EVIDENCE REPORT

Evidence-Based Management of Sickle Cell Disease

Expert Panel Report, 2014

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The observational studies included more than 220 people and studied approaches such as shunts, aspiration, exchange transfusion, hydroxyurea, hormonal therapy (e.g., stilbestrol, finasteride, and leuprolide), bicalutamide, hydralazine, sildenafil, oxygen, and hyperhydration to treat priapism in men and boys with SCD. Results were limited, reporting variable success.[174-179] Several of the studies highlighted the importance of prompt recognition and initial conservative medical management with analgesics, intravenous fluids, oxygen, and sedation if needed.[180-183]

Red blood cell transfusion therapy was inconsistently associated with improvement in acute priapism.[184-193] In addition, case reports of acute neurological events following exchange transfusion for priapism further limit enthusiasm for routine adoption of this therapy in the absence of proven benefit.[194] Both observational studies and case reports found that a variety of subsequent interventions used to treat symptoms that persist after initial conservative medical management appear to result in detumescence and retained potency. These include penile aspiration,[195,196] corporal irrigation using α-adrenergic agents (e.g., pseudoephedrine, epinephrine, etilefrine),[197-203] and the use of oral agents (e.g., PDE-5 inhibitors, pseudo-ephedrine).[204] Surgical intervention, including shunting, has been utilized most often after more conservative measures fail, with inconsistent benefit.[190,205-209]

In developing recommendations for the care of males with SCD presenting with acute priapism, the expert panel placed great value on preventing pain and future long-term sequelae.

Recommendations

1. For an episode of priapism lasting 4 hours or longer, initiate interventions to include
   - vigorous oral or intravenous hydration and oral or intravenous analgesia (***Strong Recommendation, Low-Quality Evidence***); and
   - consultation with a urologist who can perform further evaluation and intervention for symptoms which do not remit with initial conservative medical management. (***Consensus–Panel Expertise***)
2. Do not use transfusion therapy for immediate treatment of priapism associated with SCD. (***Moderate Recommendation, Low-Quality Evidence***)
3. Consult with a hematologist for possible preoperative transfusion if surgical intervention is required. (***Consensus–Panel Expertise***)

Hepatobiliary Complications

Background

Biliary tract abnormalities are common in people with SCD in general and in those with HbSS in particular. These abnormalities include cholelithiasis, acute cholecystitis, biliary sludge, and acute choledocholithiasis.[210,211] Hemolysis of any etiology results in increased secreted unconjugated bilirubin that tends to precipitate and leads to gallstones and sludge.

Cholelithiasis and Acute Cholecystitis

Ultrasound-identified rates of gallstones in people with SCD increase with age from 12 percent in those aged 2 to 4 years to 43 percent by 15 to 18 years of age.[212,213] In adults with SCD, the prevalence of gallstones can be as high as 70–75 percent.[214-217] Although gallstones are usually asymptomatic, they can be associated with acute infection and inflammation involving the gallbladder, and they may also lead to obstruction of the cystic or bile ducts and acute pancreatitis.

Despite the high prevalence of gallstones in people with SCD, acute cholecystitis occurs in less than 10 percent of children and adults with SCD. It can occur with or without the presence of gallstones and can present as severe colicky pain in the right upper quadrant (RUQ) with abdominal tenderness on physical exam. Fever, leukocytosis, nausea, and vomiting are also usually present. Nonvisualization of the gallbladder by 60 minutes after cholescintigraphy is a common radiographic finding.

Choledocholithiasis

Choledocholithiasis is the presence of gallstones in the common bile duct. Symptoms include dull pain in the RUQ, tender hepatomegaly, and rapidly increasing jaundice. According to a patient survey, choledocholithiasis occurs in less than 5 percent of people with SCD who have asymptomatic gallstones.[218,219] In symptomatic people, the rate of choledocholithiasis is higher, affecting 20 to 60 percent of people with SCD compared to 15 percent of those without SCD.[220,221] Endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy may be required to remove the offending stones.

Acute Hepatic Sequestration

Both acute hepatic sequestration (AHS) and acute intrahepatic cholestasis (AIC) (also called sickle cell hepatopathy) are associated with SCD. Each requires consideration in evaluating acute upper abdominal pain in people with SCD.

AHS is marked by hepatic enlargement compared to baseline without other explanation and a 2 g/dL or greater decline in hemoglobin concentration. Sequestration of red blood cells often develops over a few hours to a few days, and the resultant stretching of the hepatic capsule is usually painful. AHS appears to be uncommon and may be overlooked unless the size of the liver is closely monitored in cases of acute RUQ pain. About two-thirds of people with SCD have mild baseline hepatomegaly, so change in size should be monitored. In AHS, liver function tests are only mildly elevated. Acute hemolysis or other causes of hemoglobin decline should be ruled out. Recurrent episodes may occur.[222-225]

Acute Intrahepatic Cholestasis

AIC is characterized by the sudden onset of RUQ pain, increasing jaundice, a progressively enlarging and exquisitely tender liver, light-colored stools, and extreme hyperbilirubinemia (both conjugated and unconjugated) usually without urobilinogenuria. Thrombocytopenia and coagulation abnormalities may also be present. The clinical picture suggests cholestatic jaundice or choledocholithiasis but without evidence of common duct obstruction or cholangitis. AIC may prove fatal if not recognized and treated promptly.[226-230]

Diagnostic evaluation may reveal exquisite tenderness in the RUQ with a total serum bilirubin level >50 mg/dL, hypoalbuminemia, thrombocytopenia, elevated alkaline phosphatase, variable levels of transaminases, coagulopathy with increased prothrombin time (PT), and partial thromboplastin time (PTT) to values more than twice baseline in the absence of accelerated hemolysis or obstruction of the extrahepatic biliary system.[226-229,231,232]

Key Questions

KQ13. In people with SCD, what is the appropriate management of cholelithiasis and related cholecystitis to resolve symptoms and prevent perioperative complications? What is the most effective treatment strategy for people with SCD presenting with AHS and AIC to reduce mortality and resolve symptoms?

Summary of the Evidence

There were no RCTs that evaluated different management strategies for hepatobiliary complications related to SCD. Twenty-five observational studies and 53 case reports were identified and described various hepatobiliary complications associated with SCD. Overall, the quality of the evidence was low due to the observational nature of the studies and the lack of a control or comparison arm in 80 percent of the studies.

The observational studies included more than 900 people and almost uniformly focused on cholelithiasis or acute cholecystitis. One observational study, which followed people with SCD from birth, found that the incidence of cholelithiasis was 30 percent in people with SCA and 11 percent in people with HbSC.[233] Only 2 percent of the people developed symptoms that required surgical intervention.

In most of the surgical studies, cholecystectomy was shown to be effective and safe in people with SCD and cholelithiasis. When surgically feasible and available, the laparoscopic approach was associated with shorter hospital stay, reduced postoperative pain, and overall lower cost. Other case studies described people with SCD and choledocholithiasis who were treated with both open and endoscopic approaches (i.e., ERCP); however, these data were noncomparative, thus limiting the ability to apply these approaches more generally.[234-236]

The systematic review identified only low-quality literature to guide diagnostic or management approaches for hepatic sequestration or intrahepatic cholestasis. Ahn et al.[222] described 7 people identified in their institution and 37 people from the literature who had SCD and acute hepatopathy (total serum bilirubin concentration >13 mg/dL). Among the 22 severe cases, the mortality rate was 64 percent. Only 2 of 9 people who received exchange transfusion died, whereas 12 of 13 people who did not receive exchange transfusion died. This study likely included people with heterogeneous etiologies of acute liver injury, which limits inference. Other case reports[226-229] described rare cases of AIC and reported favorable results with using total blood exchange by replacing the removed blood with washed sickle-negative blood and fresh frozen plasma. The quality of the evidence in this area is very low.

Recommendations

1. Treat acute cholecystitis in children and adults with SCD with antibiotics and surgical consultation.
   (***Consensus–Panel Expertise***)
2. Treat asymptomatic gallstones with watchful waiting in children and adults with SCD. In those who develop symptoms specific to gallstones, treat with cholecystectomy. The laparoscopic approach is preferred if surgically feasible and available.
   (***Strong Recommendation, Moderate-Quality Evidence***)
3. Consult with a hematologist or sickle cell expert for possible preoperative transfusion if surgical intervention is required.
   (***Consensus–Panel Expertise***)
4. In children and adults with SCD and signs and symptoms of AHS or AIC, provide hydration, rest, close observation, and consult a sickle cell expert for further management.
   (***Consensus–Panel Expertise***)
5. In children and adults with SCD and signs and symptoms of possible AHS or severe AIC, obtain urgent consultation with a sickle cell disease expert for diagnosis confirmation.
   (***Consensus–Panel Expertise***)
6. In children and adults with SCD with confirmed AHS or severe AIC, perform simple or exchange transfusion.
   (Consensus–Panel Expertise)