Don't Forget The Bubbles

SICKLE CELL DISEASE

Facilitators Guide

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Topic: **Sickle Cell Disease**
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Duration: **up to 2 hours**
Facilitator level **ST4+**
Learners level **Most useful for those in experience seeing paediatric patients regularly; From FY1, and 5, nurses on.**
Equipment required: **None**

OUTLINE

- Basics (10 Minutes)
- Main session (2x 20 Minutes) case discussions covering the key points and evidence
- Advanced session (2 x 30 Minutes) case discussions covering grey areas, diagnostic dilemmas, advanced management and escalation
- Quiz questions (10 Minutes)
- Infographic sharing (5 Minutes): 5 take home learning points

PRE-READING FOR LEARNERS

To prepare for this session, learners could read:

https://www.stemlynsblog.org/nice-faces-the-sickle/

https://first10em.com/acute-chest-syndrome-sickle-cell-disease/

https://pedemmorsels.com/sickle-cell-disease-fever/

https://emergencymedicinecases.com/video/sickle-cell-disease/

For more information, this is a link http://sickleoptions.org/en_US/video-library/
It has many useful videos for patients and doctors about sickle cell disease, management and communication scenarios.

BASICS

Sickle cell disease (SCD) is the most common type of haemoglobinopathy followed by thalassaemia. SCD is an inherited blood disorder in which the haemoglobin does not form correctly resulting in an abnormal shape of the erythrocyte. Being a genetic, autosomal recessive disorder, the homozygote genotypes correlate to the most severe forms of the disease while heterozygotes are carriers/asymptomatic.

Sickle cell patients have more than 50% of haemoglobin S instead of the normal haemoglobin A (HbAA). Heterozygote patients with only one mutated gene are carriers (sickle cell trait) with **HbSA while patients with homozygote mutation have sickle cell anaemia (SCA) with HbSS.**

The sickle cell mutation was generated in Africa and Asia. The sickle cell trait provides a resistance against malaria (plasmodium falciparum) giving people a better chance to survive. In sub-Saharan Africa, the prevalence of sickle cell trait ranges between 10-45%. Caribbean, African, Middle East, India and Mediterranean ethnicities are the most affected.

Clinical presentation usually begins after the first year of life, when fetal haemoglobin (HbF) decreases in favour of HbA. Patients with SCA (HbSS) usually become symptomatic at this point. See this helpful summary article for more info.

To understand the clinical features of sickle cell disease, we need to understand the pathophysiology:

Patients have a genetic mutation resulting in haemoglobin S. The red blood cell shape changes when deoxygenation occurs: HbS polymerizes and stretches the normal flexible biconcave shape into an elongated rigid form (sickle shape). Sickle-shape cells, being less flexible, get stuck in small blood vessels causing vaso-occlusive disease, leading to local **ischaemia and acute inflammation.**

When re-oxygenation occurs, HbS polymers break and the erythrocyte's shape rapidly reverses into normal biconcave shape. This process of sickling and unsickling goes on and off until the erythrocyte membrane is no longer flexible.

Irreversible sickle cells undergo either intravascular haemolysis or extravascular removal by the reticulo-endothelial system resulting in **anaemia and splenic sequestration.** In addition, free haem and haemoglobin contribute to the **vascular damage.**

SCD, therefore, is not only a mechanical disease but there are also many other cellular and plasma factors as well as endothelial interaction that generate **chronic inflammation.**

There is a complex interaction between blood cells (not only red blood cells), endothelium and plasma factor which results in acute tissue hypoxia, chronic inflammation and endothelial vasculopathy.

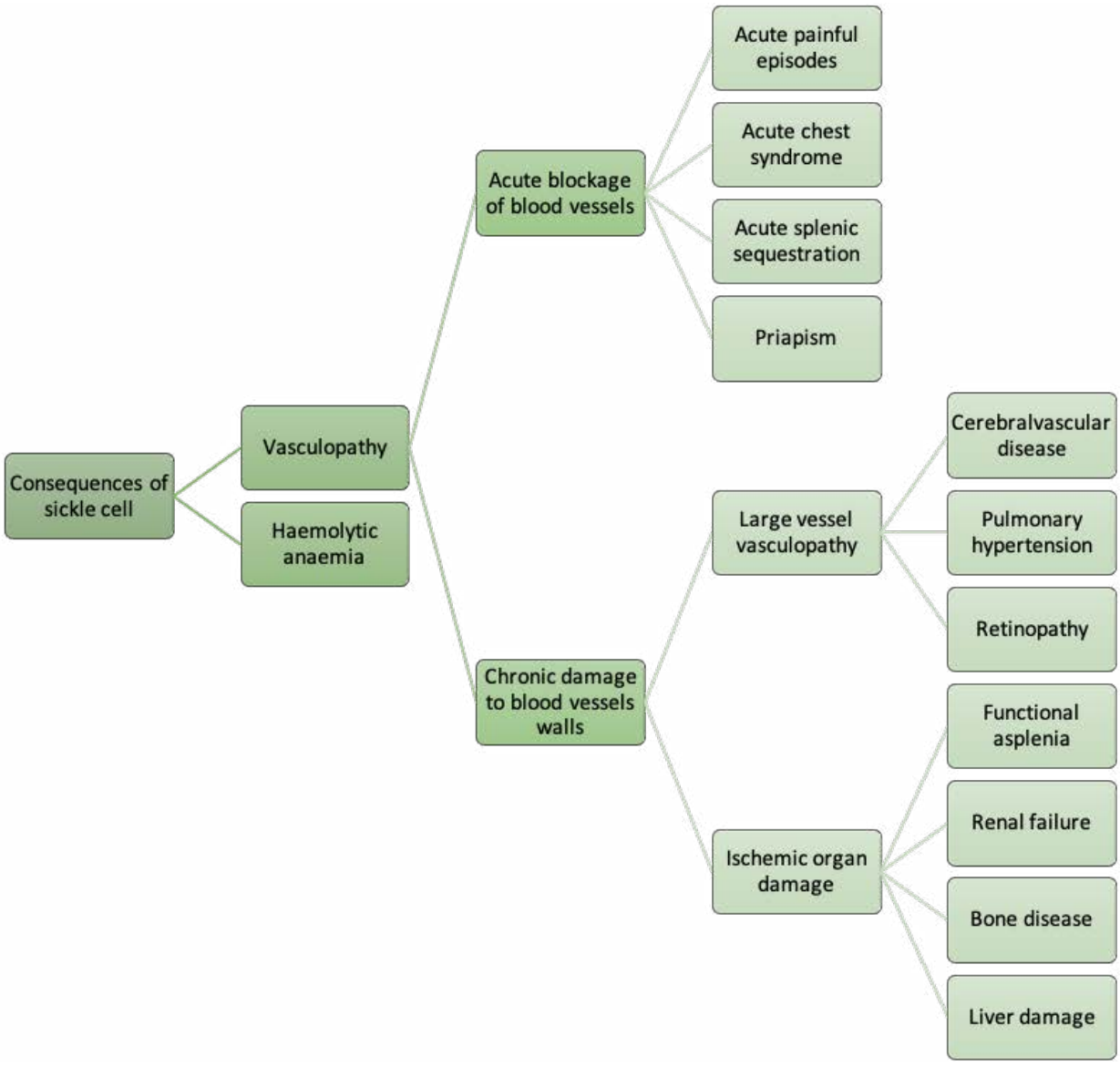
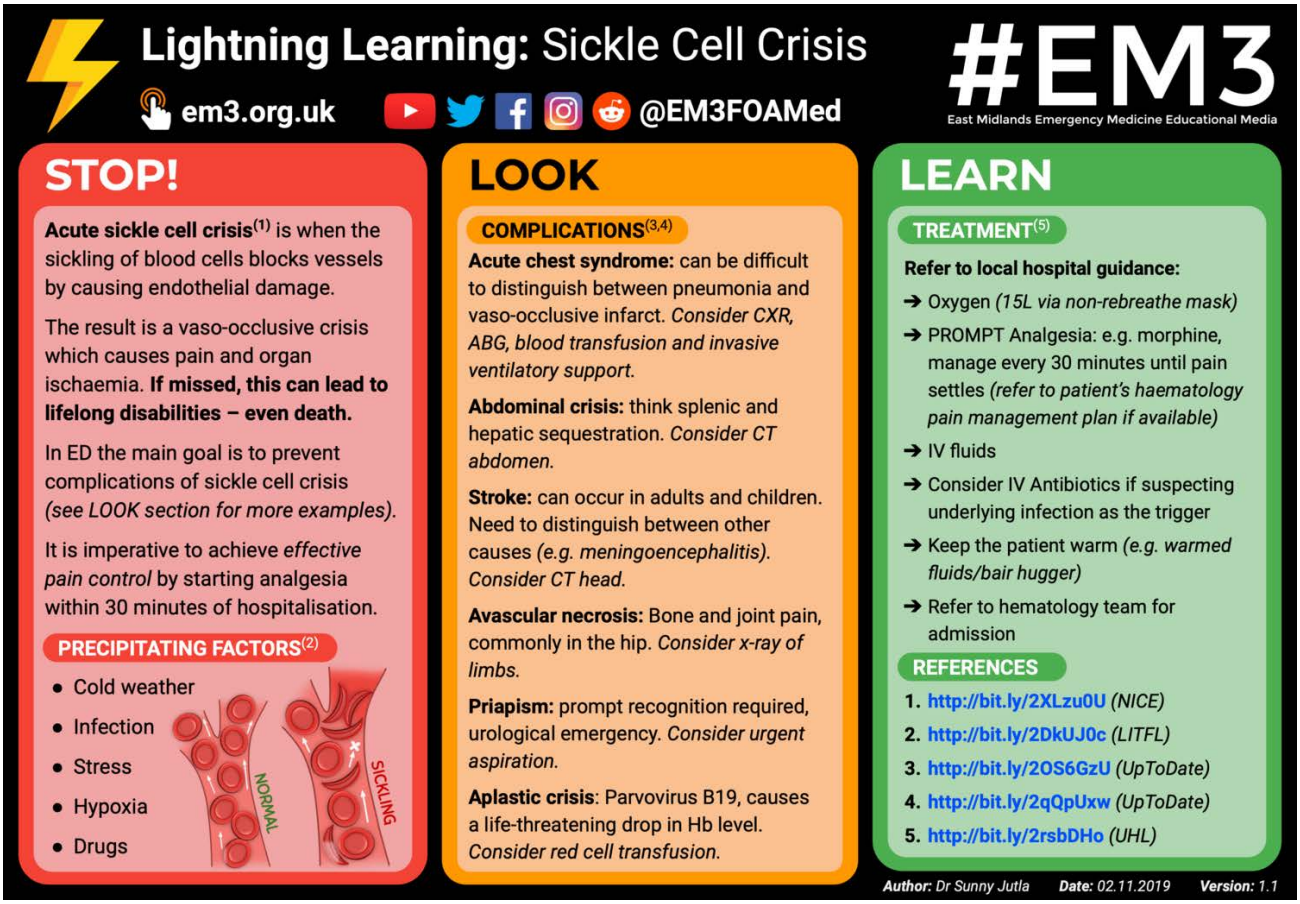


Figure 1 Clinical manifestations and long-term consequences of sickle cell disease

TRAINING AND EDUCATION ON SICKLE CELL DISEASE

Training and education are crucial to improve morbidity and mortality.
Since the pathophysiology is quite complex, clinicians should be vigilant and mindful of all the possible clinical manifestations. Haematology specialist clinics are key to manage the chronic side of the disease, while ED doctors should be able to act rapidly on the common acute emergencies.

Furthermore, educating both patients and their families is important in order to achieve good treatment compliance and better clinical outcomes.
Without medical intervention, sickle cell patients have a reduced life expectancy (about 50-80% of sickle cell patients in low income countries die within the first five years of life) while in high income countries 98% of SCD patients will reach their 18th birthday.



From EM3.org.uk with thanks

MAIN SESSION

CASE 1 (20 MINUTES): SALMONELLA OSTEOMYELITIS

A 15-month-old Kenyan boy presents to ED with right hand swelling.
He had a temperature of 38.5°C and was crying inconsolably.
His mother says that hand swelling episodes may have happened before when he was living with grandparents in Kenya. The patient was born in Mombasa, and his mother moved to the UK six months ago, while he remained with his grandparents until recently when he arrived in the UK.

On clinical examination, he has marked swelling over the proximal right ring finger plus diffuse swelling and erythema over the dorsum of the hand.

Investigations:
Bloods show Hb of 8 g/L, White cell count 13x109/L, Platelets 570 x109/L, CRP 35mg/L.
Blood film shows sickle cells and a further sample was sent for confirmation of diagnosis.
Blood culture is pending.
XR shows a patchy area of lucency with periostitis and soft tissue swelling of metacarpals or metatarsals region. (see a good x-ray example of osteomyelitis **here)**

The patient was started on intravenous antibiotics (ceftriaxone 50mg/kg OD) and was taken to theatre for exploration. In theatre, the patient was noted to have purulent fluid within the subperiosteal space of the right fourth proximal phalanx. Fluid culture yielded growth of non-typhoidal Salmonella enterica.

1. Why is it important to know whether this child has sickle cell disease? What key elements from history taking would support the diagnosis of sickle cell disease?

It is very important to know whether our patient has sickle cell or not since this would make them a high-risk patient that needs specific acute (and chronic) management. Clinicians should think about the possibility of SCD given the

ethnicity (Sub-Saharan Africa) and the presenting symptoms suggestive of dactylitis. Furthermore, the patient was born outside the UK, therefore he missed the routine newborn screening process.

Newborn screening is the best way to identify children with SCA but this can be quite challenging in Sub-Saharan Africa for logistical reasons. The majority of low-income countries lack systematic newborn screening.

Studies have been conducted to create algorithms to identify those who need to be tested for sickle cells. The Kilifi algorithm includes five clinical situations that are common sickle cell presentations - clinical jaundice, severe anaemia, bone and joint infections, and stroke.

Key history taking for Sickle Cell disease	
Ethnicity	Patients from the Caribbean, African, Middle East, India and Mediterranean regions
Family history	Do parents know if they are sickle cell carriers? Any family members with SCD? Any previous sibling death <5 years?
Pregnancy history	Mothers with sickle cell anaemia are more likely to have anaemia and strokes during pregnancy. This can also affect the foetus.
Birth history	Was the child born in the UK? If the child was not born in the UK, he might not have had the newborn screening for SCD.
Past medical history	Previous history of acute pain Dactylitis Serious infections (meningitis, sepsis, osteomyelitis and arthritis) Previous anaemia Previous blood transfusion

2. How is sickle cell disease diagnosed?

Newborn screening: sickle cell screening is done through heel-prick blood at five days of life. It has been routine practice in the UK since 2006.

Newborn screening improves the care and health of sickle cell patients by:
- referring patients early to specialist clinics
- providing early antibiotic prophylaxis
- providing adequate immunisations to prevent severe bacterial infections
- monitoring for acute and chronic complications and being able to start medications early to prevent complications.

Blood film: Some sickle cell patients may have not had any screening if they were not born in the UK. Clinical suspicion based on ethnicity should prompt adequate investigations to yield the diagnosis. Sickle cells can be seen in the blood film from the first year of life. Other associated signs can be anaemia and high reticulocyte count.

Haemoglobin electrophoresis: To reach a definitive diagnosis, Hb electrophoresis is used. This is a laboratory technique to separate normal haemoglobin from abnormal haemoglobin. Be careful if the patient has received a recent blood transfusion since it may be misinterpreted as sickle cell trait instead of sickle cell disease. In these cases, repeat the Hb electrophoresis three months after the last blood transfusion.

Afro-Caribbean patients should be screened for sickle cell before anaesthesia for possible pre-operative transfusion.

3. What could be the differential diagnosis?

The patient was diagnosed with Salmonella osteomyelitis. Overall, Staphylococcus aureus is the most common causative agent of osteomyelitis in children. However, the ratio of Salmonella to S. aureus for osteomyelitis in the sickle cell population is higher (2.2:1).

When a patient is diagnosed with Salmonella osteomyelitis, investigations for sickle cell disease should be carried out. The reason why Salmonella osteomyelitis is so common in sickle cell patients is still unclear but probably the Salmonella bacteria enters the blood-stream via micro-infarction of the gut as a result of impaired intestinal microcirculation. Infarcted areas of bone tissue can be infected with Salmonella resulting in osteomyelitis.

The other possible differential diagnosis in this case could be dactylitis due to vaso-occlusive episodes resulting in an acute painful crisis. Vaso-occlusion happens when the sickled red cells limit the microcirculation of various organs. Bones are the most common place for vaso-occlusion because the bone marrow is hypercellular and susceptible to reduced blood flow and regional hypoxia resulting in infarction.

Clinically, vaso-occlusive episodes present with localised swelling, tenderness and erythema of a region. In older children, long bones are more affected while in younger children small bones of the hands and feet are affected.

Dactylitis is far more common than osteomyelitis. However, these two entities are difficult to discern clinically and can coexist.

TIMELINE OF CLINICAL SYMPTOMS IN SICKLE CELL DISEASE:

Infancy	Younger Children	Older children
(HbF is protective until 6 months of age)	• Infections from encapsulated organisms • Parvovirus crisis • Vaso-occlusive crises in long bones • Acute chest syndrome • Stroke	• Vaso-occlusive crises • Avascular necrosis • Stroke
• Dactylitis • Splenic sequestration • Pneumococcal sepsis		

4. Why are sickle cell patients more susceptible to severe infections?

Sickle cell patients are more susceptible to severe bloodstream bacterial infections due to lack of opsonisation by antibodies or complement to remove circulating bacteria. This phenomenon is called functional asplenia.

In patients with sickle cell anaemia, functional asplenia develops at 1 year of age. After 6-8 years, anatomical asplenia occurs due to repeated spleen infarctions. Later on, some sickle cell patients would need a splenectomy so they would become surgically asplenic. Surgical asplenia is even more severe than functional asplenia.

Mortality among patients with asplenia is commonly caused by Streptococcal pneumonia. Patients with asplenia are at risk of infections by encapsulated organisms: Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis and other bacteria such E. coli and Staphylococcus aureus. Symptoms may be non-specific in the beginning with patients quickly developing septic shock and disseminated intravascular coagulation.

5. What strategies can be implemented to prevent infections in the asplenic patient?

1. Education: parents and patients should understand the lifelong risks they face, the importance of vaccination and compliance with antibiotic prophylaxis and the need for urgent action during a febrile episode. GPs and local hospitals should provide easy access to medication and vaccinations to ensure good compliance.

2. Vaccination: PCV13 (pneumococcal vaccination), meningococcal vaccines, and Hib conjugated vaccines are important to prevent life-threatening sepsis. Sickle cells patients should receive the above vaccines as per the UK calendar schedule. If the patient comes from a different country and has not received vaccinations, please refer here to catch up.

Sickle cell patients also qualify to receive the annual influenza vaccine, since influenza virus infection predisposes to bacterial pneumonia and sepsis caused by S. pneumoniae and S. Aureus.

3. Prophylactic antibiotic therapy: lifelong oral penicillin prophylaxis is recommended to all sickle cell patients since it has dramatically reduced mortality from pneumococcal sepsis in younger children. In older children, studies have not demonstrated a significant reduction of the incidence of invasive pneumococcal infection. This could also be due to the fact that pneumococcal infection rates in the community decrease significantly after 5 years of age.
It must be noted, however, that these studies were completed before the universal use of pneumococcal vaccine in infants, and before the increased prevalence of colonization and infections with penicillin resistant pneumococci.

Start penicillin prophylaxis by 90 days of life and continue for life.

Penicillin V prophylaxis	
< 1 year	62.5mg PO BD
1-5 years	125mg PO BD
>5 years	250mg PO BD

If the patient has a penicillin allergy, erythromycin is a good alternative.
If the patient travels to malaria areas, provide malaria prophylaxis.

4. Early empirical antimicrobial therapy during febrile episodes.
Fever in an asplenic patient should be managed promptly since it could be the initial signs of a fatal disease. The patient should be educated to seek medical help when fever develops to receive early antimicrobial treatment (ceftriaxone) and further support.

CASE 2 (20 MINUTES) ACUTE PAINFUL CRISIS AND PRIAPISM

A 10-year-old boy with known SCA presents to ED due to severe pain in the legs. At home, he has had 24 hours of alternating paracetamol and ibuprofen, but the pain was so unbearable that his parents came to hospital in the middle of the night. He is apyrexial. His parents are also worried as he has had 3 hours of priapism.

1. How would you evaluate this child's pain?

Pain due to vaso-occlusive crisis (VOC) is a very common presentation in sickle cell patients. Common sites of pain are bones (long bones, dactylitis) or abdominal pain. Painful crises are due to vaso-occlusion by sickled red cells generating an ischaemic tissue injury from blood flow obstruction. On average, a painful crisis may last for 4-5 days.

Studies have shown that pain is usually undertreated, as sickle cell patients may not look uncomfortable since they have learned to adapt to a lifetime of chronic pain with several non-pharmacologic therapies (distraction techniques, hypnosis, cognitive-behavioural therapy). This child's pain should be evaluated with an appropriate pain scale for his age. Furthermore, if the patient or his parents report severe pain, this should be taken seriously and acted upon.

2. What medications would you give to control pain at home?

The majority of painful crises are not severe and can be managed at home. Frequent crisis and chronic pain can negatively impact the child's development and personal growth, so effective treatment is crucial. Children should identify and avoid pain triggers. Infections, fever, acidosis, hypoxia, dehydration and exposure to extreme temperatures can trigger VOC even though often no cause is identified.

Pain can not only be managed with drugs but also with psychological coping strategies such as distraction techniques or other therapies (i.e. massage, watching TV).

Home analgesia:

- Advise families at home to increase fluid intake to avoid dehydration (dehydration will prolong painful episodes).

• Alternating paracetamol and ibuprofen is the analgesic regimen of choice in mild-to-moderate pain. Avoid long courses of NSAID treatment (>72 hours) due to the potential renal side effects of sickle cell patients who are at increased risk of chronic renal failure.

• For severe pain: a weak opiate can be added. Dihydrocodeine can be used in under 13 years of age and codeine after this age. Of note, at least 20% of children will not respond to codeine because they lack the enzyme needed to convert it to morphine.
If the patient is still in pain after using this regimen, they should be assessed in hospital. Children should not be treated with morphine at home except in exceptional circumstances and always guided by individualised care plans.

3. What medications would you give to control pain in hospital?

When sickle cell patients present to ED, they have usually already used their home pain medications and pain is still not under control. Therefore, aggressive analgesia should be given with the next step in the pain treatment ladder, which is strong opiates (morphine, oxycodone, hydromorphone or fentanyl).
Some clinicians are scared of using opioids due to concerns that they may cause acute chest syndrome. Opioids do not cause ACS but they can exacerbate hypoxia in patients with ACS. A cautious but rational use of opioids in combination with adequate monitoring is effective and safe to treat painful crises.

Morphine sulphate is the commonest strong opioid to start with. Offer a bolus of strong analgesia within 30 minutes of arrival to hospital to all patients with severe pain and with moderate pain who have already had some analgesia before presentation.

The IV route is used for rapid effect since the PO morphine requires titration and may take some time to act. If IV route is not available, the subcutaneous route is also reliable. Alternatives to morphine are hydromorphone or fentanyl. They should be used for patients who cannot tolerate morphine side effects (extreme pruritus or nausea).

Do not use pethidine since it can cause seizures and CNS hyperexcitability.

Initiate a continuous infusion (patient controlled analgesia) if repeated bolus doses of a strong opioid are needed within 2 hours.

In addition to opiates, continue to offer paracetamol and NSAIDS (unless contraindicated). Offer antiemetics, laxatives, and antihistamines to minimise morphine side effects (pruritus, nausea and constipation). Monitor vital signs for respiratory depression. Naloxone (opioid antidote) should be available in ED in case of severe respiratory depression.
A newer therapy option is ketamine. Recent studies have shown that low-dose ketamine can reduce pain in acute painful crises of sickle cell patients as well as being an opioid-sparing drug.

4. How would you treat priapism?

During a painful crisis, clinicians should also be vigilant of other concurrent problems.

Priapism is a sustained, painful and unwanted erection. Priapism is more common in teenagers which makes it complex since they're usually shy and reluctant to seek medical help. When it occurs in a pre-pubertal boy, it has a better prognosis for normal erectile function than in post-pubertal boys.

Classification of Priapism		Treatment
Stuttering	< 3 hours but several times a week	Oral etilefrine
Minor	Isolated or infrequent episodes of less than 3 hours	
Fulminant	More than 3 hours	Aspiration and irrigation of the corpora cavernosa with epinephrine or etilefrine

A prolonged attack (>3 hours) should be treated as a surgical emergency.
If untreated, it may result in cavernosal fibrosis and subsequent impotence.
In addition, blood transfusion may be indicated as part of the overall management plan if a shunt needs to be performed.

Other non-pharmacological treatments are bladder emptying, exercise such as jogging, warm baths and analgesia.

ADVANCED CASE 1 (30 MINUTES) ACUTE CHEST SYNDROME

A 6-year-old girl from Saudi Arabia was referred by her General Practitioner to the local emergency department. She complained of cough and runny nose for 3 days. She is known to have sickle cell anaemia. She had had several episodes of acute pain crises in the past. She attends sickle cell clinics regularly.
She is on folic acid 5mg OD PO, penicillin V 250mg BD PO. For a pain crisis she has PRN paracetamol, ibuprofen and dihydrocodeine. She also suffers from asthma occasionally and she is on salbutamol inhalers as required.

Vitals: Temperature 39.5, HR 100 beats per minute, Respiratory Rate 35, saturations 90% at room air. Blood pressure 95/60 mg/Hg.
On examination, she has pallor, no jaundice. On auscultation, there is bilateral wheeze. On abdominal palpation, the spleen is enlarged.
You order some investigations including a Chest CXR.

1. What features might you see on the chest XR that will help you to diagnose the patient?

https://radiopaedia.org/articles/sickle-cell-disease-acute-chest-syndrome-1?lang=gb

Acute chest syndrome is an acute inflammatory lung injury that usually follows vaso-occlusive crisis. It is defined by the presence of a new pulmonary infiltrate on a chest XR in association with fever and respiratory symptoms (cough, chest pain, desaturations and wheezing). It is the most prominent cause of mortality in children with SCD and it is the second most common cause for hospitalisation in these patients.
The most common findings on CXR are segmental atelectasis/consolidation in the lower lobe, and/or pleural effusion. Other sickle cell disease sequelae can be seen such as bone infarcts, rib enlargement and cardiomegaly from anaemia.

Young children present with a mild disease simulating a community-acquired pneumonia (bacterial or viral). Older children and adults usually present with ACS 2-3 days after hospitalisation due to pulmonary infarction (in situ sickling), hypoventilation due to rib infarction (which may be exacerbated by recent narcotic administration) or fat embolism.

Haemoglobin is usually lower than baseline and white cells count is often raised.

2. What would be the appropriate acute management?

The treatment for ACS is mainly supportive:

• Oxygen: supplemental oxygen should be given only when the patient is hypoxic (saturation of oxygen < 94%). As a side effect, oxygen can suppress bone marrow and increase transfusion needs.
• Incentive spirometry or chest physiotherapy: prevent atelectasis in the wakeful child with incentive spirometry. If the patient is not able to comply with incentive spirometry due to age or extreme thoracic wall pain, then request chest physiotherapy with positive expiratory pressure. Incentive spirometry has also demonstrated to improve outcomes in SCD without respiratory symptoms and with back pain.

• Mechanical or non-invasive ventilation: children with ACS may require ventilatory support. They should be admitted to hospital in case of clinical deterioration to receive ICU treatment.

• Fluid therapy: fluids should be given carefully. Prescribe 75% of daily maintenance fluid of normal saline or 5% dextrose and normal saline. Avoid fluid boluses unless the patient is very hypovolemic (sepsis, vomiting illness).

Overhydration can:
- produce atelectasism, worsening acute chest crisis
- result in hyperchloremic metabolic acidosis which may promote sickling
- result in pulmonary oedema (especially if there is a concurrent use of opiates for pain control which increases vascular leak).

• Antimicrobials: Sickle cell patients with ACS should receive antibiotics since they are key to decreasing inflammation. Pulmonary infections have a crucial role in the pathology of acute chest syndrome: bacteria and viruses can infect the lung creating an excessive inflammatory response due to systemic endothelial dysfunction triggering ACS. The regimen should include a macrolide and third generation cephalosporin in order to cover Chlamydia pneumoniae, Mycoplasma pneumoniae, Streptococcus pneumoniae and Staphylococcus aureus.
Antibiotic therapy should be reviewed once blood culture results are available. Tamiflu can be considered if results are positive for influenza.

• Bronchodilators: asthma and bronchospasm can contribute to ACS as a risk factor. Therefore, inhaled bronchodilators are advised even though the evidence of efficacy remains weak according to a recent Cochrane review.
• Corticosteroids: there is a lot of controversy on steroidal treatment. A low dose steroid has demonstrated to improve morbidity and to reduce the need of blood transfusion. However, there are documented adverse events such as haemorrhagic cerebrovascular accidents or recurrence of VOC after drug withdrawal, which represent a drawback in its regular use.
• Anticoagulants: tinzaparin (low-molecular-weight heparin) has been shown to reduce the duration and severity of VOC pain by ameliorating vaso-occlusion however is not used systematically in ACS.
• Inhaled NO: SCD patients have reduced nitric oxide due to a chronic inflammatory state that worsens the ACS. Many clinicians have studied the role of NO in SCD but, unfortunately, studies have not shown a significant difference in symptom improvement and resolution of ACS episodes in patients with inhaled NO therapy vs placebo.

3. Would you consider this patient for blood transfusion?

Top-up transfusion should be considered giving the acute presentation and the severe anaemia. Before any transfusion, discuss the case with the local haematologist. There are 2 types of blood transfusions that may be indicated in sickle cells patients:

"Top-up" transfusion:
Top-up transfusions aim to improve oxygen delivery, to restore Hb to a normal steady state (target Hb should be less than 10 g/dl or haematocrit 0.35 to avoid increased blood viscosity.

Blood volume for top-up:
[Desired Hb – Actual Hb] X Weight (kg) x 3 = volume of packed red cells.
Rate of 5ml/kg/hour. Furosemide is not required as it increases blood viscosity.

Top-up Acute transfusion indications:
Acute anaemia due to parvovirus B19 infection, acute splenic or hepatic sequestration
Acute chest syndrome with a fall in haemoglobin of more than 1g/dl Hb
Preparation for surgery

Exchange transfusion:
Aim to reduce HbS % <30% with a target Hb less than 11.5 g/dl or haematocrit less 0.35 by performing a total exchange of 1-2 times the calculated blood volume.
It can be performed by either manual or automated exchange. Usually, children would have had a top-up already but the haemoglobin would still be low.
This treatment is usually done in the ICU setting.

Indications for exchange transfusion
Stroke or acute neurological deficit
Severe acute chest syndrome likely to require respiratory support
Multiorgan failure
Retinal artery occlusion
Hepatic failure
Priapism unresponsive to therapy

4. What is the role of hydroxycarbamide?

Oral hydroxycarbamide (previously called hydroxyurea) increases foetal haemoglobin production and therefore, it decreases sickled haemoglobin. It also improves red cell hydration, decreases the neutrophil count and modifies red cell–endothelial cell interactions. Hydroxycarbamide is indicated in sickle cell patients because it decreases the incidence of pain episodes, acute chest crises and the number of transfusions required.
Hydroxycarbamide should be offered to all children with HbSS/Sβ0 thalassaemia aged 9–42 months regardless of the clinical severity of their illness.

It should also be offered to patients with severe complications
(if they are not already taking it):
- 3 or more episodes of acute vaso-occlusive painful episodes each year
- Recurrent or severe Acute Chest Syndrome

ADVANCED CASE 2 (30 MINUTES): STROKE IN SICKLE CELL DISEASE PATIENT

An 8-year-boy from Nigeria presented to ED with an acute right sided hemiplegia. He is known to have sickle cells and he is under the care of the haematology department. He has been on holiday for 2 months in Nigeria and has not been compliant with his usual treatment. On examination, he looks pale and you can feel the spleen on abdominal palpation.

1. How common is cerebro-vascular disease in sickle cell patients?

5-10% of children with SCA will have a stroke during their lifetime. Peak age is between 2-10 years. Furthermore, ¾ of children with a positive past medical history of stroke will go on to have another or several more strokes since acute neurological ischaemia is more likely to occur in children with pre-existing cerebrovascular lesions during acute anaemic events or with other acute complications.

Proximal vessel stenosis predisposes children to acute cerebral infarction. Occasionally older children present with subarachnoid or intracerebral bleeds, which may be related to single or multiple cerebral artery aneurysms.

Children can experience intellectual impairment, increased frontal lobe related attention problems, impaired executive functioning and behavioural issues due to cerebro-vascular disease.

About 20% of children with SCD will have a silent cerebral infarct on MRI that are not associated with an overt neurological episode. They're associated with mild cognitive impairment and may be discovered with a neurocognitive test.

2. What would be the acute management of this child?

Acute management:

- Urgent imaging with CT scan and/or MRI/MRA to define the event and exclude a haemorrhagic component.
- If neuroimaging shows intracerebral or subarachnoid haemorrhage, refer urgently to the neurosurgical team.
- Exchange transfusion to reduce the risk of progression of the lesion.

For specific diagnosis and treatment of acute stroke, read the RCPCH Stroke guidelines:
https://www.rcpch.ac.uk/sites/default/files/2019-04/20160203%20Key%20Recommendations%2008.04.19.pdf

3. What is the role of transcranial dopplers in primary prevention of strokes?

In children, cerebral ischaemic damage is often due to stenotic lesions in the internal carotid artery (ICA), middle cerebral artery (MCA) or anterior cerebral artery (ACA). The high blood flow velocities through these stenotic segments can be detected using transcranial doppler ultrasound (TCD). Annual screening with TCD is recommended to all SCD patients > 2 years old.

Patients with a time-averaged mean velocity in the ICA/MCA/ACA segments >200cm/sec are at high risk for stroke.

Patients in the high-risk group can receive regular blood transfusions in order to reduce the risk of having a stroke. A clinical trial on children with abnormal TCD and already on regular blood transfusions showed that switching to hydroxycarbamide was equivalent to transfusion for primary prevention of stroke.
Patients with conditional velocities (170-200cm/sec) are at moderate risk and should be closely monitored.

4. What strategies are useful for secondary stroke prevention?

Chronic transfusions can reduce the risk of recurrent stroke from 50-70% to 13% (secondary stroke prevention). Hydroxycarbamide is less effective at secondary stroke prevention so it is used only when transfusions are contraindicated.

The aim of the transfusion is to maintain HbS level < 30%. Top-up transfusions should be done every 3-4 weeks and continued throughout childhood.
Children on regular transfusion should be vaccinated against hepatitis B (if they are not immune already).

A common long-term side effect of transfusion therapy is iron overload, therefore iron chelation should be started in the following scenarios:
- after 1 year of transfusions
- serum ferritin> 1000 ng/mL on 2 readings 4 weeks apart
- evidence of iron load in the liver through MRI.

Indications for regular, long-term transfusion
Primary and secondary stroke prevention
Recurrent acute chest syndrome not prevented by hydroxycarbamide.
Recurrent painful episodes not prevented by hydroxycarbamide

Prevention for silent strokes:
The option of chronic transfusion should be discussed with parents.
Regular transfusions decrease the number of further neurological events even in silent infarcts. There is no evidence on how to screen children for silent cerebral infarcts but there should be a low threshold for MRI when there are cognitive concerns including poor school performance.

5. In the above case, what could be the cause of the pallor (anaemia)?

Acute splenic sequestration presents with an acute fall of Hb (more than 2 g/dl below the steady-state of Hb), an elevated reticulocyte count and splenomegaly. It is a serious complication with high mortality if not recognized.

Prompt intervention with transfusion can be life-saving. Children with recurrent splenic sequestration should be considered for splenectomy.

Differential diagnosis:

Transient red cell aplasia: usually due to Parvovirus B19 infection.
The haemoglobin drop is over a period of a week with very low reticulocytes.
It may be associated with fever, headache and abdominal pain. IgM for Parvovirus is usually positive. It takes about 7 days for the reticulocytes to recover and top-up transfusion is often needed.

Malaria: the patient was in Nigeria for 2 months and has not been compliant with treatment. Unlike sickle cell carriers, sickle cell patients are at higher risk of contracting malaria and suffering from severe disease. Malaria can present with pallor and jaundice. Thick and thin films should be ordered to look for parasites.

QUIZ QUESTIONS: (10 MINUTES)

Question 1.

Which of the following statements is FALSE concerning Sickle Cell Anaemia?

A: It is a recessive autosomal inherited blood disorder

B: The sickle shape of the cell is due to an abnormality in haemoglobin

C: Symptoms are never seen in children

D: Fatigue is a common symptom

Answer:

Clinical presentation usually begins after the first year of life, when foetal haemoglobin (HbF) decreases in favour of HbA. Patients with SCA (HbSS) usually become symptomatic at this point when HbF decreases and HbSS increases.

Question 2.

Why is sickle cell disease more common near the equator (Africa, Caribean countries)?

A. Sickle cell trait is a genetic mutation that provides protection against malaria

B. Sickle cell disease is a genetic mutation that provides protection against malaria

C. Sickle cell disease is a genetic mutation that provides protection against trypanosomiasis

D. Sickle cell trait is a genetic mutation that provides protection against trypanosomiasis

Answer:

Sickle cell trait provides protection against malaria while sickle cell disease confers high risk for malaria parasite infection.

Question 3.

What infections are sickle cell patients more at risk of?

A. Pneumococcal sepsis

B. Rotavirus gastroenteritis and dehydration

C. Recurrent UTIs

D. Mycoplasma pneumonia

Answer:

Sickle cell patients have functional asplenia and they are at high risk for encapsulated bacterial infections, especially Streptoccocus pneumoniae.

Question 4.

Transfusions in sickle cell patients are indicated in patients with:

A. Any surgical procedures

B. Acute fulminant priapism unresponsive to treatment

C. Asymptomatic functional asplenia

D. Moderate acute chest syndrome without hypoxia

Answer:

Blood transfusions are indicated in major surgical procedures, acute priapism > 3 hours not responsive to treatment, severe acute chest syndrome with hypoxia requiring ICU.

Question 5.

What are specific treatments for sickle cell disease?

A. Regular blood transfusions

B. Hydroxycarbamide

C. Bone marrow transplant

D. All of the above

Answer:

Specific treatments for sickle cell disease are regular blood transfusions and hydroxycarbamide. Bone marrow transplant is a curative treatment for sickle cell patient but it is a high-risk therapy and only used in selected patients.

Question 6.

In an outpatient sickle cell visit, what would you be a priority to assess?

A. Haemoglobin A1C level

B. Saturation of oxygen

C. Reflexes

D. Vaccination history

Answer:

Vaccination history is key to prevent infective complications: sickle cell patients should receive all the scheduled vaccinations including pneumococcal vaccine in addition to annual flu vaccine and meningococcal vaccination.

INFOGRAPHICS (2 minutes)

1. Think about sickle cell disease in patients who come from or whose ancestors come from Africa, Caribbean, Middle east and Mediterranean regions

2. Sickle cell patients are high risk for serious bacterial infections bcause they have functional asplenia

3. Never underestimate pain in Sickle cell patients: evaluate pain with an adequate pain scale and treat it aggressively

4. A person with sickle cell disease can have a good quality of life by getting regular check-ups and following treatments prescribed by doctors

5. Be aware of potential life-threatening SCD complications, such as chest crises, severe infections or cerebrovascular disease. If in doubt, consult with a local haematologist regarding sickle cell patient management

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