# Sickle cell disease

PAEDIATRICS

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# What I will cover

- **How sickle cell disease is diagnosed in children**
  - Newborn screening
  - Diagnosis after birth in late presentation

- **Early management of sickle cell disease in children**
  - Prophylactic medication and vaccinations
  - Treatment
  - Monitoring

- **Early childhood complications of sickle cell disease**
  - Dactylitis
  - Splenic sequestration
  - Aplastic crisis

# Sickle cell disease

## DIAGNOSIS

# Diagnosis in newborns

## Newborn screening

Screening for haemoglobinopathies through the newborn heel prick test has occurred in the UK since 2006

## Test type

Southmead use capillary electrophoresis first, then use isoelectric focussing to confirm diagnosis. HPLC can also be used.

## What is detected?

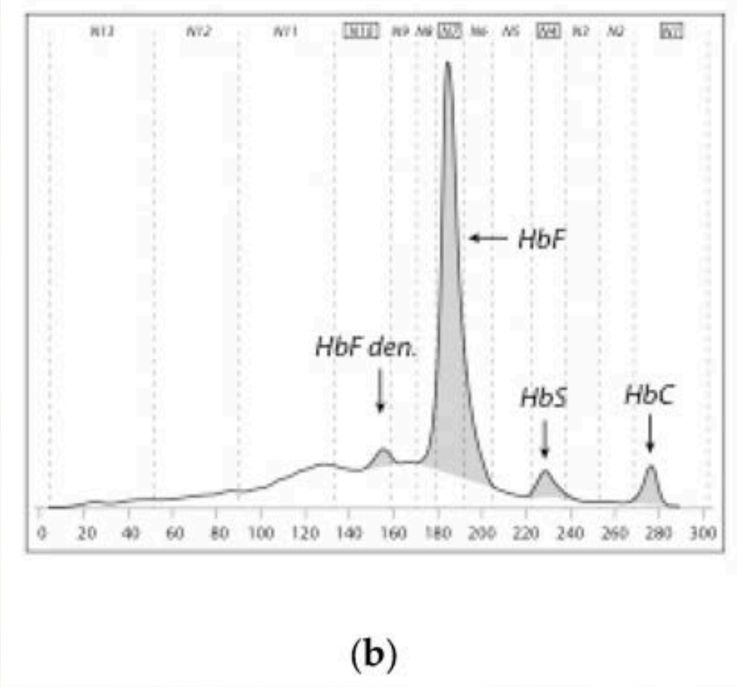
A diagnosis of sickle cell disease is made when there is no HbA, but instead a sickling haemoglobin along with HbF.

HbF is present in high quantities after birth (around 80% of total haemoglobin), and reduces to adult levels (normal is <2%) by 9-12 months.

**BCL11A** downregulates HbF production after birth, and instead promotes beta chain synthesis to make HbA.

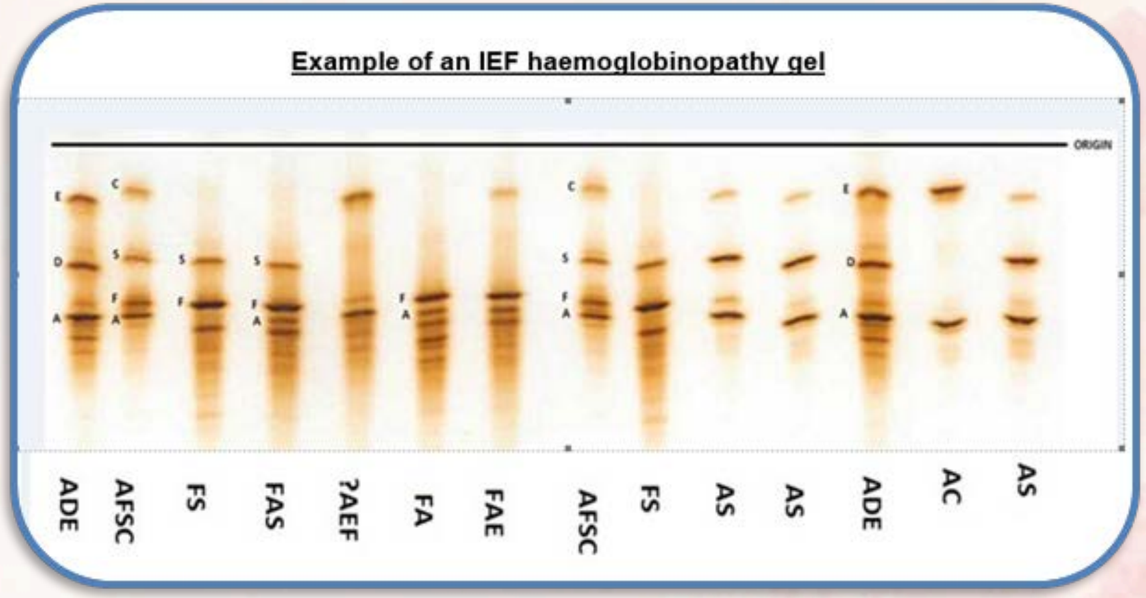
# Sickle screening

Two positive tests are required to confirm a diagnosis.




Capillary electrophoresis - pherogram showing HbSC

*Image from International Journal of Neonatal Screening*




Gel electrophoresis (isoelectric focussing)

*Image from NBT website*

# Diagnosis in later childhood

Chronic anaemia of uncertain cause - picked up routinely

Sepsis

Acute anaemia - aplastic crisis

**Possible first presentations may include...**

Jaundice

Painful crisis

Abdominal pain and swelling (splenic sequestration)

Stroke

# Diagnosis in later childhood

## Screening

High performance liquid chromatography is first line, with a confirmatory test to follow if abnormal haemoglobin detected.

| Peak Name | Calibrated Area % | Area % | Retention Time (min) | Peak Area |
|---|---|---|---|---|
| P1 | --- | 0.0 | 0.72 | 1027 |
| F | 10.9* | --- | 1.07 | 257544 |
| P3 | --- | 0.1 | 1.53 | 1276 |
| Unknown | --- | 0.9 | 2.10 | 21177 |
| Ao | --- | 2.1 | 2.25 | 49920 |
| A2 | 4.1* | --- | 3.61 | 105865 |
| S-window | --- | 81.9 | 4.35 | 1971613 |

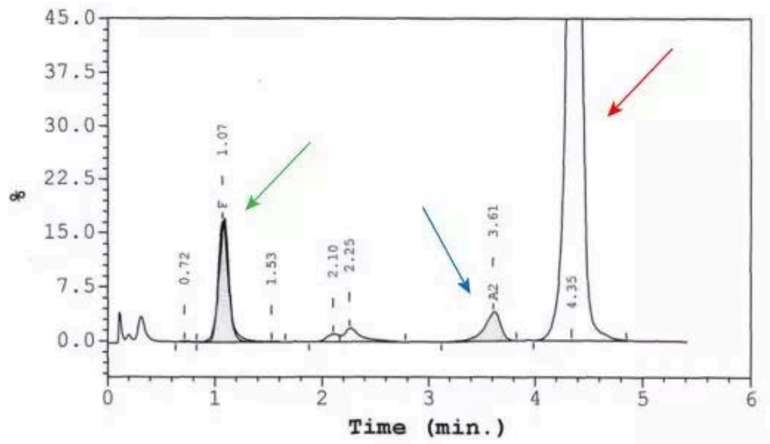
Total Area: 2,408,421



**F Concentration = 10.9* %**
**A2 Concentration = 4.1* %**

*Values outside of expected ranges

Analysis comments:




Patients with sickle cell disease often have higher than normal HbF levels, but if very high (>20%) after 1 year of age and the patient is not on hydroxycarbamide, consider genetic testing for possible hereditary persistence of fetal haemoglobin (HPFH).

HPFH may lead to a milder disease phenotype.

# Sickle cell disease

## MANAGEMENT

# First appointment in clinic

- Full personal and family history, including details of siblings and their status
  - Parents and all siblings should have FBC and HPLC if not previously documented
- Initiate lifelong **prophylaxis** with:
  - Penicillin V - due to asplenia
  - Folic acid - due to chronic haemolysis
- Discuss **immunisations** as per The Green Book (see next slide)
- Start **growth chart** (risk of faltering growth)
- Check **bloods** - baseline FBC, reticulocytes, renal and liver function, G6PD screen
- Repeat the patient's **HPLC** at 1 year of age - Hb should be stable and HbF% should be at adult level

# Immunisations

Children should receive all routine vaccinations as per national schedule.

Additional vaccines include:

- MenACWY and Meningitis B
- Pneumococcal vaccination - an additional dose in childhood, then 5 yearly boosters lifelong
- Lifelong influenza vaccination

Why do they need all of this?

**Box 7.1 Practical schedule for immunising individuals with asplenia, splenic dysfunction or complement disorders***

*Note: Since these vaccines do not protect against all strains, antibiotic prophylaxis should also be strongly considered*

**First diagnosed or presenting under 1 year of age**

Children should be fully immunised according to the national schedule, and should also receive:

- two doses of MenACWY vaccine at least 4 weeks apart during their first year
- an additional priming dose of PCV13, such as to receive a total of two priming doses of PCV13 with an 8-week interval in their first year
- a booster dose of MenACWY conjugate vaccine 8 weeks after the vaccinations scheduled at one year of age
- an additional booster dose of PCV13, to be administered at least 8 weeks after the routine PCV13 booster scheduled at 1 year of age, and
- one dose of PPV23 after the second birthday[¥] and at least 8 weeks after the last dose of PCV13

**First diagnosed or presenting at 1 year to under 2 years of age**

If not yet administered, give the routine vaccines due at 1 year of age: Hib/MenC, PCV13, MMR and MenB vaccines, plus:

- one dose of MenACWY conjugate vaccine at least 8 weeks after the vaccines scheduled at 1 year of age
- an additional booster dose of PCV13, to be administered at least 8 weeks after the routine PCV13 booster scheduled at 1 year of age, and
- one dose of PPV23[¥] after the second birthday

**First diagnosed or presenting from two years to under ten years of age**

Ensure children are immunised according to the national schedule, and they should also receive:

- one dose of MenACWY conjugate vaccine and
- one dose of PPV23[¥]
- If they have not received the routine 2+1 schedule for MenB, ensure they have received two doses of MenB 8 weeks apart since first birthday
- If they have not received any PCV previously, they should receive a dose of this first followed by the dose of PPV23 at least 8 weeks later

**First diagnosed at age ten years onwards**

Older children and adults, regardless of previous vaccination, should receive:

- one dose of PPV23[¥], MenB and MenACWY conjugate vaccine
- an additional MenB vaccine dose 4 weeks later

**All patients aged over 6 months**

Annual influenza vaccine each season (see Chapter 19)

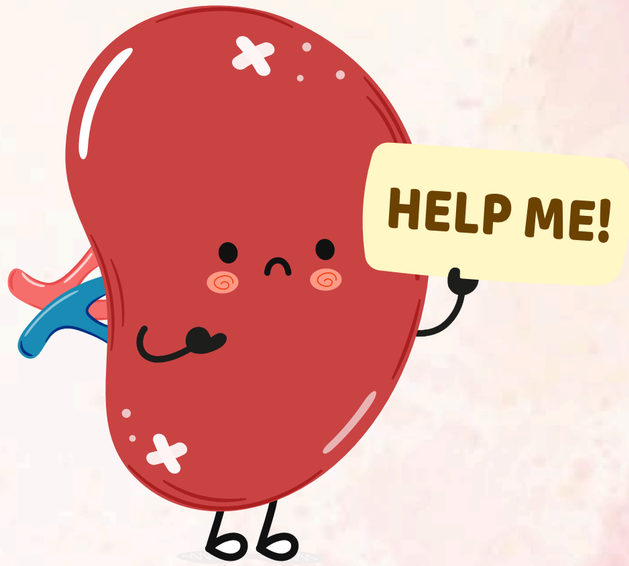
* Patients on complement inhibitor therapy (Eculizumab or Soliris®) are not at increased risk of pneumococcal disease and do not require PPV23 or additional doses of PCV13 (see Chapter 25).

[¥] Patients with asplenia and splenic dysfunction should receive boosters of PPV23 at five yearly intervals.

# Splenic function in sickle cell

**Splenic function is abnormal from infancy onwards.**

- Once haemoglobin starts to switch from HbF to HbS, sickling ensues in the spleen
- Ongoing sickling leads to ischaemia, progressive fibrosis and eventually autosplenectomy
- Radiological asplenia is not universal. Some patients have splenomegaly and hypersplenism, but patients are still functionally asplenic.




Some patients will have acute episodes of red cell trapping in the spleen called **splenic sequestration**. Will be covered in more detail in following slides.

# Monitoring - stroke risk

Stroke is common in children with sickle cell disease - children with SCD are **333 times more likely** to experience a stroke than their peers.

Ischaemic stroke is most common in childhood. The risk switches to haemorrhagic stroke in early adulthood, largely due to the development of small fragile collaterals (Moya moya disease)

Transcranial dopplers (TCDs) are routinely performed during annual review from age 2 onwards. This can detect early risk of stroke by identifying those with turbulent blood flow within their cerebral circulation.

Patients with abnormal TCDs may be offered chronic transfusion therapy to reduce the risk of stroke.

# Treatment options

## Hydroxycarbamide

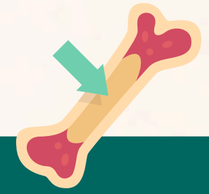
**BABYHUG** trial (2012) showed a reduction in acute complications and demonstrated safety in children from age 9 months.

Hydroxycarbamide is now offered to all children with HbSS/HbS Beta zero thalassaemia from age 9 months.


## Transfusion

Top up transfusions are used more commonly than red cell exchange in children.

The **STOP** trial showed benefit in chronic transfusion for patients with abnormal TCDs.



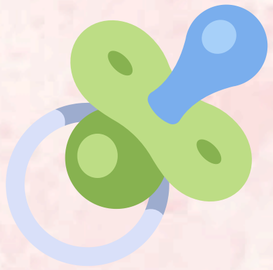
## Stem cell transplant and gene therapy

Patients over the age of 2 with a severe disease phenotype are eligible for **stem cell transplant** if they have a matched sibling donor.

**Gene therapy** is available for patients with no sibling donor over the age of 12 with frequent painful crisis. (**CLIMB** study)

# Sickle cell disease

## ACUTE COMPLICATIONS (PAEDS SPECIFIC)



# Dactylitis


## Who gets it?

Very young children - usually under the age of 2 years - are at risk of dactylitis.

## Why does it happen?

Sickling occurs as cells pass through the small vessels of the fingers, causing swelling and pain.

## How is it managed?

Management is conservative, with fluids and analgesia.

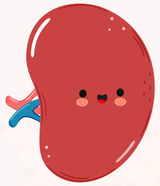
# Splenic sequestration

**Sickling causes red cell trapping in the spleen. This leads to rapidly developing splenomegaly and apparent acute anaemia**

Abdominal pain and a palpable spleen are the most common symptoms. Can present as shock/circulatory collapse given the reduction in circulating volume

Check reticulocyte count - would expect this to be raised


Cautious transfusion to steady state haemoglobin - **AVOID OVER-TRANSFUSION**



Monitor spleen size during inpatient stay - will normally improve quickly with appropriate management

# Aplastic crisis - parvovirus B19

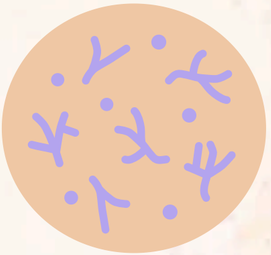
Fever

Respiratory symptoms

Headache

Classic ‘slapped cheek’ syndrome is uncommon

Check the **reticulocyte count**!



| | | | | |
|---|---|---|---|---|
| **RBC** | * | 0.53 | $10^{12}$/L | 3.90 - 5.30 |
| **Haemoglobin** | * | 14 | g/L | 115 - 140 |
| **Haematocrit** | * | 0.048 | L/L | 0.34 - 0.40 |

**Reticulocyte count**

| | |
|---|---|
| On admission: | 30 |
| Baseline: | *257 |

Management - transfusion to baseline haemoglobin

# Thank you!

ANY QUESTIONS?