemolytic anaemias Common or important causes include (1) infections (e.g. malaria, ba- besiosis); (2) drugs and chemicals (e.g. nitrofurantoin); (3) mechan- ical (e.g. incompetent prosthetic heart valves); (4) thermal (e.g. faulty blood warmer); and (5) venom. Microangiopathic haemolytic anaemia (MAHA) MAHA describes the anaemia observed in a spectrum of disorders including haemolytic uraemic syndrome, thrombotic thrombo cytopenic purpura, and complement-mediated thrombotic micro angiopathies. These anaemias may be a component of a congenital or acquired disorder and may result from both immune and nonimmune mechanisms. Introduction Mechanisms of haemolysis After release into the circulation, normal red blood cells (RBCs) survive for approximately 120 days. As the circulating red cell mass decreases (anaemia), less oxygen is transported from the lungs to other tissues. In response, the kidneys increase their synthesis and secretion of erythropoietin, which stimulates erythropoiesis, in order to restore normal red cell mass and oxygen delivery (see also Chapter 22.6.1). A deficient red cell mass results from inadequate production (hypoplasia), loss (haemorrhage), or premature destruc- tion (haemolysis) of the red cells. In cases where red cell survival is reduced by haemolysis to such an extent that normal bone marrow cannot compensate, a haemolytic anaemia results. The haemolytic anaemias are either genetically determined or acquired. Consequences of haemolysis The clinical and laboratory changes associated with haemolysis reflect the physiological mechanisms responsible for restoring red cell mass and removing free haemoglobin from the plasma. These changes are outlined in Box 22.6.12.1. Within several days

 of the onset of haemolysis and the development of anaemia, in- creased erythropoiesis results in erythroid hyperplasia (decreased myeloid/erythroid ratio) in the bone marrow and reticulocytosis (polychromasia and macrocytosis) in the peripheral blood. The per- ipheral blood film may also exhibit microspherocytes, fragmented RBCs, and nucleated RBCs. If the haemolysis and anaemia begin early in life and persist, extramedullary erythropoiesis can develop in the spleen, liver, and lymph nodes. Chronic anaemia and the re-

sulting marrow hyperplasia can also result in long-bone deform- ities. Free haemoglobin in the circulation binds to the serum protein haptoglobin. Haptoglobin–haemoglobin complexes are removed from the intravascular space by the reticuloendothelial system. If the rate of haemolysis is greater than the liver's ability to synthesize haptoglobin, serum haptoglobin levels fall. In patients with severe haemolysis, haemoglobinaemia and haemoglobinuria may develop. At low plasma haemoglobin levels, much of the free haemoglobin is reabsorbed in the proximal renal tubules. The renal tubular cells catabolize the haemoglobin, converting iron into haemosiderin, which is eventually shed along with renal tubular cells into the urine resulting in haemosiderinuria. Haemosiderinuria is a reliable in- dicator of chronic intravascular haemolysis. At higher levels, free haemoglobin is found in the urine. Within the reticuloendothelial system, haemoglobin is metabolized and released into the serum as unconjugated bilirubin. The bilirubin is conjugated in the liver, ex- creted in the gut, converted to faecal urobilinogen, partially reab- sorbed, and excreted by the kidneys as urinary urobilinogen. The intracellular enzyme lactate dehydrogenase is released from lysed red cells into the plasma. Congenital haemolytic anaemias Congenital haemolytic anaemias result from inherited defects in the red cell membrane, red cell enzymes, or haemoglobin. Inherited defects in the red cell membrane include hereditary spherocytosis, elliptocytosis, pyropoikilocytosis, spherocytic elliptocytosis, stomatocytosis, and xerocytosis. Inherited disorders of red cell enzymes include glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency. Inherited defects in haemoglobin synthesis include the haemoglobinopathies and thalassaemias. These inherited anaemias are reviewed in depth in Chapters 22.6.7, 22.6.10, and 22.6.11. Acquired haemolytic anaemias Immune haemolytic anaemias Immune haemolysis may occur when IgG, IgM, or IgA antibodies and/or complement bind to the erythrocyte surface. The red cell- bound antibodies may induce extravascular haemolysis, intra- vascular haemolysis, or both. Red cells coated with IgG typically undergo extravascular haemolysis during their transport through the reticuloendothelial system. Interactions between the Fc portion of IgG and surface Fc receptors allow the macrophages to phago- cytose the coated erythrocytes. IgM, IgA, and, occasionally, IgG ac- tivate and fix complement to the erythrocyte surface. Macrophages also have receptors for the activated complement component C3b and likely phagocytose red cells through this pathway. The fixed complement can also induce intravascular haemolysis through ac- tivated membrane complex-mediated lysis. The direct antiglobulin test (DAT) or direct Coombs' test detects the presence of IgG antibody or complement on the red cell surface. IgM and IgA antibodies are not directly detectable with standard testing reagents. Rather, their presence may be indirectly demon- strated by the detection of complement on the erythrocyte. In rare cases, the haemolytic anaemia is due to noncomplement-fixing IgM or IgA antibodies. In this situation, the DAT will be falsely negative. Eluates can be obtained from the antibody-coated red cells to de- termine the specificity of the antibody. Alternatively, the antibody may be free in the serum and its specificity determined by the in- direct antiglobulin test or indirect Coombs' test. The presence of antibody or complement on the red cell, however, need not reflect ongoing haemolysis. Rather, the diagnosis of haemolytic anaemia rests on clinical findings and other laboratory data, such as red cell morphology, haemoglobin, bilirubin, haptoglobin, lactate dehydro- genase levels, reticulocyte count, and the presence or absence of haemoglobinaemia, haemoglobinuria, or haemosiderinuria. The serological findings provide information as to whether an immune basis exists and what type of immune haemolytic anaemia may be present. Autoantibodies, alloantibodies, and drugs may induce im- mune haemolytic anaemias. Autoimmune haemolytic anaemia Haemolytic antibodies directed against the individual's own red cells may arise as a primary/idiopathic event or may be secondary

to lymphoid malignancies, connective tissue disorders, and infection. Autoimmune haemolytic anaemia is best classified according to the temperature at which the antibody optimally binds to the erythro- cyte. The four major types of autoimmune haemolytic anaemia are warm autoimmune haemolytic anaemia, cold agglutinin-mediated autoimmune haemolytic anaemia, paroxysmal cold haemoglobin- uria, and mixed-type autoimmune haemolytic anaemia. The classic Box 22.6.12.1 The main features of haemolytic anaemia Increased red cell production • Reticulocytosis • Polychromasia • Macrocytosis • Erythroid hyperplasia • Bone changes Increased red cell destruction • Decreased haemoglobin levels • Increased unconjugated bilirubin levels • Decreased haptoglobin levels • Increased faecal and urinary urobilinogen • Haemoglobinaemia • Haemoglobinuria • Haemosiderinuria • Splenomegaly • Increased plasma lactate dehydrogenase levels • Microspherocytes • Fragmented RBCs • Nucleated RBCs

22.6.12 Acquired haemolytic anaemia 5481 clinical and serological findings of these anaemias are shown in Table 22.6.12.1. Warm autoimmune haemolytic anaemia Aetiology The offending antibody in warm autoimmune haemo- lytic anaemia is typically a polyclonal IgG (but can be IgM or IgA) and can be found on the red cell, in the serum, or both. The exact specificity of the antibody is often difficult to determine. With rare exceptions, warm-reactive autoantibodies bind to all red cells tested, while others appear to have broad specificity within the Rhesus (Rh) system. Occasionally, warm reactive autoantibodies will exhibit specificity against an individual antigen such as Rh(D), Rh(C), or Kell. Clinical features Warm autoimmune haemolytic anaemia can be idiopathic or secondary to an underlying infection, malignancy, or autoimmune disease. This disease can arise at any age but is more common in older individuals, probably because of its association with lymphoid malignancies. Women are affected slightly more often than men. Clinical signs and symptoms can range from mild to life-threatening and are related to the severity of the anaemia and ongoing haemolysis. The DAT is positive for IgG and/or comple- ment. In its mildest form the DAT is positive but red cell survival is not significantly affected. Symptomatic patients present with an- aemia, jaundice, and splenomegaly. Most patients with warm auto- immune haemolytic anaemia have a chronic, stable anaemia. In its severest form, patients present with fulminant intravascular haem- olysis, progressive anaemia, congestive heart failure, respiratory distress, and neurological abnormalities. As with other haemolytic anaemias, the peripheral smear often demonstrates anisocytosis and reticulocytosis with spherocytes and macrocytes (Fig. 22.6.12.1.) The platelet count is usually normal except in patients with Evans' syndrome where the autoantibody destroys both red cells and plate- lets. Rarely, patients with clinical and laboratory findings consistent with a warm autoimmune haemolytic anaemia may have a negative DAT. These cases have been attributed to IgA, IgM, or low affinity IgG antibodies. Alternatively, bound IgG has been reported below the level of routine DAT detection. In the latter situation, an eluate may demonstrate a pan-agglutinating antibody. Treatment Corticosteroids, which presumably block macrophage Fc receptor activity and inhibit antibody production, are the primary therapy for idiopathic warm autoimmune haemolytic anaemia. Prednisone at a dose of approximately 1 mg/kg/day is effective in most patients. Higher doses rarely provide additional benefit, but do increase the number and severity of side effects. Treatment con- tinues until a haemoglobin level greater than 100 g/litre is reached. The initial dose of prednisone can then be tapered to 20 to 30 mg/ day within a few weeks. Thereafter, the dose is reduced by 2.5 to 5.0 mg/day per month with careful monitoring of the patient's la- boratory parameters. Once the patient has been in remission for 3 to 4 months at a dose of 5 mg/day, withdrawal of steroids may be considered. Splenectomy and rituximab are considered second-line ther- apies. Rituximab (chimeric anti-CD20 monoclonal

antibody) has been demonstrated to have a favourable response rate and safety profile in patients with autoimmune haemolytic anaemia. Splenectomy should be performed only in steroid-refractory pa- tients or patients requiring unacceptably high doses of prednisone to maintain remission. Alternative therapies include cyclophos- phamide, danazol, alemtuzumab, ciclosporin, and mycophenolate mofetil. These therapeutic options should be reserved for patients unfit for splenectomy or who have failed to respond to steroids, rituximab, and surgery. The decision to transfuse patients with warm autoimmune haemo- lytic anaemia requires careful consideration. Due to the panreactive nature of most warm autoantibodies, all cross-matched RBCs for transfusion will appear incompatible. Transfusion of ABO- and Table 22.6.12.1 Classic clinical and serological findings observed in the immune haemolytic anaemias WAIHA CAIHA Mixed type AIHA PCH Clinical presentation Extravascular Haemolysis Haemagglutination and vascular obstruction; intra- and extravascular haemolysis Combined warm and cold autoimmune haemolysis Acute, severe, intravascular haemolysis Autoantibody type IgG (rare IgM or IgA) IgM IgG & IgM Biphasic IgG (Donath–Landsteiner antibody) Autoantibody specificity Broadly reactive; relative specificity for Rh antigens may be observed I or I; rare Pr Usually unclear P antigen DAT IgG and/or C3 C3 IgG and C3 C3 AIHA autoimmune haemolytic anaemia; CAIHA cold agglutinin autoimmune haemolytic anaemia or cold agglutinin disease; PCH paroxysmal cold haemoglobinuria; WAIHA warm autoimmune haemolytic anaemia. Fig. 22.6.12.1 The peripheral blood changes in warm autoimmune haemolytic anaemia. There is marked anisocytosis and anisochromia with many macrocytes and microspherocytes. The macrocytes reflect the reticulocytosis. Magnification ×1000, Leishman stain.

section 22 Haematological disorders 5482 Rh-compatible blood should not be withheld because of this sero- logical incompatibility if clinically indicated for a patient with symp- tomatic anaemia. Active serum autoantibodies can, however, mask the presence of clinically significant alloantibodies. Therefore, the most important consideration before transfusion is to confirm the presence or absence of alloantibodies in the patient’s serum. Various autologous and allogeneic red cell absorption techniques exist to remove the autoantibody from a sample of the patient’s serum and allow identification of any existing alloantibodies. If clinically significant alloantibodies are present, red cells lacking the corres- ponding antigen(s) should be selected for transfusion. If possible, it is recommended that patients be antigen typed and provided with RBCs which are matched for all clinically significant antigens in order to prevent subsequent alloimmunization and delayed haemo- lytic transfusion reactions. Transfusions in life-threatening situ- ations should not be delayed, however, if the above-mentioned tests are not readily available or completed. Cold agglutinin-mediated autoimmune haemolytic anaemia Aetiology Cold agglutinin-mediated autoimmune haemolytic an- aemia accounts for approximately one-quarter of all cases of auto- immune haemolytic anaemia. The autoantibodies are typically IgM and are most active at low temperatures (4°C); however, rare examples of IgG and IgA cold-reactive autoantibodies have been reported. In the lower temperatures of the peripheral circulation, the IgM autoantibodies bind to red cells and activate complement. In warmer areas of the circulation, the IgM dissociates from the erythrocyte leaving activated complement fixed to the red cell sur- face. The major mechanism of haemolysis in stable disease is thought to be extravascular clearance of C3b-coated erythrocytes in the liver. However, intravascular haemolysis also occurs. The autoantibody specificity is usually anti-I. Anti-i specificity is associated with in- fectious mononucleosis. Other specificities, including against the Pr protein, have been reported but are rare. Cold agglutinin-mediated autoimmune haemolytic anaemia can be classified as primary and secondary. The primary or idiopathic form,

referred to as cold haemagglutinin disease (CHAD), is a chronic condition typically characterized by the presence of a monoclonal IgM-κ, usually with specificity for the I-antigen. Recent studies have found evidence of bone marrow clonal lymphoproliferation in most of these patients. The secondary form, referred to as cold agglutinin syndromes, may be acute or chronic. Chronic cold agglutinin syn- drome is most often seen in the setting of malignancy. Acute cold agglutinin syndrome is most classically associated with mycoplasma pneumonia and Epstein–Barr virus infections. Clinical features In cold agglutinin disorders, the signs and symp- toms of disease result from either the agglutination of red cells or from haemolysis. Acute cold agglutinin syndrome is commonly seen in adolescents and young adults following infection with Mycoplasma pneumoniae or infectious mononucleosis. Haemolysis occurs approximately 1 to 2 weeks after infection and is most com- monly associated with a rise in polyclonal anti-I IgM antibody with M. pneumonia or polyclonal anti-i IgM antibody with infectious mononucleosis. Chronic cold autoimmune haemolytic anaemia occurs most com- monly in older people, either idiopathically (primary) or associated with an underlying condition such as chronic lymphocytic leu- kaemia or Waldenström macroglobulinaemia (secondary). Patients may experience chronic intravascular haemolysis and anaemia that are exacerbated by cold temperature. Patients are often also plagued by episodes of cold-induced acrocyanosis and Raynaud’s phenom- enon. Exacerbation of the haemolytic anaemia may be triggered by a febrile infectious illness or major trauma. This exacerbation has been attributed to the repletion of complement levels during acute phase reactions in patients who are normally complement de- pleted during their steady state of cold agglutinin disease. Repletion of complement levels is thought to increase complement-mediated haemolysis during these episodes. Monoclonal IgM antibodies with κ light chains and anti-I specificity usually cause the red cell agglutination and haemolysis in primary cold agglutinin disease. In typical cases the cold agglutinin titre is very high (>1:105). The thermal amplitude of the cold agglutinin, not the titre of the antibody, most accurately predicts the severity of the disease. Examination of the peripheral smear in patients with cold agglu- tinins shows red cell agglutination (Fig. 22.6.12.2). The DAT is positive for complement. (a) (b) Fig. 22.6.12.2 (a, b) The peripheral blood smear changes noted in a patient with cold agglutinins. Magnification (a) ×40; (b) ×400 Wright Giemsa stain.

22.6.12 Acquired haemolytic anaemia 5483 Treatment Primary chronic CHAD can be managed through both pharmacological and nonpharmacological methods. Patients should avoid cold exposure whenever possible. In situations of symptomatic anaemia, blood transfusions can be given provided some precautions are taken. Antibody screening and compatibility testing should be performed at 37°C. Blood should be given slowly through a blood warmer. Hypothermia must be avoided during sur- gery (especially surgical procedures involving extracorporeal cir- cuits). Plasma exchange may be helpful as a temporizing measure in acute situations due to the primarily intravascular location of IgM. Corticosteroids and splenectomy are rarely effective. Rituximab, an anti-CD20 monoclonal antibody, has demonstrated some clinical effectiveness in published cases of cold agglutinin disease, however complete remissions are uncommon. Higher response rates and frequency of complete remission have been reported with a com- bination of fludarabine and rituximab, suggesting that this com- bination therapy may be preferred. Limited data suggests a role for eculizumab, a monoclonal anti-C5 antibody, in the treatment of CHAD. However, further studies are needed to better elucidate the efficacy of this agent. There is no evidence-based therapy for the treatment of secondary cold agglutinin syndrome, and treatment of the underlying disease is important when possible. Acute CHAD following a viral infection is always self-limited. Supportive measures, including transfusions and avoidance of cold, may suffice. Treatment of the

mycoplasma infection shortens the duration and severity of the haemolysis. Corticosteroids are usually unhelpful, and splenectomy is almost never indicated. Paroxysmal cold haemoglobinuria Aetiology Paroxysmal cold haemoglobinuria (PCH) is the rarest form of autoimmune haemolytic anaemia. The disorder is caused by the polyclonal complement-fixing Donath–Landsteiner IgG antibody. In the cold, this antibody binds to, and irreversibly fixes, complement to the red cell membrane. Upon return to warmer tem- peratures, the antibody dissociates from the red cell and intravas- cular haemolysis occurs by activation of the complement cascade. The Donath–Landsteiner antibody appears to have anti-P specifi- city. The P antigen is a high-incidence antigen allowing it to bind to practically all red cells. In the past, PCH was commonly associated with congenital or tertiary syphilis. Presently, PCH is most commonly seen in chil- dren during or after a viral or bacterial infection, including measles, mumps, Epstein–Barr virus, varicella, cytomegalovirus, influenza, mycoplasma, and Haemophilus influenzae. Rarely, adults may present with PCH after a viral infection, or in association with a lymphoma or myeloproliferative disorder. Clinical features Patients present with symptoms of acute intravas- cular haemolysis, and the physical exam shows signs of jaundice and anaemia. Laboratory abnormalities will reflect acute intravascular haemolysis, and all complement levels may be low after haemolytic episodes due to consumption. Aside from findings commonly seen with haemolytic anaemias, review of the peripheral blood smear may show neutrophil erythrophagocytosis. During or shortly after a haemolytic episode, the DAT may be positive for complement but will be negative for IgG. The DAT, however, may be negative in some cases, and patients with a Coombs' negative haemolytic anaemia should be worked up further with the Donath–Landsteiner test. The Donath–Landsteiner test is specific for PCH. Treatment No specific therapy for paroxysmal cold haemo- globinuria exists. Most postinfectious cases of paroxysmal cold haemoglobinuria are self-limited and require only supportive care, including avoiding exposure to the cold. Transfusion is indicated only for severe haemolysis and life-threatening anaemia. Crossmatch compatible P-antigen positive blood may be used for transfusion. Transfusions with extremely rare P-antigen-negative blood should be reserved only for those patients who do not respond to random donor blood. The use of a blood warmer should be considered. As most cases of acute PCH are self-limited, immunosuppres- sive or other pharmacological therapies are typically not indicated. Steroids have not been shown to be useful. Data on the use of thera- peutic plasma exchange, rituximab, and eculizumab are limited. Mixed-type autoimmune haemolytic anaemia Aetiology Rarely, autoimmune haemolytic anaemias may be classi- fied as mixed type. This diagnosis should be reserved for those auto- immune haemolytic anaemias involving both warm autoantibodies and cold autoantibodies that have pathological serological features. This is in contrast to the estimated 30% of warm autoimmune haemolytic anaemias that are associated with the presence of benign cold agglutinins (titre ≤64 with a thermal reactivity <30°C). The warm-reactive IgG autoantibodies are indistinguishable from anti- bodies encountered in warm autoimmune haemolytic anaemia. The IgM autoantibodies may be of high titre and high thermal amplitude like those seen in cold-agglutinin syndrome or may have low titres at 4°C and have high thermal amplitudes, reacting at 30°C or above. These IgM autoantibodies usually have no distinguishable specifi- city, but on occasion have I or i specificities. Clinical features Mixed-type autoimmune haemolytic anaemia may be idiopathic or secondary. Frequent association with systemic lupus erythematosus has been reported. The haemolytic anaemia is often severe and chronic with intermittent exacerbations. Exposure to cold has been reported to increase haemolysis in some cases. The DAT is typically positive for both IgG and complement, and the eluate will contain a warm reactive IgG autoantibody. Complex serum reactivity will be noted in all phases of testing. Treatment Steroids, splenectomy, rituximab, or

cytotoxic agents may provide therapeutic benefit in mixed-type autoimmune haemo- lytic anaemia. If blood transfusions are necessary, selection of blood should adhere to transfusion guidelines outlined earlier for warm autoimmune haemolytic anaemia. Administration of blood through a warmer should be considered. Drug-induced immune haemolytic anaemia Drugs may induce antibodies to bind to the erythrocyte surface resulting in a positive DAT or haemolysis. Drug-induced anti- bodies may be classified as either drug-dependent antibodies or drug-independent antibodies. Drug-dependent antibodies may only be detected if the drug is present in the test system, while drug-independent antibodies do not require the in vitro addition of the drug for detection. Both types of antibodies may be associated with haemolysis. Patients with an unexplained haemolytic anaemia should have a complete medication history taken with each drug

section 22 Haematological disorders 5484 considered as a potential aetiology. Clinical evidence supporting the role of a particular drug in a haemolytic anaemia includes the asso- ciation of haemolysis with drug initiation and resolution of haem- olysis with drug cessation. Drug-dependent antibodies Certain drugs bind to the red cell membrane with a high affinity. Association of the drug with the membrane constituents allows the drug to act as a hapten. The antibodies produced are commonly IgG and are directed predominantly against the drug. The drug-coated red cells undergo extravascular destruction via Fc receptor-mediated recognition by splenic macrophages. The extravascular haemolysis can develop gradually, but may be life-threatening if left untreated. After the offending drug is identified and withdrawn, haemolysis will often resolve quickly. However, the positive DAT and the haem- olysis may persist for weeks if the drug is bound firmly enough to the RBC membrane to prevent its clearance from the circulation. Laboratory workup typically reveals a DAT that is positive for IgG. The eluate and serum will not react with RBCs unless they are coated with drug. Penicillin and some of the cephalosporins are the most notorious examples of this phenomenon. Approximately 3% of pa- tients receiving large doses of penicillin (millions of unit per day) intravenously will develop a positive DAT. Only rarely do patients develop haemolytic anaemia. Other drugs are not thought to strongly adhere to the RBC membrane. The mechanism by which these drugs induced a haemolytic anaemia is controversial and has previously been re- ferred to as the immune complex mechanism of drug-induced haemolytic anaemia. In this scenario, the drug may loosely bind to the RBC membrane and induce the binding of IgM or IgG anti- bodies that activate complement and cause intravascular haem-olysis. Alternatively, it is hypothesized that IgM antibodies bind to circulating drug to form immune complexes which loosely adhere to RBCs and induced complement mediated intravascular haem-olysis. The DAT is often positive for complement. The patient’s serum and eluate will only show reactivity if drug is present in the reaction mixture. The onset of the haemolysis is often abrupt and resultant anaemia can be severe. Haemoglobinaemia, haemo- globinuria, and renal failure are common. Once the offending drug is withdrawn, the haemolysis stops. Antibodies induced by second- and third-generation cephalosporins are thought to act via the mechanism. Drug-independent antibodies Some drugs stimulate the synthesis of red cell autoantibodies. The mechanisms of antibody stimulation are not well understood, but may include immune dysregulation, molecular mimicry, and/or drug adsorption causing alteration of RBC membrane antigens. Patient serum and red cell eluates react with normal red cells in the absence of the drug. The autoantibodies are indistinguishable from those found in warm autoimmune haemolytic anaemia. The DAT usually becomes positive after 3 to 6 months of drug administration. The haemolysis typically ceases within 2 weeks after the withdrawal of the drug, but the DAT can remain positive for up to 2 years. α- Methyldopa, L-dopa, procainamide, mefenamic acid,

fludarabine, and sulindac are examples of drugs that can stimulate the produc- tion of red cell autoantibodies. Nonspecific protein adsorption A drug-induced positive DAT may also reflect nonimmunological adsorption of protein, including immunoglobulins. Haemolysis due to nonimmunological protein adsorption has been associated with β-lactamase inhibitors, platinum-based chemotherapeutic agents, and cephalosporins. These drugs may alter RBC membranes so that immunoglobulins nonspecifically adhere to their surfaces, causing a positive DAT. Although previously not thought to cause haemolysis, these bound immunoglobulins may mediate RBC destruction in some cases. Alloimmune haemolytic anaemias Acute haemolytic transfusion reactions Aetiology Catastrophic cases of alloimmune haemolysis may occur following the transfusion of ABO-incompatible red cells. Naturally occurring IgM anti-A and anti-B antibodies bind to the incompat- ible red cells and activate complement resulting in intravascular haemolysis. Human error leading to the mis-identification of pa- tients, their blood samples, or the units of red cells to be transfused, is responsible for virtually all cases of ABO incompatibility. Other non-ABO IgG alloantibodies can cause acute, severe haemolysis, and acute haemolysis may also be seen following the administration of ABO-incompatible plasma containing components. Although apheresis platelets may frequently be transfused across ABO groups without adverse consequences, high levels of anti-A, anti-B, or anti- A,B in these units have been reported to cause acute haemolytic re- actions in some recipients. Clinical features Acute haemolytic transfusion reactions pre- sent within 24 h of transfusion. Symptoms of an acute haemo- lytic transfusion reaction may begin after the infusion of as little as 10 ml of incompatible blood. The signs and symptoms include fever, chills, nausea, vomiting, hypotension, respiratory distress, haemoglobinuria, and chest, flank, back, or infusion site pain. Despite treatment, acute haemolytic transfusions reactions can result in renal failure, disseminated intravascular coagulation, and even death. When a possible acute haemolytic transfusion reaction is first recognized, the transfusion must be immediately stopped and a full investigation should be undertaken. All labels, paperwork, and the patient’s identification band should be rechecked for ac- curacy. The blood bank paperwork and workup should also be re- viewed. All units previously cross-matched or dispensed but not yet transfused must be retrieved to prevent any additional reac- tions. A post-transfusion blood sample should be obtained to de- termine if a haemolytic reaction has occurred. A positive DAT or the visual evidence of haemolysis in the serum is supportive of the diagnosis of acute haemolysis, particularly if neither of these is ob- served on a pre-transfusion blood sample. Further evaluation may involve repeat ABO and Rh typing, antibody identification, and crossmatches using both pre- and post-transfusion specimens to determine the identity of the causative antibody. In some cases, nonimmune-related haemolysis may instead be the cause of the acute reaction. Overheating of blood in a blood warmer, attempts to transfuse blood rapidly through a small-bore needle, and con- comitant administration of hypotonic solutions and drugs have been associated with haemolysis.

22.6.12 Acquired haemolytic anaemia 5485 Treatment Once an acute haemolytic transfusion reaction is sus- pected, the blood transfusion should be stopped immediately, as the mortality rate is correlated with the amount of incompatible blood that is transfused. Treatment should be guided by the clinical con- dition of the patient. Intravenous access should be maintained for aggressive treatment of hypotension with intravenous fluids. Pressor agents (low-dose dopamine) have been used for mitigation of renal complications, although the effectiveness of this intervention is con-troversial. Other critical measures include monitoring the urine output and promoting renal blood flow with diuretics (furosemide or mannitol). Transfusion of platelets, plasma, or cryoprecipitate

may be necessary for the treatment of life-threatening bleeding sec- ondary to disseminated intravascular coagulation. Heparin has also been used in the treatment of disseminated intravascular coagula- tion; however, caution is urged due to the potential for haemorrhage. Limited data suggest that eculizumab may be effective in the treat- ment of an acute ABO-mediated haemolytic transfusion reaction if given shortly after the causative transfusion, presumably due to its ability to inhibit complement-mediated intravascular lysis. Delayed haemolytic transfusion reactions Aetiology Delayed haemolytic transfusion reactions typically occur in patients who have been alloimmunized to RBC antigens by previous transfusions or pregnancies. Approximately 2 to 3% of transfusion recipients become alloimmunized to non-ABO red cell antigens, although this figure may be much higher in certain patient populations, such as those with sickle cell disease. Haemolysis is not generally seen during the primary immune response since the trans- fused red cells often disappear from the circulation before antibody titres reach clinically significant levels. In the absence of further anti- genic stimuli, antibody titres may diminish to undetectable levels. Subsequent transfusion of red cells possessing the offending antigen, however, will induce an anamnestic response with reappearance of the IgG antibodies within hours to days. Binding of the IgG anti- body to the transfused antigen-positive red cells results in a posi- tive DAT and possibly mild to moderate extravascular haemolysis. Although numerous specificities are described, antibodies against the Rh, Kidd, Duffy, Kell, and MNS system antigens are commonly implicated in delayed haemolytic transfusion reactions. Clinical features Most patients experiencing a delayed haemolytic transfusion reaction present with fever, jaundice, and decreasing haemoglobin levels 1 to 2 weeks after the transfusion of incompat- ible red cells. Delayed haemolytic transfusion reactions are often discovered during evaluation for fever of unknown origin or when the haemoglobin level fails to increase following transfusion. Treatment Treatment is rarely necessary; acute kidney injury or disseminated intravascular coagulation is uncommon. If a delayed haemolytic transfusion reaction is suspected, both the patient’s serum and an eluate from the circulating red cells should be tested for alloantibodies. If alloantibodies are present, their specificities should be determined. Donor red cell units lacking the offending antigen should be selected for all subsequent transfusions, even if the antibody is no longer detectable on routine antibody screens. Passenger lymphocyte haemolysis Aetiology Recipients of a haematopoietic or a solid-organ trans- plant may experience delayed extravascular haemolysis. In this circumstance, lymphocytes of donor origin produce haemolytic antibodies against ABO or other red cell antigens possessed by the recipient. Clinical features Haemolysis due to passenger lymphocytes is most commonly seen in out-of-group yet ABO-compatible liver and bone marrow transplants (group A or group B recipients of group O tissue) but can also occur in recipients of lung, heart, and kidney transplants. A positive DAT and haemolysis can begin within several days after the transplant and continue for several months. Treatment If significant ABO haemolysis occurs, patients should be transfused with group O red cells. If non-ABO haemolysis is pre- sent, elution of the patient’s red cells may help to identify the anti- body specificity and allow transfusion of antigen-negative red cells. Haemolytic disease of the newborn Haemolytic disease of the newborn occurs when maternal IgG anti- bodies cross the placenta and bind to fetal red cells resulting in extra- vascular haemolysis. Usually these antibodies possess specificities within the Rh or ABO blood group systems. Occasionally the anti- bodies are directed against other red cell antigens such as the Kell, Kidd, and Duffy. In the mildest cases, anaemia develops after birth and is of little clinical consequence. In more severe cases the neo- nate develops progressive anaemia and jaundice within the first week of life. If left untreated, bilirubin may reach levels associated with kernicterus causing brain damage and death. In the most severe cases, the fetus develops

profound anaemia during gestation and may be stillborn or delivered grossly oedematous (hydrops fetalis). An infant with hydrops fetalis also has ascites, hepatosplenomegaly, and erythroblastosis and usually dies shortly after birth. Rh incompatibility Although incompatibility for the A and B blood group antigens is now the most common cause of haemo- lytic disease of the newborn, the most severe cases have historic- ally been attributed to the anti-Rh(D) antibody. In the majority of these cases, haemolytic disease of the newborn occurs in Rh(D)- negative women carrying a Rh(D)-positive fetus. The mother de- velops anti-D IgG antibodies following exposure to the D antigen during a previous pregnancy, or as a result of the transfusion of D-antigen-positive red cells. Rh(D) alloimmunization may be due to transplacental haemorrhage from the fetus at the time of de- livery. Spontaneous transplacental haemorrhage can also occur during gestation, particularly during the third trimester, as well as with ectopic pregnancy, spontaneous or therapeutic abortion, chorionic villus sampling, amniocentesis, caesarean section, and trauma. Approximately 16% of untreated Rh(D)-negative women who deliver a Rh(D)-positive child will become alloimmunized to the D antigen if not treated with prophylactic Rh immune globulin. Exposure of a Rh(D)-negative mother to as little as 0.1 ml of fetal D- positive blood can result in sensitization. It is essential to identify pregnant women at risk for Rh(D) haemolytic disease of the newborn to prevent sensitization. All pregnant women should have their ABO and Rh types identified as early as possible. Their serum should be screened for alloantibodies against the D antigen and other red cell antigens. Pregnant women who are D-antigen negative and have an initial negative antibody screen should have their serum retested for alloantibodies at 28 weeks' gestation. If the initial antibody screen is found positive,

section 22 Haematological disorders 5486 antibody titres should be followed at 2- to 4-week intervals to de- termine whether further sensitization is occurring. A rising titre of anti-D antibody or other clinically significant red cell alloantibodies indicates ongoing sensitization and possible haemolytic disease of the fetus and newborn. The presence of an antibody, however, does not indicate ongoing haemolysis in all cases. Naturally occurring IgM antibodies are common during pregnancy but do not cross the placenta. Furthermore, fetal red cells may lack the antigen corres- ponding to the mother's antibody. Molecular typing of fetal DNA is available for many red cell antigens including D, E/e, C/c, Jka/Jkb, and K1/K2. Middle cerebral artery peak systolic velocity measured by Doppler ultrasonography is a noninvasive and accurate tool that can be used to monitor and assess the severity of haemolysis. If the fetus is experiencing significant haemolysis and anaemia, clinical intervention must be prompt. Before 34 weeks of gestation, intra- uterine transfusion with leucoreduced and irradiated blood lacking the offending antigen should be performed. After 36 weeks' ges- tation, induced labour should be considered. Upon birth of an 'at-risk' fetus, a sample of cord blood should undergo a DAT and have measurements of haemoglobin and bilirubin performed. If the DAT on the cord blood sample is positive and the mother's antibody screen remains negative, haemolytic disease secondary to ABO in- compatibility or antibodies against low-incidence red cell antigens should be considered. In affected infants, phototherapy can be used to decrease bili- rubin levels. Infants with severe anaemia or severe jaundice should undergo exchange transfusion. A nonsensitized Rh(D)-antigen- negative mother's blood should also be tested to determine the amount of fetomaternal haemorrhage at delivery. Administration of 300 µg of IgG anti-D (RhIg) within 72 h of delivery will protect up to 99% of D-antigen-negative mothers from developing anti-D antibodies. Prophylactic administration of RhIg at 28 weeks' ges- tation and following invasive procedures or traumatic events will virtually eliminate the chance of alloimmunization. Patients with large transplacental haemorrhages quantitated by the Kleihauer–

Betke acid-elution technique should receive additional RhIg at a dose equivalent to 300 µg for every 15 ml of fetal RBCs or 30 ml of fetal blood. ABO incompatibility Although 20% of pregnancies are ABO in- compatible, severe haemolytic disease of the newborn due to ABO incompatibility is rare. Group A and group B infants of group O mothers are at greatest risk, due to the IgG antibody anti-A,B made by group O individuals. Unlike with the Rh(D) antigen, ABO-haemolytic disease of the newborn occurs during the first pregnancy as often as subsequent pregnancies. Most cases are asymptomatic to mild, and exchange transfusion with group O red cells is rarely required. The decrease in severity observed in cases due to ABO incompatibility may be due to decreased surface ex- pression of the A and B antigens on fetal cells, and the presence of A and B antigens on many tissues leading to dilution of the anti- body effect. Nonimmune acquired haemolytic anaemias Red cell survival may also be reduced by a number of noninherited, nonimmune mechanisms. As red cells circulate, they are vulner- able to a variety of insults that may cause structural or metabolic alterations. These changes generally result in reduced red cell deformability leading ultimately to extravascular haemolysis. These insults include infection, mechanical trauma, and exposure to chemicals, heat, or venom. They often also cause intravas- cular haemolysis by directly lysing the red cell membrane. Other causes of acquired nonimmune haemolytic anaemias are listed in Box 22.6.12.2. Infection Infectious causes of haemolysis are primarily parasites and bacteria. Direct parasitization of red cells by Plasmodium falciparum, P. vivax, and P. malariae causes both intravascular haemolysis due to direct membrane destruction and extravascular haemolysis due to mem- brane alteration and activation of the reticuloendothelial system. Infrequently, in utero infection of the fetus with Toxoplasma gon- dii resembles severe haemolytic disease of the newborn. Infants are born hydropic and severely anaemic. Premature delivery and still- birth are common. Babesia microti, endemic in areas of the Northeast and Midwest of the United States of America, is transmitted by ticks and causes severe haemolysis during the erythrocytic phase of its life cycle. Bacterial infections, particularly Gram-negative organisms which produce endotoxin or proteolytic enzymes, may produce mechanical haemolysis by inducing disseminated intra- vascular haemolysis or red cell membrane damage via degradation of membrane phospholipids and proteins. Bartonella bacilliformis endemic to western South America causes Oroya fever character- ized by fever, chills, musculoskeletal pain, and acute intravascular haemolysis. Clostridium perfringens releases enzymes that degrade the RBC membrane, and clostridial sepsis has been associated with rapid, massive haemolysis. Chemical Drugs and chemicals known to cause haemolysis through direct oxidative damage are summarized in Tables 22.6.12.2 and 22.6.12.3. In most cases, the strong oxidant activity of these chem- icals overwhelm normally functioning reduction mechanisms re- sponsible for protecting haemoglobin and the red cell membrane. Variability in the absorption of the chemical or its metabolism Box 22.6.12.2 Other causes of acquired haemolytic anaemia • Paroxysmal nocturnal haemoglobinuria • Lipid disorders • Liver disease:

— Hepatitis

— Cirrhosis

— Gilbert’s disease • Chronic alcoholism (Zieve syndrome) • Wilson’s disease • Vitamin E deficiency • Hypersplenism • Hyperbaric oxygen therapy • Total body irradiation • Chronic large granular lymphocytic leukaemia • Renal disease • Cardiopulmonary bypass • Freshwater/saltwater drowning

22.6.12 Acquired haemolytic anaemia 5487 determines whether a particular individual will develop chemical- induced haemolytic anaemia. Often it is the chemical's metabolite that is responsible for inducing haemolysis. The red cells of new- borns do not have functional reduction mechanisms and thus are more sensitive to oxidant activity. Mechanical Mechanical fragmentation of erythrocytes can occur when for- eign material is placed within the vasculature, when fibrin strands or platelet thrombi obstruct small blood vessels, or when direct physical forces compress superficial blood vessels. Thrombotic microangiopathies, which result in a microangiopathic haemolytic anaemia, are discussed in the following microangiopathic haemo- lytic anaemias section. Foreign material Mechanical haemolysis occurs most commonly with artificial valvular prostheses, particularly when accompanied by turbu- lent blood flow. Bacterial endocarditis and associated valvular vegetations can also cause fragmentation of red cells. Haemolysis also occurs in up to 10% of patients with transjugular intrahepatic portosystemic shunts. Increased cardiac output as a result of an- aemia, exercise, or medications can increase the rate of red cell fragmentation. The peripheral smear usually demonstrates schistocytes and microspherocytes. Severe haemolysis usually re- quires surgical repair. March haemoglobinuria Haemoglobinuria can occur in soldiers or joggers following ex- tended periods of marching or running on a hard surface, or in karate or conga drummer enthusiasts following practice. This mech- anical haemolysis appears to be the result of red cell compression in superficial blood vessels during the period of contact between the extremity and the hard surface. The peripheral smear is normal. Treatment is unnecessary as the syndrome is otherwise symptomless and lacks significant clinical sequelae. Thermal haemolysis Normal red cells undergo fragmentation and lysis when heated to temperatures of 49°C or higher. The two most common clinical situ- ations associated with heat-induced red cell lysis are the use of faulty blood warmers during transfusion or patients who have sustained extensive burns. Venom Haemolysis has been observed following bee and wasp stings, spider bites, and snake bites. The haemolysis occurs secondary to dissem- inated intravascular coagulation or as a result of proteolytic enzymes contained within the venom. Microangiopathic haemolytic anaemia MAHA is a descriptive term for a haemolytic anaemia due to intravascular RBC fragmentation which produces schistocytes. MAHA is a component of numerous congenital and acquired immune and nonimmune disorders. Due to its diverse aetiolo- gies, MAHA is described separately in this text. Thrombotic microangiopathies (TMAs) are a frequent cause of MAHA; however, MAHA may also be seen in numerous other settings, including the presence of intravascular devices as previously de- scribed. Thrombotic microangiopathies are characterized by the presence of MAHA and thrombocytopenia and have a variety of Table 22.6.12.2 Some drugs that may induce haemolysis in G6PD-deficient individuals Antimalarials Sulfones Primaquine Thiazolesulfone Pamaquine Dapsone Pentaquine Nitrofurans Chloroquine Nitrofurantoin Quinidine Nitrofurazone Quinine Furazolidone Quinacrine Antipyretics/analgesics Sulfonamides Acetanilide Sulfanilamide Aspirin Sulfacetamide Paracetamol (acetaminophen) Sulfapyridine Phenacetin Sulfamethoxazole Aminopyrine Sulfafurazole Other drugs Sulfamethoxypyridazine Methylene blue Sulfoxone Nalidixic acid Sulfadiazine Chloramphenicol Sulfamerizine Doxorubicin Sulfisoxazole Dimercaprol Sulfadimidine Probenecid Other chemicals Vitamin K analogues Napthalene Phenazopyridine Trinitrotoluene p-Aminosalicylic acid Toluidine blue Ciprofloxacin Norfloxacin Note: see also Chapter 22.6.11. Table 22.6.12.3 Chemicals that cause haemolysis Oxidative haemolysis Nitrofurantoin Arsine gas Sulfonamides Chlorate Sulfones (dapsone) p-Aminosalicylic acid Phenazopyridine p-Nitroaniline Phenacetin Nitrobenzene derivatives Phenylhydrazine Vitamin K analogues Phenothiazine Paraquat Isobutyl nitrate Naphthalene (mothballs) Amyl nitrite Hydrogen peroxide Nonoxidative haemolysis Copper Lead

section 22 Haematological disorders 5488 aetiologies. In thrombotic microangiopathies, the red cells are fragmented during their forced passage through vessels con- taining microthrombi. The degree of anaemia is variable. The per- ipheral smear reveals findings typical of mechanical haemolysis including schistocytes, microspherocytes, and a reticulocytosis (Fig. 22.6.12.3). Varying degrees of thrombocytopenia are also observed. The primary TMAs include thrombotic thrombocytopenic pur- pura (TTP), shiga toxin-mediated haemolytic uraemic syndrome, complement-mediated TMA, drug-induced TMAs, and other rare hereditary disorders of vitamin B12 metabolism and coagulation. Systemic disorders may also lead to the development of MAHA, including preeclampsia, HELLP, malignant hypertension, severe infections, disseminated malignancies, DIC, autoimmune dis- orders and haematopoietic progenitor cell or solid-organ transplant. Systemic disorders and mechanical causes of MAHA must be dis- tinguished from the primary TMA syndromes, as therapy for the former is typically directed at the underlying disorder. Several of the primary TMA syndromes will be discussed further in the following sections. Shiga toxin-mediated haemolytic uraemic syndrome Shiga toxin-mediated haemolytic uraemic syndrome is primarily, but not exclusively, a disease of childhood. The disorder consists of widespread damage to the vascular endothelium and fibrin de- position. These pathological changes are frequently most severe in the renal arterioles and glomerular capillaries. The disorder usu- ally develops following a febrile illness. Numerous reports have documented the development of haemolytic uraemic syndrome following infections with toxin-secreting strains of Escherichia coli (strain O157:H7) or shigella. Initial nausea, vomiting, and diarrhoea can develop into severe abdominal pain and bloody diarrhoea. Acutely, the child may develop hypertension, oliguria, purpura, bleeding, and anaemia. If left untreated, convulsions, coma, and death may occur. Mortality rates in young children are reported to be low (3%), however the disease is more severe with a higher mortality in adults. The peripheral smear exhibits schistocytosis and thrombocytopenia. Therapy consists mainly of supportive care, transfusion, control of blood pressure, and dialysis. Thrombotic thrombocytopenic purpura TTP is caused by either a congenital deficiency of or an acquired inhibitor to a serum metalloprotease (ADAMTS13) which is re- sponsible for cleaving unusually large multimers of von Willebrand factor. Left uncleaved, the large von Willebrand factor multimers in- duce TTP by causing the agglutination of circulating platelets. TTP occurs mainly in adults and more commonly involves the central nervous system, although renal abnormalities can occur. Patients may present with fever, purpura, petechiae, anaemia, thrombocyto- penia, and neurological abnormalities. The neurological sequelae include convulsions, coma, paralysis, delirium, and stroke. The per- ipheral smear demonstrates schistocytes, thrombocytopenia, and a reticulocytosis. Congenital TTP may be treated with plasma in- fusions. In acquired TTP, front-line therapy includes steroids and daily plasma exchange with plasma or virally-inactivated solvent- detergent plasma. Plasma exchange accomplishes one or more of the following: (1) removal of the antibody to the protease; (2) removal of large multimers of von Willebrand factor; and/or (3) replenishment of normal protease. In patients who do not initially respond to plasma exchange, a thorough re-evaluation for alternative diseases should be under- taken. The addition of rituximab should be considered, although the optimal dose and schedule have not been established. Other op- tions include the use of cryo-poor supernatant as the replacement fluid. Cryo-poor supernatant contains markedly reduced levels of normal von Willebrand factor which is believed to enhance the formation of microthrombi in some patients. Additional reported therapies in refractory or relapsing patients have included Cytoxan, ciclosporin, vincristine, bortezomib, mycophenolate mofetil, N- acetylcysteine, and splenectomy. Clinically significant bleeding is uncommon in TTP, and prophylactic platelet transfusions are typically

unnecessary unless the patient requires an invasive pro- cedure where the risk of bleeding is significant. Although there is some concern that platelet transfusions may ‘fuel the fire’ in patients with TTP, evidence supporting this assumption is lacking and platelets should not be withheld in the setting of clinically sig- nificant bleeding. Complement-mediated TMA Complement-mediated TMA is the result of the uncontrolled ac- tivation of the alternative complement pathway due to mutations or antibodies to complement regulatory proteins. Mutations may include loss of function mutations in regulatory genes (CFH, CFI, or CD46) or gain-of-function mutations in effector genes (CFB or C3). Functional deficiencies in factor H have also been reported due to CFH antibodies. Patients with complement-mediated TMA present with acute kidney injury and hypertension, MAHA, and thrombocytopenia. The ADAMTS13 level is typically not severely deficient and the stool is negative for the Shiga toxin. As normal plasma levels of C3, C4, CFB, CFH, and CFI do not exclude the diagnosis of complement-mediated haemolytic uraemic syndrome, screening for mutations and antibodies to the complement proteins is required. Initial treatment of complement-mediated haemolytic Fig. 22.6.12.3 The peripheral blood changes in microangiopathic haemolytic anaemia. This patient had recurrent thrombocytopenic purpura and the marked fragmentation of the red cells together with microspherocytosis is evident on the blood film. Magnification × 1000, Leishman stain.

22.6.12 Acquired haemolytic anaemia 5489 uraemic syndrome is supportive. Eculizumab can be considered a first-line therapy if available. Plasma exchange may be useful in some patients, and immunosuppressive therapy should also be considered in patients with antibody-mediated disease. Combined liver–renal transplant is curative for complement-mediated muta- tions of CFH, CFI, CFB, and C3. FURTHER READING Berentsen S, Randen U, Tjonnfjord (2015). Cold agglutinin-mediated autoimmune hemolytic anemia. Hematol Oncol Clin N Am, 29, 455–71. Crowther M, et al. (2011). Evidence-based focused review of the treat- ment of idiopathic warm immune haemolytic anemia in adults. Blood, 118, 4036–40. Davenport RD (2012). Hemolytic transfusion reactions. In Popovsky M (ed) Transfusion reactions, pp 1–51. AABB Press, Bethesda, MD. Davidson RJL (1969). March or exertional hemoglobinuria. Semin Hematol, 6, 150. Fung MK, et al. (ed.) (2014). Technical manual, 18th edition. American Association of Blood Banks, Bethesda, MD. Furlan M, et al. (1998). Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med, 339, 1578–84. George JN, Nester CM (2014). Syndrome of thrombotic microangiopathy. N Engl J Med, 371, 654–66. Hows J (1986). Donor-derived red blood cell antibodies and immune hemolysis after allogeneic bone marrow transplantation. Blood, 67, 177–81. Judd WJ (2001). Practice guidelines for prenatal and perinatal immunohematology, revisited. Transfusion, 41, 1445–52. Marsh GW, Lewis SM (1969). Cardiac hemolytic anemia. Semin Hematol, 6, 133–45. Naik R (2015). Warm autoimmune haemolytic anemia. Hematol Oncol Clin N Am, 29, 445–53. Petz LD, Garratty G (2004). Immune hemolytic anemias. Churchill Livingstone, Philadelphia. Ramsey G (1991). Red cell antibodies arising from solid organ trans- plants. Transfusion, 31, 76–86. Price EA, Schrier SL (2013). Extrinsic nonimmune haemolytic anemias. In: Hoffman R, et al. (eds) Hematology: basic principles and practice, pp. 628–37. Elsevier Saunders, Philadelphia. Shanbhag S, Spivak J (2015). Paroxysmal cold hemoglobinura. Hematol Oncol Clin N Am, 29, 473–8 Shirey RS, et al. (2002). Prophylactic antigen-matched donor blood for patients with warm autoantibodies: an algorithm for transfusion management. Transfusion, 41, 1435–41. Tsai H-M, Lian EC-Y (1998). Antibodies to von Willebrand factor- cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med, 399, 1585–94. Weinstock C, et al. (2015). Successful use of eculizumab for treatment of an acute haemolytic reaction after ABO-incompatible red blood cell transfusion. Transfusion, 55, 605–10.

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