

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

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Introduction

Children with Sickle Cell Disease (SCD) may present with worsening jaundice. The reasons and investigation of this are complex, in part because these children may have abnormal liver function tests and because of the multiple complications associated with (SCD). The child may present with jaundice as their presenting complaint, but more often the child will present with acute pain, sepsis or abdominal pain and the jaundice is an incidental finding. The causes of worsening jaundice and its investigation are outlined below.

Liver Function Tests in Sickle Cell Disease

There is a wide range of variation in bilirubin level between individuals, with levels 20-150 $\mu\text{mol/l}$ in the steady state. The bilirubin level depends on several variables specific to the individual including:

- The type of sickle cell disease eg 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.

It is important to know the steady-state value when interpreting bilirubin levels during acute illness since increases in bilirubin occur during most acute episodes of vaso-occlusion and infection, and if it is elevated the total and conjugated fractions should be checked. The bilirubin is most commonly unconjugated although the conjugated fraction may also be increased.

The AST and LDH are usually elevated in the steady state due to background haemolysis, since both enzymes are red cell- and liver- derived, and so are not specific for the liver, whereas the ALT is exclusive to the liver and is more useful in detecting acute liver impairment. A raised ALT in the steady state may be an indication of liver disease and should be monitored.

Alkaline phosphatase is not a good marker of liver/biliary disease in children since it varies with growth, and the gGT is more sensitive and specific for biliary obstruction due to stones, bile duct injury or cholangiopathy.

Monitoring for liver disease should be performed routinely in SCD patients although there are very few evidence based recommendations.

Causes of Increased Bilirubin Levels above baseline in Children with Sickle Cell Disease (above normal steady state)

Common

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

Less Common

- Cholecystitis
- Gall stones
- Splenic sequestration

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- Acute pancreatitis
- Malaria

Rare

- Hepatic sequestration
- Acute viral hepatitis
- Ischaemic cholangiopathy
- G6PD deficiency causing acute haemolysis
- Delayed haemolytic transfusion reaction
- Autoimmune haemolysis
- Intrahepatic cholestasis secondary to SCD
- 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.

Specific points in the history relevant to the jaundice should initially focus on identifying the more common diagnoses including:

- Speed of onset of the appearance or increase in jaundice
- Colour of the urine and stools (dark urine or pale stools)
- Associated pain preceding the onset of jaundice
- Any recent blood transfusion
- History of gall stones or cholecystitis?
- Any recent travel abroad or history of malaria
- History of splenomegaly or splenic sequestration
- History of known viral or autoimmune hepatitis
- Known G6PD deficiency and contact with a known precipitant of haemolysis

Examination

Full examination should be performed and look for:

- Fever
- Scleral jaundice
- Signs of cholecystitis - abdominal tenderness, presence or absence of bowel sounds
- Splenomegaly
- Hepatic enlargement or tenderness
- Pulse oximetry in air

Initial Investigations

- FBC, reticulocyte count and blood film (e.g. red cell fragments, bite cells, spherocytes)

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- Blood Group & Antibody Screen
- Direct Anti-globulin Test (DAT) if there is a history of recent transfusion
- Haemoglobinopathy screen if recent transfusion (HbA, HbS, HbF%)
- CRP and lactate
- U&E and creatinine,
- Liver function tests including ALT, γ GT, alkaline phosphatase, split bilirubin
- LDH
- Serum amylase and lipase, bone profile
- Blood cultures if temperature $> 38^{\circ}\text{C}$
- Urine for MC&S
- Stool culture if diarrhoea
- Malaria screen if recent travel to malarial area
- Abdominal Ultrasound: liver, biliary tree, gall bladder, pancreas and spleen

Initial General Management

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. Fever should be managed appropriately

- Maintenance intravenous fluids should be started if oral fluid intake is inadequate, if there are no bowel sounds or if there is diarrhoea or vomiting. Avoid fluid overload.
- In the absence of fever Penicillin V prophylaxis should be continued
- If fever $> 38^{\circ}\text{C}$ or there are no bowel sounds intravenous antibiotics should be started:
 - As per your local anti-microbial policy e.g. Cefuroxime (if not allergic) 20mg/kg (max 750mg) 8 hourly unless the child is septic and unwell – consider starting Tazocin and Gentamicin and adjust antibiotics according to blood culture results. If the patient has a known allergy to penicillin please liaise with your local microbiology team and consider alternatives such as Ciprofloxacin (4mg/kg 12 hourly intravenously) and gentamicin.
- If the patient is taking hydroxycarbamide 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 $< 80 \times 10^9/\text{L}$, reticulocytes $< 80 \times 10^9/\text{L}$, $\geq 50\%$ increase in serum creatinine, $> 100\%$ increase ALT).
- If there is abdominal pain and the child is immobile in bed – start incentive spirometry and maintain oxygen saturations – be vigilant for onset of acute chest syndrome.
- Chest X-ray if there is chest pain, hypoxia, chest signs, or an acute abdomen.

Consider further investigations according to clinical picture

- 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 $< 100 \times 10^9/\text{L}$.

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- If there is evidence of acute haemolysis, check G6PD activity. G6PD status is usually already known and results should be available from initial testing in the notes, or from the Red Cell Laboratory - if there is no previous record a G6PD Assay should be ordered on EPR.
- Biochemical evidence of acute hepatitis (ALT > 110 IU/ml or more than twice normal) and request INR, ammonia, lactate, alpha-feto protein, caeruloplasmin, zinc, copper, creatinine kinase, lipid profile, viral serology (Hepatitis A-E, CMV 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.
- If the ultrasound of the abdomen shows gall stones with inflammation of the gall bladder and cholecystitis seems likely, the paediatric surgeons should be involved at an early stage.
- If there is Ultrasound evidence of dilated proximal parts of the biliary tree suggestive of obstruction, discuss with the paediatric hepatologists - ERCP may be indicated.
- If vomiting, a nasogastric tube may be necessary in addition to nil-by-mouth, intravenous fluids and antibiotics (cefuroxime). If the child is septic then consider broadening the cover to Tazocin and Gentamicin (or local antibiotic protocol).
- Management is typically conservative during the acute episode.
- At discharge it should be ensured that the patient has a follow-up appointment with the paediatric hepatologists. Further investigations such as MRCP or ERCP will be organised by their team.
- Following an episode of acute biliary obstruction secondary to gall stones, an elective cholecystectomy is usually discussed with the patient/family by the surgical team, including different surgical approaches (laparoscopic vs open operation).
- Incentive spirometry and analgesia maintain oxygen saturations to reduce the risk of associated acute chest syndrome.

Acute Hepatitis

- This is suggested by a significant increase in serum ALT to > twice upper limit of normal and raised conjugated bilirubin.
- Viral, autoimmune and inherited causes should be tested for as above with monitoring of INR.
- The Paediatric Hepatology team at Kings College should be contacted at an early stage for advice on management and the child should be discussed with a paediatric haematology consultant.

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

Delayed Haemolytic Transfusion Reaction

- Typically (but not always) the DAT will be positive, with a high LDH and reticulocyte count, and low or falling haemoglobin.
- Discuss with the Blood Transfusion lab and send further EDTA cross match samples to allow for identification of an alloantibody. The transfusion lab should be warned that further blood transfusion may be necessary and the 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 severe or life-threatening anaemia develops, and transfusion will usually be necessary if the haemoglobin falls below 50g/l or anaemia is symptomatic. Children with known cerebrovascular disease usually need a higher minimum haemoglobin to reduce the risk of cerebral ischaemia.
- 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 methylprednisolone 1mg/kg or intravenous immunoglobulin to cover this (see Hyperhaemolysis guideline).

Autoimmune Haemolysis

- There is an increased incidence of autoimmune haemolytic anaemia in children with SCD, particularly if they have been transfused. This is similar to a delayed haemolytic transfusion reaction, although typically the autoantibody reacts with all red cells (pan-reactive) and it is not possible to obtain fully compatible blood units for transfusion. The DAT may be positive.
- 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 Transfusion Lab should be alerted to such patients at an early stage, and given as much notice as possible if a blood transfusion is likely to be necessary.

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, up to 900umol/L, and the other liver function tests typically not markedly different from steady state.
 - In isolated hyperbilirubinaemia, if the child is well, ursodeoxycholic acid should be started at 10mg/kg bd orally. Daily blood tests including LFTs, ALT and INR should be monitored for signs of liver failure; the child can be discharged once the bilirubin is falling.
 - Typically, the jaundice improves within a week and the problem does not recur.

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- Liver failure associated with intrahepatic cholestasis
 - The child is ill with abdominal pain, jaundice, vomiting and hepatomegaly.
 - Blood tests show very high bilirubin levels and only a modest increase in AST and ALT. There is a progressive coagulopathy, and development of acute liver failure.
 - The Paediatric Hepatology team at Kings College Hospital (KCH) should be contacted at an early stage, and typically the patient will be transferred to HDU/PICU at KCH for intensive support. Please also contact the Paediatric Haematology team at King's to inform them of the patient's planned transfer.
 - The haemoglobin should be maintained at 100g/l with HbS <30%, and this will usually require urgent exchange blood transfusion unless the starting haemoglobin is very low.
 - Mortality is 20-40%.

Chronic Liver Disease in Sickle Cell Disease

Children with progressive changes in their steady state LFTs, including persistently abnormal LFTs - ALT, gGT, albumin, bilirubin (including conjugated bilirubin) should be investigated further (imaging, the panel of investigations including for viral hepatitis, autoimmune liver disease and obstructive cholangiopathy), and discussed with the Paediatric Hepatology Team at King's.

King's Paediatric Hepatology on-call SpR 09.00-17.00 Switchboard 020 3299 9000 bleep 491 or Extension 37812, 17.00-09.00 or weekends and Bank Holidays Phone 07866-792368

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Additional contacts can be found on the STSTN website (www.ststn.co.uk)

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