

The Investigation and Management of Acutely Increased Jaundice in Children with Sickle Cell Disease

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Abstract Page

This guideline is aimed at all children in King's College Hospital with sickle cell disease (SCD) and a history of increased jaundice. The guideline applies to patients with SCD who are currently under the care of the Paediatric Haematology or Hepatology teams. It is mainly aimed at being a tool for the medical team managing these patients, but any member of the multidisciplinary team may find it useful.

Background

In the steady state, the bilirubin level varies widely, from 20 - 150 $\mu\text{mol/l}$. This variation depends on the type of sickle cell disease (bilirubin is typically near-normal in HbSC disease), the rate of haemolysis, the co-inheritance of Gilbert's syndrome and the presence of underlying liver disease. Typically, most of the bilirubin is unconjugated, although conjugated fraction could also be increased. It is important to know the steady-state reading when interpreting bilirubin levels during acute illness. Increases in bilirubin occur during most acute episodes of vaso-occlusion and infection.

Contents of guideline:

- Causes of increased bilirubin level
- Initial assessment
- Examination
- Initial investigations
- Initial management
- Further investigations
- Further specific management of common causes
- Sickle cell intrahepatic cholestasis.
- References



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Jaundice in Children with Sickle Cell Disease

In the steady state, the bilirubin level varies widely, from 20 - 150 $\mu\text{mol/l}$. This variation depends on the type of sickle cell disease (bilirubin is typically near-normal in HbSC disease), the rate of haemolysis, the co-inheritance of Gilbert's syndrome and the presence of underlying liver disease. Typically, most of the bilirubin is unconjugated, although conjugated fraction could also be increased. It is important to know the steady-state reading when interpreting bilirubin levels during acute illness. Increases in bilirubin occur during most acute episodes of vaso-occlusion and infection.

Causes of Increased Bilirubin Levels in Children with Sickle Cell Disease

Common

- Infection or fever
- Acute vaso-occlusion causing increased haemolysis

Less Common

- Cholecystitis
- Gall stones
- Splenic sequestration
- Acute pancreatitis
- Malaria

Rare

- Hepatic sequestration
- Acute viral hepatitis
- Ischaemic cholangiopathy
- G6PD deficiency causing acute haemolysis
- Delayed haemolytic transfusion reaction
- Autoimmune haemolysis
- Sickle cell intrahepatic cholestasis
- Hepatic iron overload
- Other liver disease incidental to SCD

Initial Assessment

If the child is in pain, analgesia should be given according to the Pain Guidelines and the guidelines on the 'Management of Acute Abdominal Pain in Children with Sickle Cell

Disease' should be followed. History should initially focus on identifying the more common diagnoses including:

- How quickly has the jaundice developed or increased?
- Has the urine been dark or the stools pale?
- Was there any pain preceding the development of jaundice?
- Has the child had blood transfusion recently, frequently or ever?
- Is there a history of gall stones or cholecystitis?
- Has there been recent travel abroad or history of malaria?
- Is there a history of splenomegaly or splenic sequestration?
- Is there a history of known viral or autoimmune hepatitis?

Examination

Full examination should be performed and look for:

- Fever
- Scleral jaundice
- Signs of cholecystitis
- Splenomegaly
- Hepatic enlargement or tenderness

Initial Investigations

- FBC, U&E's, reticulocyte count
- Group and save
- CRP
- Liver function tests including ALT, γ GT, alkaline phosphatase, split bilirubin
- LDH
- Serum amylase
- Blood cultures if temperature $>38^{\circ}\text{C}$
- Urine for microscopy and culture
- Pulse oximetry on air
- Stool culture if diarrhoea
- Ultrasound of the liver, bile ducts, gall bladder, pancreas and spleen
- Direct Coomb's test and serum ferritin if there is a history of transfusion

Initial Management

The child's condition should be stabilised and appropriate analgesia given.

- Intravenous fluids should be started according to normal hydration guidelines if the pain is severe, there are no bowel sounds or if there is diarrhoea or vomiting. There is no indication to hyperhydrate.
- If the ultrasound of the abdomen shows gall stones with inflammation of the gall bladder and cholecystitis seems likely, the paediatric hepatologists should be involved at an early stage. Ultrasound evidence of dilated proximal parts of the biliary tree suggests obstruction and requires consideration for ERCP.
- Penicillin V should be continued at the prophylactic dose unless the temperature is $>38^{\circ}\text{C}$ or there are no bowel sounds; in which case intravenous antibiotics should be started:
 - Cefuroxime (if not allergic) 20mg/kg (max 750mg) 8 hourly
- If the patient is taking hydroxyl-urea, it should be continued unless the patient is nil-by-mouth, the blood tests show evidence of toxicity (neutrophils $< 1.0 \times 10^9/\text{L}$,

platelets $< 80 \times 10^9/L$, reticulocytes $< 80 \times 10^9/L$, $\geq 50\%$ increase in serum creatinine, $> 100\%$ increase ALT).

Further Investigations

The following investigations may be appropriate depending on the initial findings:

- Chest X-ray if there is chest pain, hypoxia, or chest signs, or an acute abdomen.
- Ultrasound of kidneys, ureters and urinary bladder if there is haematuria, renal colic or severe lower abdominal pain.
- Parvovirus B19 serology if the reticulocyte count is $< 100 \times 10^9/L$.
- If there is evidence of acute haemolysis, determine G6PD status. In general this will already have been determined and results should be on EPR or in the notes, or available from the Red Cell Laboratory. If there is no record of G6PD status, G6PD Assay should be ordered on EPR.
- If there is acute hepatitis (ALT > 150 IU/ml) request 'Core investigations > 3 years' on EPR which includes INR, ammonia, lactate, alpha-feto protein, caeruloplasmin, zinc, copper, creatinine kinase, lipid profile, hepatitis A, B, E and EBV serology, autoantibodies, immunoglobulins.

Further Specific Management of Common Causes

This will depend on the initial diagnosis. Acute sequestration should be managed according to the appropriate guidelines.

Cholecystitis

- This is usually diagnosed with a combination of typical symptoms and signs, such as fever and right subcostal pain, increased conjugated bilirubin and gallstones with a thickened gall bladder on ultrasound examination.
- The paediatric surgical team should be involved in the care of the patient at an early stage.
- If vomiting is severe a nasogastric tube may be necessary in addition to nil-by-mouth, intravenous fluids and cefuroxime.
- Management is typically conservative.
- Antibiotic therapy usually includes metronidazole and IV ceftriaxone.
- At discharge it should be ensured that the patient has a follow-up appointment with the paediatric hepatologists. Further investigations such as ERCP will be organised by their team.
- After acute biliary obstruction secondary to gall stones, an elective cholecystectomy (often laparoscopic) could be considered depending on surgical aspects and the views of the patient/family.

Acute Hepatitis

- This is suggested by a significant increase in serum ALT (> 150 IU/l and conjugated bilirubin).
- Blood tests should be requested as mentioned above.
- The Paediatric Hepatology team should be contacted at an early stage for advice on management and the child should be discussed with a paediatric haematology consultant.

- If fulminant hepatic failure develops a blood transfusion (exchange or top-up) will usually be appropriate. The child will usually be managed on Rays of Sunshine Ward, HDU or PICU.

Delayed Haemolytic Transfusion Reaction

- Typically (but not always) the DCT will be positive, the LDH and reticulocyte count high, and the haemoglobin low or falling.
- The case should be discussed with the Blood Bank and further samples sent to allow identification of the alloantibody. The blood bank should be warned that further blood transfusion may be necessary and most-compatible units of red cells identified.
- Further blood transfusion should be avoided if possible as it may exacerbate haemolysis. However it is important to transfuse if life-threatening anaemia develops, and transfusion will usually be necessary if the haemoglobin falls below 5g/dl or anaemia is symptomatic. Children with known cerebrovascular disease will usually require a higher minimum haemoglobin.
- If transfusion results in increased haemolysis and only a small increase in haemoglobin, repeat transfusion will be necessary, and it may be helpful to give prednisolone 1mg/kg or intravenous immunoglobulin to cover this.

Autoimmune Haemolysis

- There is an increased incidence of autoimmune haemolysis in children with SCD, particularly if transfusion has been given. In some ways this is similar to delayed haemolytic transfusion reaction, although typically the autoantibody will react with all red cells and so it will be impossible to find a fully compatible unit.
- Immunosuppression should be started with corticosteroids.
- Transfusion should be avoided if possible, but should be given if severe or life-threatening anaemia develops.
- The Blood Bank should be warned of such patients at an early stage, and given as much notice as possible if a blood transfusion is likely to be necessary.

Sickle cell intrahepatic cholestasis

- Benign hyperbilirubinaemia
 - This is a multifactorial condition in which cholestasis typically develops in a child with SCD in the absence of any obstructive or other identifiable cause.
 - Typically the child is well, but serum bilirubin reaches very high levels, of up to 900mmol/L. Other liver function tests are usually not very derailed.
 - If there is isolated hyperbilirubinaemia and the child is well, ursodeoxycholic acid should be started at 10mg/kg bd. Blood tests should be performed daily to monitor for liver failure, with INR and ALT. The child can be discharged once the bilirubin starts to fall.
 - Typically jaundice improves within a week and the problem does not recur.
- Liver failure associated with intrahepatic cholestasis
 - The child is ill with abdominal pain, jaundice, vomiting and hepatomegaly.
 - Blood tests show very high bilirubin levels but only modest increase in transaminases. There is a progressive coagulopathy, and acute liver failure develops.
 - The Paediatric Hepatology team should be informed at an early stage, and typically the patient will be transferred to HDU/PICU for intensive support.

- Liver biopsy is contraindicated during acute sickle cell episode or while developing coagulopathy.
- The haemoglobin should be maintained at 10g/dl with HbS<30%, and this will typically require an exchange blood transfusion unless the starting haemoglobin is very low.
 - Mortality is 20-40%.

References

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