REVIEW

Gastrointestinal and Hepatic Complications of Sickle Cell Disease

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This article has an accompanying continuing medical education activity on page e70. Learning Objectives—At the end of this activity, the learner should be able to identify the main intra-abdominal complications of sickle cell disease and explain the reason for their occurrence.

Sickle cell disease (SCD) is an autosomal recessive abnormality of the β-globin chain of hemoglobin (Hb), resulting in poorly deformable sickled cells that cause microvascular occlusion and hemolytic anemia. The spleen is almost always affected by SCD, with microinfarcts within the first 36 months of life resulting in splenic atrophy. Acute liver disorders causing right-sided abdominal pain include acute vaso-occlusive crisis, liver infarction, and acute hepatic crisis. Chronic liver disease might be due to hemosiderosis and hepatitis and possibly to SCD itself if small, clinically silent microvascular occlusions occur chronically. Black pigment gallstones caused by elevated bilirubin excretion are common. Their small size permits them to travel into the common bile duct but cause only low-grade obstruction, so hyperbilirubinemia rather than bile duct dilatation is typical. Whether cholecystectomy should be done in asymptomatic individuals is controversial. The most common laboratory abnormality is an elevation of unconjugated bilirubin level. Bilirubin and lactate dehydrogenase levels correlate with one another, suggesting that chronic hemolysis and ineffective erythropoiesis, rather than liver disease, are the sources of hyperbilirubinemia. Abdominal pain is very common in SCD and is usually due to sickling, which resolves with supportive care. Computed tomography scans might be ordered for severe or unremitting pain. The liver typically shows sickled erythrocytes and Kupffer cell enlargement acutely and hemosiderosis chronically. The safety of liver biopsies has been questioned, particularly during acute sickling crisis. Treatments include blood transfusions, exchange transfusions, iron-chelating agents, hydroxyurea, and allogeneic stem-cell transplantation.

Keywords: Liver Disease; Gallstones; Abdominal Pain.

Sickle cell disease (SCD) is an autosomal recessive abnormality of the β-globin chain of hemoglobin (Hb) that changes the sixth amino acid from glutamic acid to valine.[1] The resulting Hb S polymerizes reversibly when deoxygenated to form a gelatinous network that stiffens the erythrocyte membrane and increases viscosity, producing the characteristic sickle shape. Such sickled cells lose flexibility needed to traverse small capillaries and have "sticky" membranes that adhere to the endothelium of small venules. These abnormalities result in microvascular occlusion and red blood cell destruction.

The heterozygous sickle trait is found in 8%–10% of the African American population.[1] Less commonly, Hb S combines with either Hb C or β-thalassemia. Fetal Hb F, which accounts for 80% of the Hb concentration at birth, declines to less than 1% by 6 months. It interferes with Hb S polymerization, and its concentration directly correlates with improvement in disease severity and prognosis. Hydroxyurea, which increases the concentration of Hb F, ameliorates the severity of painful crises in SCD.

The Spleen in Sickle Cell Disease

The spleen is almost always involved in SCD (Figure 1). It is usually infarcted within the first 18–36 months of life, paralleling the disappearance of protective Hb F, resulting in hyposplenism or asplenism.[2] Splenic atrophy increases susceptibility to infection with encapsulated bacteria. The onset of functional asplenia is reflected by the appearance of irreversibly sickled cells, anisocytosis, Howell-Jolly bodies, and siderocytes.

Splenic infarction caused by occlusion of the small splenic vessels from sickling is the most common in patients with sickle cell (SC)-Hb C or SC-thalassemia disease.[3] This is due to the near-normal Hb levels that produce a relatively high blood viscosity and to splenomegaly found in a majority of adults with these diseases. It might also occur with SC trait even in nonhypoxic conditions.[4] Splenic infarction presents with left upper quadrant pain, nausea and vomiting, a friction rub over the splenic area, and leukocytosis. With resolution of splenic abscesses or infarcts, pseudocysts might develop.[5]

Sequestration syndrome, or the rapid pooling of blood, usually affects the pulmonary circulation. Before the development of hyposplenism, it can cause rapid splenic enlargement and a drop in Hb.[6] In homozygous SCD, sequestration occurs in infants and children because progressive fibrosis of the spleen

Abbreviations used in this paper: CDL, choledocholithiasis; CT, computed tomography; Hb, hemoglobin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; SCD, sickle cell disease.

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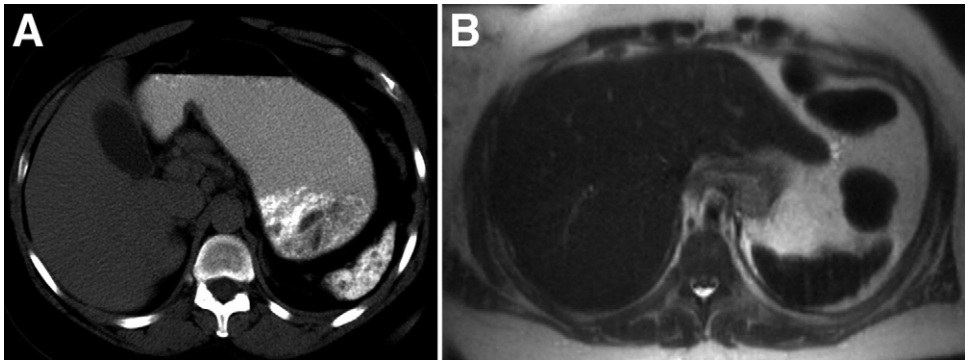

Figure 1. A 47-year-old woman with SCD and history of autosplenectomy. Unenhanced CT of the abdomen (*A*) shows increased density of the small spleen. On MRI (*B*) the spleen is also small and diffusely hypointense on all sequences, consistent with findings of dense calcification on CT. The calcifications and small size make detection of the spleen difficult on ultrasound.

impairs its ability to sequester blood. In SC-thalassemia, on the other hand, sequestration might occur at any age because the spleen is chronically enlarged. Hypovolemic shock and death might occur within hours if not prevented by transfusions. Occasionally, the organ might rupture. Splenomegaly might also be due to extramedullary hematopoiesis or to hemosiderosis.[5]

The Liver in Sickle Cell Disease

Acute Processes

There are several causes of right upper quadrant pain as it specifically relates to SCD. In patients admitted for acute vaso-occlusive crisis (severe pain in chest, abdomen, and joints), the liver is involved in about 39% of cases.[7] These patients present with abdominal meteorism, right upper quadrant pain, or acute painful hepatomegaly. The type of liver injury is usually cholestatic or mixed rather than purely hepatocellular, usually with normal synthetic function.

Liver infarction in SCD has been observed in 34% of autopsies.[8] In half of these cases, an associated cause of infarction (cardiac dysfunction or sepsis) is present. The resulting high blood viscosity predisposes to infarction despite the dual blood supply of the liver. Infarction might also occur in those with SC trait[9] or SC-Hb C disease.[10]

Acute sickle hepatic crisis affects about 10% of patients admitted for painful crisis.[11] It simulates acute cholecystitis with right upper quadrant pain, fever, leukocytosis, and variable increases in serum transaminases and bilirubin levels. The AST and ALT levels are usually 1–3 times normal,[12] although levels of greater than 1000 IU/L have been reported.[13] Unlike cholecystitis, the liver is usually enlarged and tender.

An uncommon complication is acute hepatic sequestration with jaundice and right upper quadrant pain associated with an enlarged liver and a drop in hematocrit accompanied by an appropriate reticulocytosis.[14,15] This is thought to be due to obstruction of sinusoidal flow by masses of sickled erythrocytes, trapping them in the liver. With resolution of the sinusoidal obstruction, erythrocytes might return to the circulation, causing a rapid rise in Hb; this suggests that not all sequestered cells are destroyed. The result can be death as a result of hypervolemia, heart failure, and intracerebral hemorrhage.[16]

A rare but potentially fatal complication known as SC intrahepatic cholestasis is thought to represent an unusually severe form of hepatic crisis.[17,18] There is widespread sickling in the sinusoids, resulting in hepatic ischemia. It is characterized by right upper quadrant pain, nausea, vomiting, tender hepatomegaly, and leukocytosis. There is extreme hyperbilirubinemia (from hemolysis, intrahepatic cholestasis, and renal impairment), with the conjugated fraction exceeding 50% of the total. In addition, there is a modest elevation of transaminase levels and coagulopathy. Patients die of liver failure and/or a hemorrhagic diathesis.

Rarely, liver abscesses occur as a result of diminished removal of bacteria from the bloodstream as a result of functional asplenism and reduced IgG antibodies to polysaccharide antigens.[19] It should be considered in a patient with fever and right upper quadrant pain and might represent a secondarily infected hepatic infarct.[20] Rarely, the liver abscess is due to *Yersinia enterocolitica* because iron overload and desferrioxamine therapy increase susceptibility to this organism.[21]

The clinical course of acute hepatitis B in patients with SCD might be the same as in control patients[22] or marked by higher bilirubin levels.[11] Seropositivity for hepatitis B surface antigen in SC patients is up to 3.3% of the population in the United States.[23] Vaccination against hepatitis B has been shown to be effective in SC patients.[24]

A hepatic bile-filled cyst (biloma), presumably the result of a hepatic infarction, has been described in a patient with right upper quadrant pain, fever, and jaundice.[25] Cocaine hepatotoxicity has been described in a patient in SC crisis.[26] The patient subsequently developed hepatic failure, which is rare in SCD. Occasionally, large vessel obstruction of the hepatic or portal veins[27,28] has been encountered in SCD.

Chronic Processes

Chronic liver disease in SCD might be due to hemosiderosis and hepatitis. It is possible that repeated small, clinically silent microvascular occlusions occur throughout the life of an SCD patient, eventually leading to liver fibrosis, superimposed on other causes of chronic liver disease. The high rate of liver cirrhosis of 18% among young patients with SCD, causing death in 11% of cases, supports this view.[29,30]

With increased longevity of patients with SCD, iron overload has become an issue. It stems from accumulation of transfused iron, increased gastrointestinal absorption as a result of intensive erythropoiesis, and iron deposition as a result of continu-

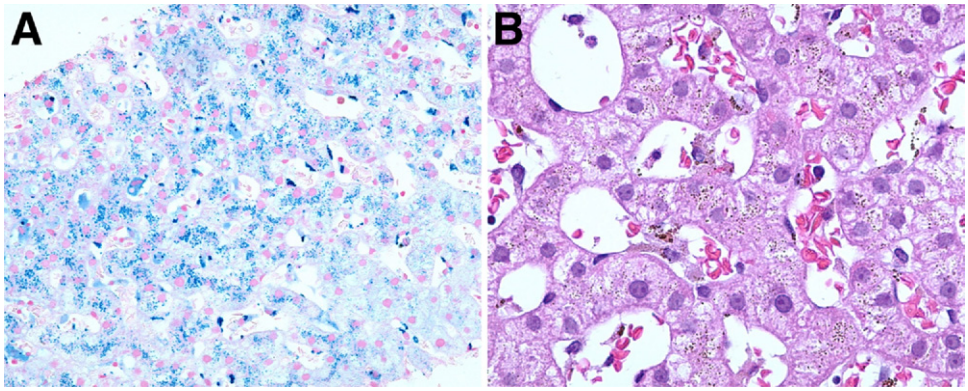

Figure 2. Gomori's iron stain. (*A*) Liver; original magnification, 20×. Hepatocytes show diffuse severe iron deposition. Kupffer cells show strong reactivity to iron. (*B*) Liver; original magnification, 400×. Dilation and filling of sinusoids with sickled red blood cells in aggregates. Marked hepatocelluar cytoplasmic iron deposition (grade 3 siderosis) is probably related to chronic transfusions.

ous hemolysis. The iron is deposited in the reticuloendothelial system, including the Kupffer cells (Figure 2).

Hepatitis C was prevalent in this highly transfused population before the screening of blood products.[23] In thalassemia, interferon and ribavirin resulted in a sustained virologic response of 45%.[31–33]

Focal nodular hyperplasia is characterized by nodules of regenerative hepatocytes distributed diffusely throughout the liver, with atrophy of the intervening parenchyma.[34,35] Minimal fibrosis and lack of hepatic dysfunction differentiate it from cirrhosis. It might be due to obstructive portal venopathy with areas of compromised blood flow.

Patients with SCD might develop zinc deficiency as a result of increased renal loss of zinc[36] and increased fecal loss with deferoxamine therapy.[37] Zinc deficiency might result in elevated ammonia levels because the urea cycle is inhibited by the absence of zinc, a cofactor for this pathway. This elevation of ammonia can theoretically worsen hepatic encephalopathy and can be corrected by zinc therapy.[38] Zinc supplementation also decreases the number of pain crises in these patients.[39]

The Gallbladder in Sickle Cell Disease

Cholelithiasis, diagnosed by ultrasound, is found in 26%–58% of SCD patients versus 17% in patients with SC-Hb C disease and SC-β-thalassemia[40–42] (Figure 3). Those with stones have a higher mean bilirubin level than those without stones.[42] Gallstones are typically of the black rather than brown pigment type as a result of elevated bilirubin excretion. About 50% of them can be seen on plain films because the bilirubin is typically in the form of its calcium salt.[43,44] With increasing age, cholesterol gallstones might develop.

The incidence of choledocholithiasis (CDL) in SCD with cholelithiasis has been described as being more than or equal to that found in patients with cholesterol gallstones,[45,46] ranging from 19%–26%. The smaller size of the bilirubin compared with cholesterol gallstones might permit them to move more readily from the gallbladder into the common bile duct. Because of their small size and friability, they might produce only low-grade obstruction. As a result, although serum bilirubin or transaminases are not reliably associated with CDL in SCD,[46] incremental hyperbilirubinemia (with levels more than 5 mg/dL) is a better predictor of CDL than is bile duct dilatation or elevation in either alkaline phosphatase or serum aminotransferase levels.[47] This differs from cholesterol CDL in which biliary duct dilatation and elevated serum alkaline phosphatase level are good noninvasive predictors. SCD might rarely cause ischemic cholangiopathy characterized by multiple stenoses and dilations of the intrahepatic bile ducts.[48]

Cholecystitis presents with abdominal pain, nausea and vomiting, fever, and/or jaundice, a constellation of symptoms that has multiple possible etiologies in SCD. Symptoms of acute cholecystitis and/or biliary tract obstruction might be due to vascular lesions.[49]

Cholecystectomy is the most frequent surgery in patients with SCD, comprising almost 40% of the procedures on SC patients.[50] Some authors advocate early cholecystectomy in asymptomatic patients for several reasons. First, emergency surgery might lead to complications such as SC crisis, longer hospital stay, and long operative time required to remove a diseased gallbladder.[44,51] Histopathologic chronic cholecystitis does not correlate with clinical symptoms.[52] Furthermore, one study reported no serious complications in their patients undergoing elective cholecystectomy.[53] In addition, SC patients

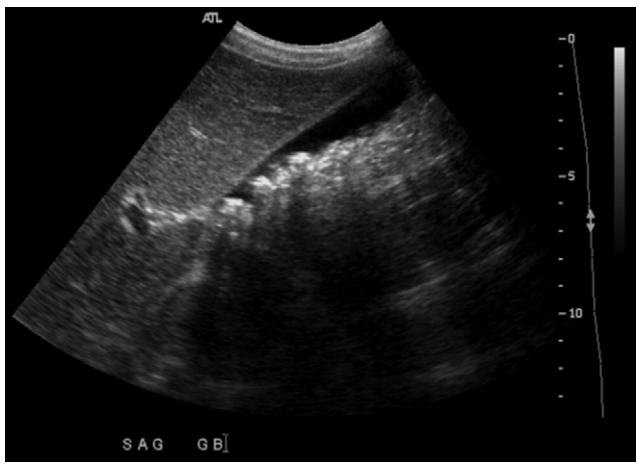

Figure 3. A 40-year-old woman with SC anemia presents with right upper quadrant abdominal pain. Ultrasound of the abdomen demonstrates numerous mobile, echogenic gallstones with dense posterior acoustic shadowing, consistent with pigmented gallstones.

are living longer, and medical management is simplified by eliminating gallstones as a diagnostic possibility. The use of laparoscopic cholecystectomy in this high-risk patient population decreases hospital time without increasing complications.[54,55]

In contrast, other authors believe that patients with silent gallstones might not develop symptomatic biliary tract disease and that prophylactic cholecystectomy might be associated with an equal or higher mortality rate than postponing surgery until symptoms develop.[56,57] The perioperative mortality rate of elective cholecystectomy has been reported to be 1% and the rate of postoperative complications to be more than 30%.[50,54]

Preparation of the patient before surgery and management during and after the operation are essential. Changes in oxygen tension, pH, osmolality, and hydration might trigger the sickling of erythrocytes. Early ambulation and humidified oxygen are essential postoperatively to avoid atelectasis that might lead to sickling within the pulmonary circulation. A conservative transfusion regimen designed to increase the Hb level to 10 g/dL is as effective as an aggressive regimen designed to decrease the Hb S level to less than 30% and with fewer transfusion reactions.[50] Exchange transfusions that avoid the potential for hyperviscosity from overtransfusion are currently the preferred method for increasing the hematocrit level preoperatively.

Rare Complications of Sickle Cell Disease

The abdominal crisis is due to small infarcts of the mesentery and abdominal viscera causing severe abdominal pain, signs of peritoneal irritation, and a plain film often showing a generalized ileus. The clinical picture might be indistinguishable from other acute abdominal diseases.

Acute pancreatitis might develop in the absence of other etiologies, perhaps as a result of microvascular occlusion and ischemic injury. Patients with acute pancreatitis might develop pulmonary symptoms caused by acute chest syndrome or the pancreatitis itself.

Peptic ulcer disease is found in 35% of patients with SCD and epigastric pain.[58] Interestingly, duodenal ulcers are not associated with high acid outputs.[58,59] This suggests that these ulcers might, instead, be due to reduced mucosal resistance, possibly from ischemia.[58]

An uncommon complication is ischemic bowel caused by intravascular sickling, resulting in microvascular occlusion.[60] Sickle cell crisis might represent a shock equivalent causing vascular spasm and ischemic necrosis. One report documented fatal small bowel necrosis with hypotension.[61] The rarity of ischemic bowel in SCD might be due to the extensive collateral circulation in the mesentery and bowel wall. Abdominal pain of presumed vaso-occlusive origin, often termed "girdle syndrome" because of the circumferential distribution of the pain, rarely presents as ischemic colitis.[62]

Pseudomembranous colitis without *Clostridium difficile* has been associated with SCD and treated with exchange transfusions.[63] Abnormal hydrogen breath tests might reflect disordered gastrointestinal motility or abnormalities of intestinal microflora.[64]

Laboratory Diagnosis

Abdominal pain is very common in SCD and is usually due to sickling, which resolves with supportive care. These acute complications often need just clinical examination, basic blood tests, and sometimes an abdominal ultrasound. Any fever should be evaluated, although it might just be due to the vaso-occlusive crisis.

An elevated bilirubin level, mostly unconjugated, is the most common laboratory abnormality. This represents an increased load of erythrocyte breakdown products on an acutely damaged liver.[65] Marked hyperbilirubinemia with only mild elevation of ALT and normal coagulation profiles might occur with minimal to no symptoms.[66] This hyperbilirubinemia resolves spontaneously within weeks. There is some enhancement of bilirubin conjugation in patients with SCD as a result of bilirubin induction of uridine diphosphate–glycuronyltransferase, which is elevated in these patients.[67] Bilirubin and lactate dehydrogenase (LDH) levels correlate with one another, suggesting that chronic hemolysis and ineffective erythropoiesis, rather than liver disease, are the sources of hyperbilirubinemia. There is a correlation between AST and LDH, indicating some contribution of erythrocyte AST from hemolysis to the serum levels of AST.[11] In addition, AST elevation might be partly due to muscle breakdown because there is a concomitant elevation of creatine phosphokinase. Thus, hepatocyte injury is better reflected by an increase in ALT, rather than AST, levels. Alkaline phosphatase level is commonly elevated particularly during pain crises mainly as a result of bone rather than liver isoenzymes.[68] This is further shown by the correlation of serum 5′ nucleotidase elevations with γ-glutamyltransferase, but not with increases in alkaline phosphatase level.[69]

Ferritin levels correlate with liver iron concentrations in some studies[70] but not others.[71–73] Increases in ferritin level during a crisis might be due to inflammation, liver disease, or hemolysis.

Although not frequently ordered, liver spleen scans with technetium (Tc)-99m sulfur colloid might show reduced splenic activity as a result of splenic atrophy[74] or splenic sequestration.[75] Splenic infarction might be seen as total or segmental lack of uptake by the spleen.[43] Although the spleen might not be visible on Tc-99m sulfur colloid scans, it might instead be seen on bone scan because of multiple infarctions and calcifications.[43] In converse, when the spleen is functioning by liver-spleen scan, then it is not seen on bone imaging.[76]

With severe right upper quadrant pain, the Tc-99m diisopropyl–iminodiacetic acid scan might show prolonged nonvisualization of the gallbladder, consistent with acute cholecystitis, or more commonly, delayed visualization consistent with chronic cholecystitis.[77] Demonstration of the gallbladder on hepatobiliary radionuclide scan effectively excludes acute calculous cholecystitis.

Computed tomography (CT) scan might be ordered in patients with unremitting or severe abdominal pain.[78,79] Abnormalities in 17 of 30 patients altered treatment, showing liver or splenic disease or basal pulmonary pathology presenting as abdominal pain.[78] Areas of splenic infarction are seen as low-density lesions.[79] Sequestration syndrome causes hypoechoic appearance on ultrasound and low attenuation on CT scan[6] associated with a dramatic drop in Hb levels. Nonenhanced blood vessels on CT scan of the liver are due to increased hepatic density from hemosiderosis and decreased blood density from anemia.[43]

On magnetic resonance imaging (MRI), liver iron concentration is inversely correlated with T2 values as a result of the

paramagnetic properties of hemosiderin.[70] Iron shortens the T1 and T2 relaxation times, darkening the images.[80] The advantage of MRI compared with liver biopsy is its noninvasiveness and low interstudy variability, making it a good tool for serial evaluation of chelation efficacy and simultaneous measurements of cardiac iron levels, although it is expensive. Although MRI can separate those patients with liver iron levels greater or less than 100 μg/mg of liver, it is unable to differentiate between 100–400 μg/mg.[81] Those with splenomegaly have a hypercellular spleen with hemosiderin and ferritin deposits that decrease the signal intensity. The calcified and fibrotic spleen also has decreased intensity on T1 and T2 weighted images[43] (Figure 1).

Areas of functional spleen might appear hypoechoic on ultrasound and low density on CT scan, giving a picture that could be confused with splenic abscesses.[76] The functional spleen, however, takes up Tc-99m sulfur colloid unlike abscesses. Furthermore, liver abscesses take up gallium or indium 111-labeled white blood cells,[43] unlike areas of functional spleen.

In the pancreas, hemosiderin tends to deposit in the acinar cells rather than in the islet cells.[82] This can cause increased echogenicity. MRI demonstrates a moderate decrease in signal intensity in the pancreas on T1 weighted images and a more marked decrease on T2 weighted images compared with the liver.

Although not usually performed during an acute sickle crisis, a liver biopsy might show prominent aggregations of sickled red cells, Kupffer cell enlargement, and hemosiderosis, perhaps resulting in hypoxia, fibrosis, and repair (Figure 2).[8] In the absence of splenic function, there is an abnormal propensity of the sickled cells to interact with the macrophages, resulting in erythrophagocytosis.[83] However, there is no correlation between the degree of intrahepatic sickling and the transaminase levels. Shrunken hepatocytes or perivenular necrosis, features characteristically seen in ischemic or anoxic livers, are generally not seen in SCD.[83] Ischemic necrosis is found in patients in shock or in postmortem examinations; the latter most likely represents agonal anoxia. Cholestasis is common, sometimes as a result of extrahepatic obstruction, but biliary cirrhosis is rare. The safety of liver biopsies has been questioned, especially in those in acute sickling crisis.[84] Patients with complications from liver biopsy have chronic venous outflow obstruction, marked hepatic sequestration of erythrocytes, and sinusoidal dilatation.

Treatment

Transfusions should be given to correct anemia with Hb below 5 g/dL because Hb S has a low oxygen affinity and achieves good oxygenation despite the anemia.[85] Urgent transfusion is often required for a sudden severe anemia when blood is sequestered in an enlarging spleen or liver or when parvovirus infection causes a transient aplastic crisis. Patients should not be transfused above their baseline Hb level.

Exchange transfusions, in which patients are given blood at the same time as they are venesected, minimize the sludging and vaso-occlusion caused by an increase in blood viscosity from blood with high packed cell volume. The aim is to decrease the percentage of Hb S to below 20%. Exchange transfusions result in a lower iron load and a slower increase in ferritin levels compared with conventional transfusions.[85] They are considered in patients with prolonged, refractory vaso-occlusive crises with a stable baseline Hb. Exchange transfusions can also be used for intrahepatic cholestasis along with fresh frozen plasma to correct any coagulopathy because these interventions can reverse this potentially fatal syndrome.[86] Chronic intrahepatic cholestasis, a rare event, might be treated with regular exchange transfusions.[87] Erythrocytapheresis, which removes sickled cells and older erythrocytes, reduces iron accumulation.[88]

Deferoxamine is an iron-chelating agent that causes excretion of iron in the urine and bile, resulting in decreases in serum ferritin and ALT levels.[37,89] Recently deferasirox and deferiprone have been introduced, with the advantage of oral rather than subcutaneous administration.[89,90]

Hydroxyurea increases Hb F levels, reducing the frequency of pain crises, lowering transfusion requirements, and causing a return of splenic function as determined by liver-spleen scans.[91] It is used in patients with severe complications, usually non-gastroenterological. Bone marrow or peripheral blood progenitor cell transplantation is mainly done when there is a history of a stroke.[92]

Cadaveric and living-related donor liver transplantation has been performed in SC patients with liver failure or cirrhosis.[93,94] Perioperative transfusions were used to keep Hb S levels below 20%–25%. Allogeneic stem cell transplantation can be curative in young patients.[95] In adults, nonmyeloablative allogeneic hematopoietic stem-cell transplantation can reverse the sickle cell phenotype.[96]

Prognosis

Whether hepatic dysfunction can lead to increased mortality is controversial. Although one study showed no increased risk of death related to liver disease, with only 1% of patients developing fulminant hepatic failure,[97] others implicated cirrhosis as a direct cause of death in 11% of patients.[30] A favorable outcome of fulminant liver failure might occur after exchange transfusions.[98]

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Conflicts of interest

The authors disclose no conflicts.