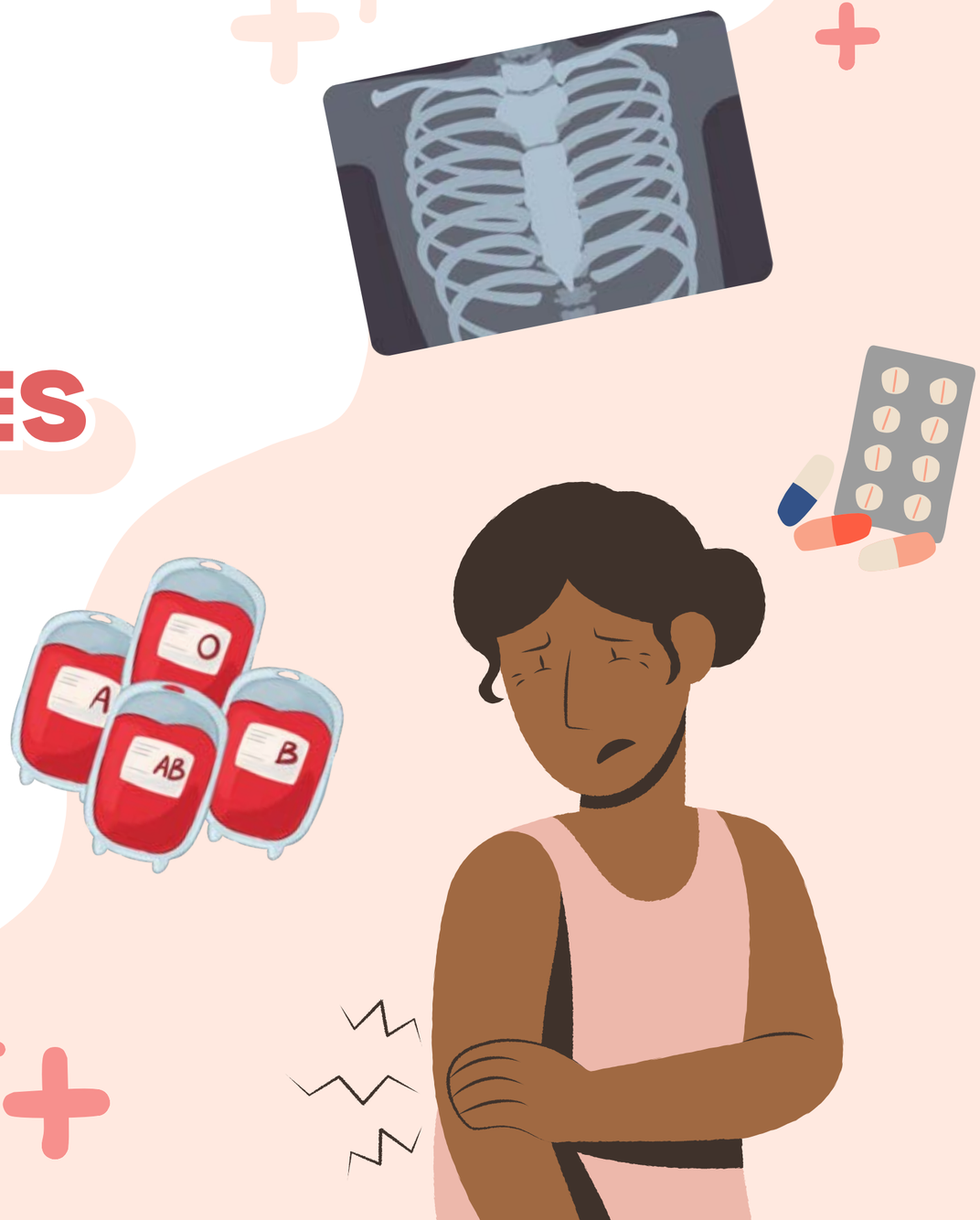
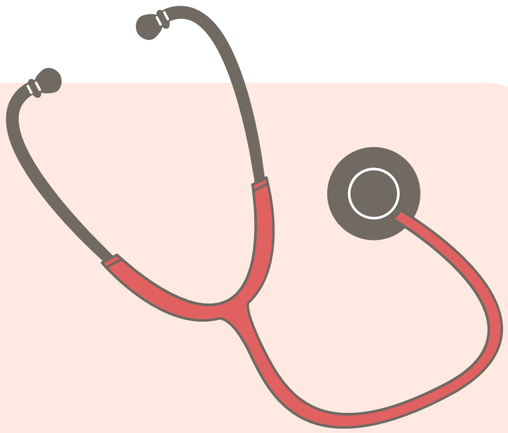
HAEMOGLOBINOPATHIES FOR THE MEDICAL TAKE



Dr Amy Cooper
Haemoglobinopathy QI Fellow



Today we will cover

What are haemoglobinopathies?

- Basic science underlying conditions
- How to apply this knowledge in understanding the management of the conditions

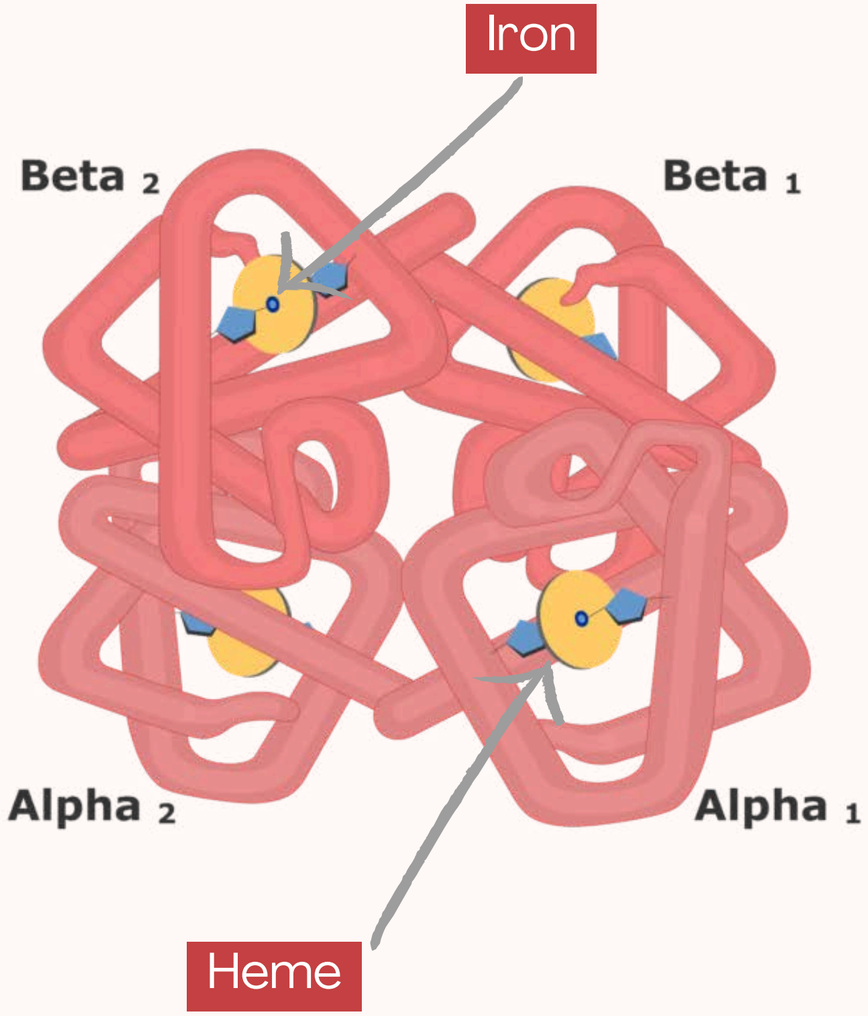
What complications of haemoglobinopathies can you see on the medical take?

- Sickle cell disease
- Thalassaemia

HAEMOGLOBIN

- Consists of two alpha and two beta globin chains
- Heme sits inside the globin chain and holds one iron molecule (4 per haemoglobin)
- The iron molecule reversibly binds oxygen (allowing it to carry and give up the O2 molecule)

Reminder - this is what Hb measures!



NORMAL HAEMOGLOBIN SYNTHESIS

Chromosome 16

ζ	α	α

Chromosome 16

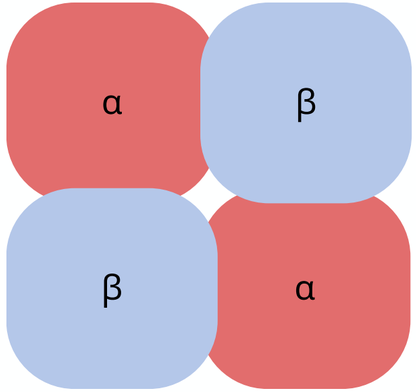
ζ	α	α

Chromosome 11

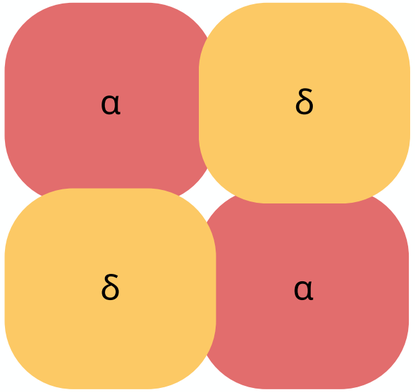
ε	γ	δ	β

Chromosome 11

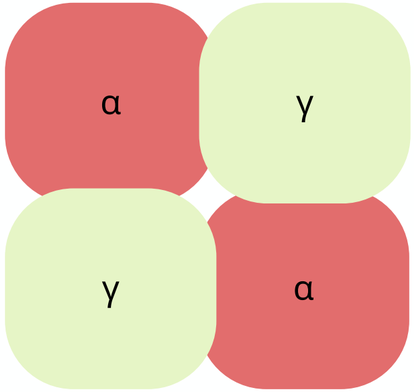
ε	γ	δ	β



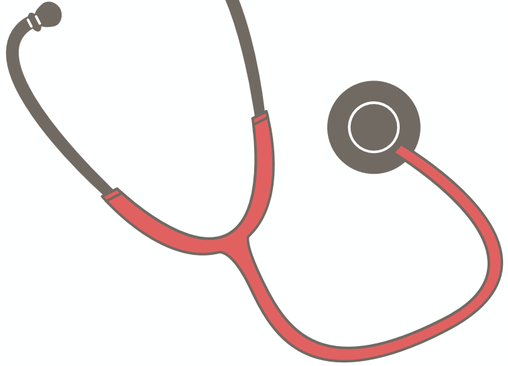
HbA



HbA2



HbF



HOW CAN HAEMOGLOBIN SYNTHESIS GO WRONG

Structural abnormalities

Haemoglobin is made, but the structure is different to normal haemoglobin due to a genetic mutation (usually affecting the beta gene). Examples include:

- HbS
- HbC

Abnormalities in haemoglobin production

Mutations in alpha or beta genes reduce the production in alpha or beta chains. This reduces the amount of normal haemoglobin. These conditions are called thalassaemias.

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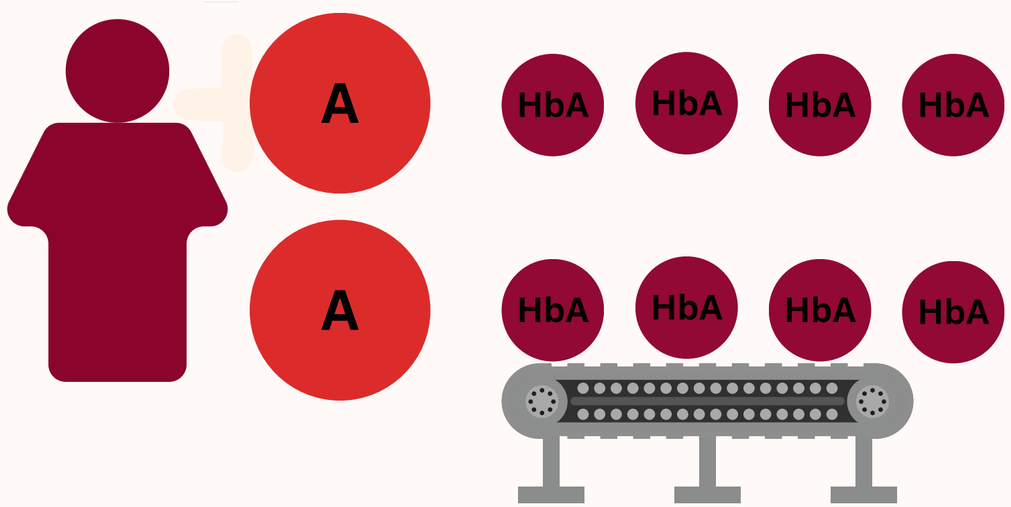
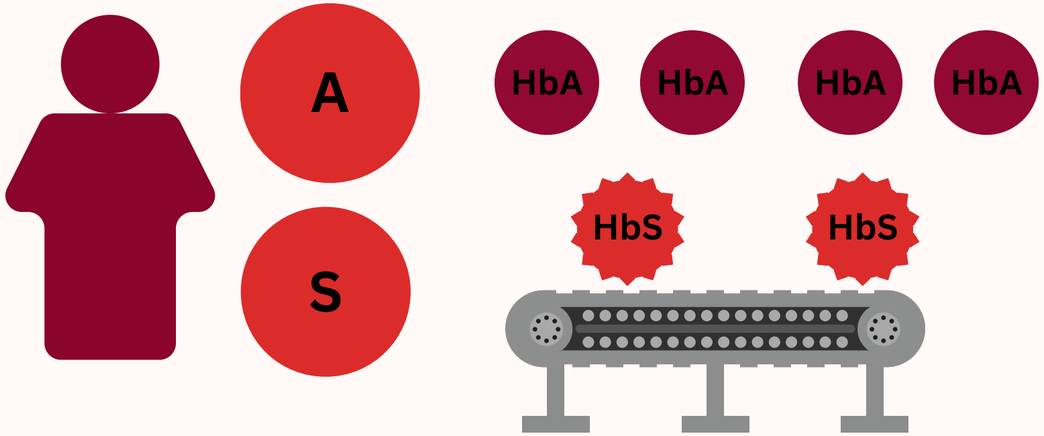
Haemoglobinopathy
Coordinating Centre

A NOTE ON HAEMOGLOBIN SYNTHESIS

- Inheritance of sickle cell disease is **autosomal recessive**

- Haemoglobin genes are **codominant**
- Both alleles are expressed independently, which means they both create haemoglobin
- HbS is made less efficiently than HbA - this is compensated in trait





HBSS SICKLE CELL DISEASE

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ζ	α	α

Chromosome 16

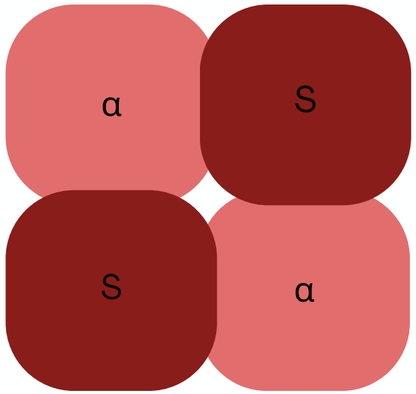
ζ	α	α

Chromosome 11

ε	γ	δ	βS

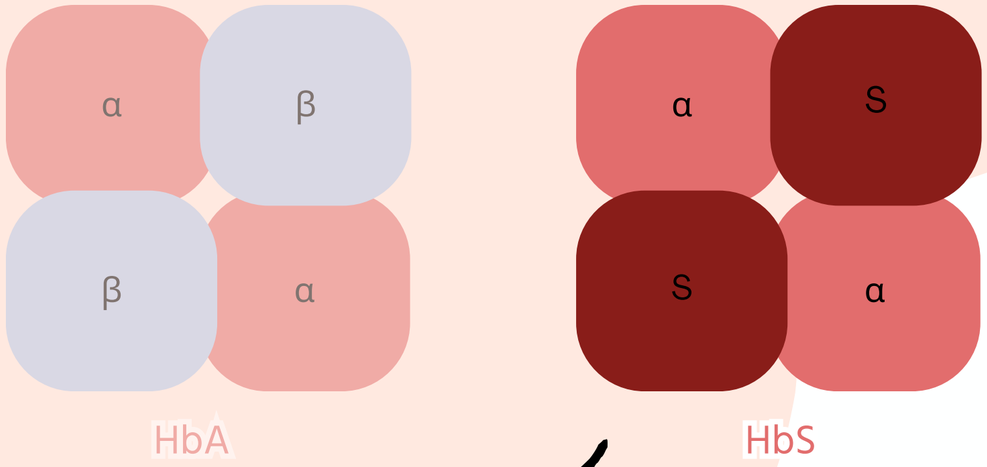
Chromosome 11

ε	γ	δ	βS

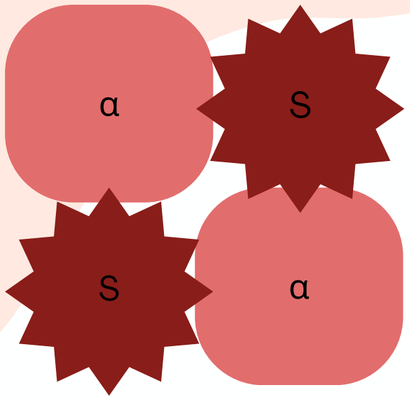


HbS

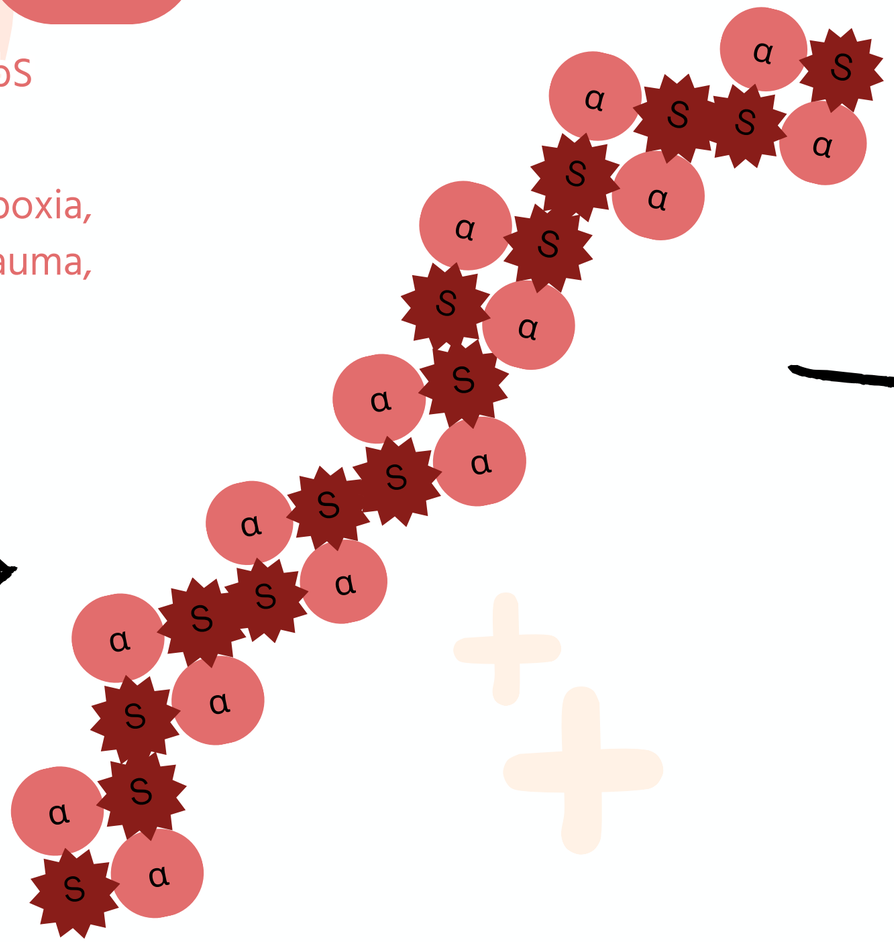
SICKLE CELL DISEASE (HBSS)



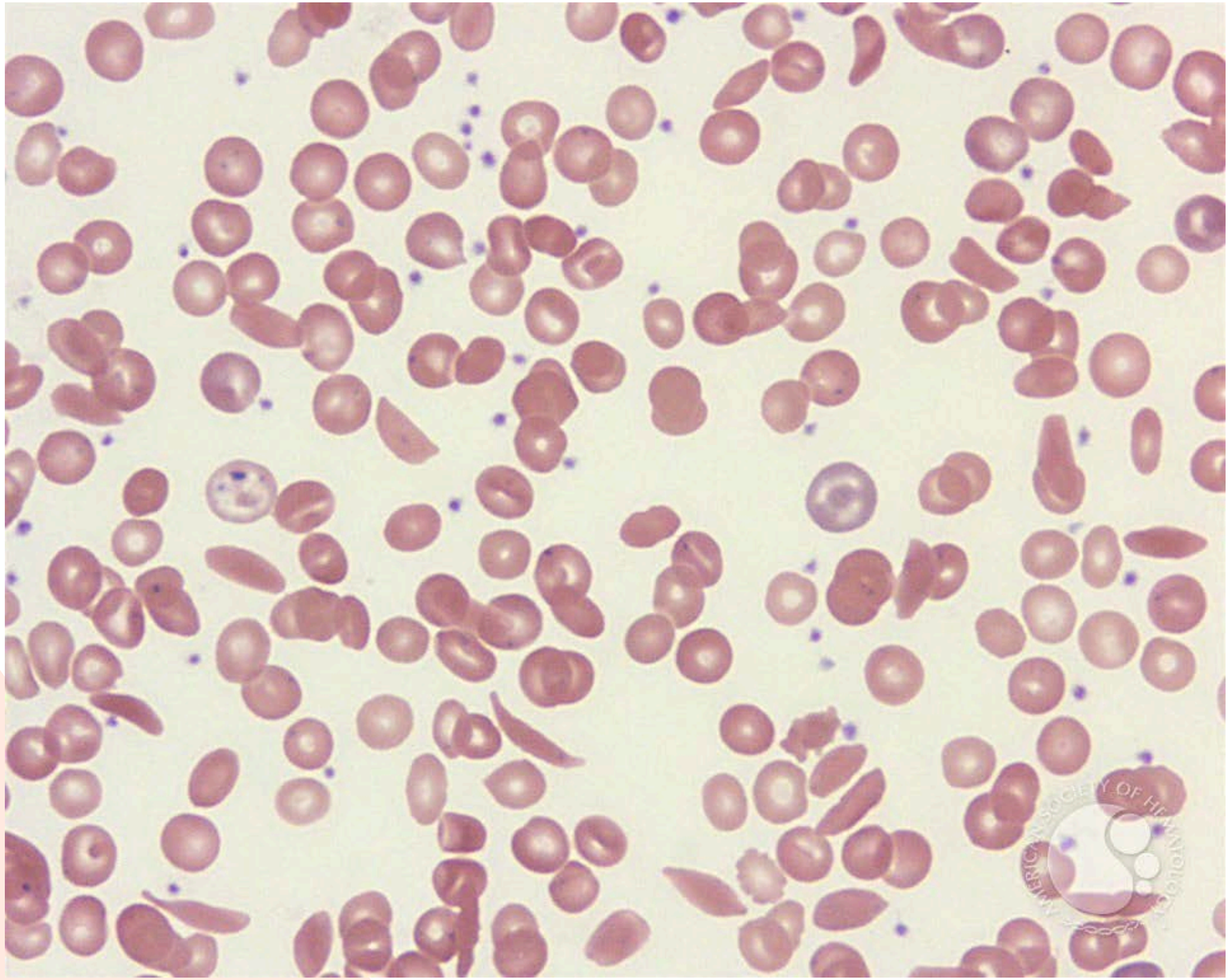
Stress (e.g. hypoxia, infection, trauma, cold exposure)



Polymerisation



Sickling



OTHER TYPES OF SICKLE CELL DISEASE

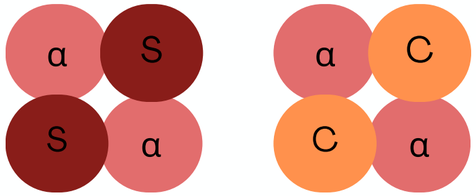
Chromosome 11

ε	γ	δ	βS

Chromosome 11

ε	γ	δ	βC

= HbSC disease



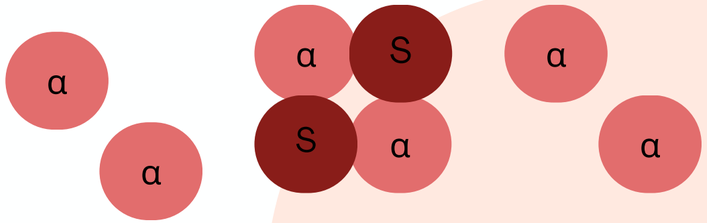
Chromosome 11

ε	γ	δ	βS

Chromosome 11

ε	γ	δ	~~βO~~

= HbS/beta thalassaemia



WHAT DO SICKLED CELLS DO IN THE BODY?

Vaso-occlusion

Sickled cells are rigid and non-deformable. They can get stuck in small vessels leading to ischaemia, organ damage and pain

Haemolysis

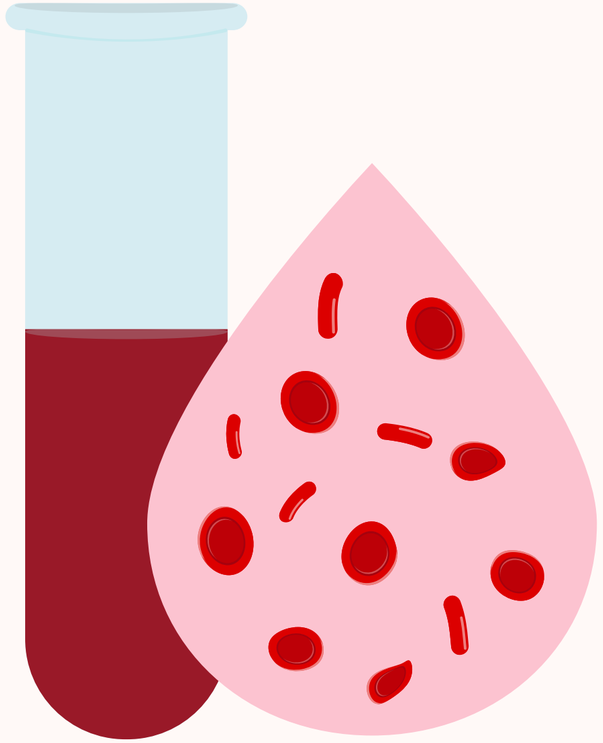
The abnormal sickled cells are destroyed through intravascular haemolysis. The lifespan of a sickle cell is around 10 days.

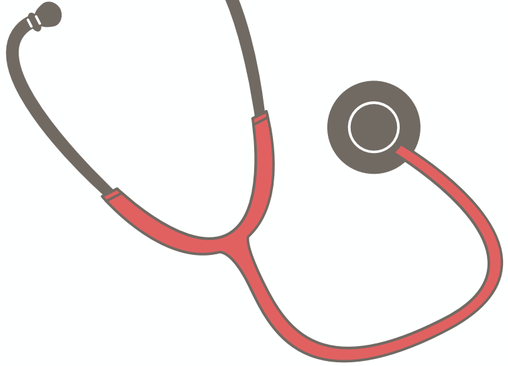
Haemolysis causes local vascular damage and promotes systemic inflammation

A NOTE ON ANAEMIA

- Patients with sickle cell disease have been anaemic since birth
- Able to tolerate anaemia with minimal side effects
- Usual Hb can range from 50-90 with HbSS, and 90-130 with HbSC

Anaemia without symptoms does not usually require blood transfusion





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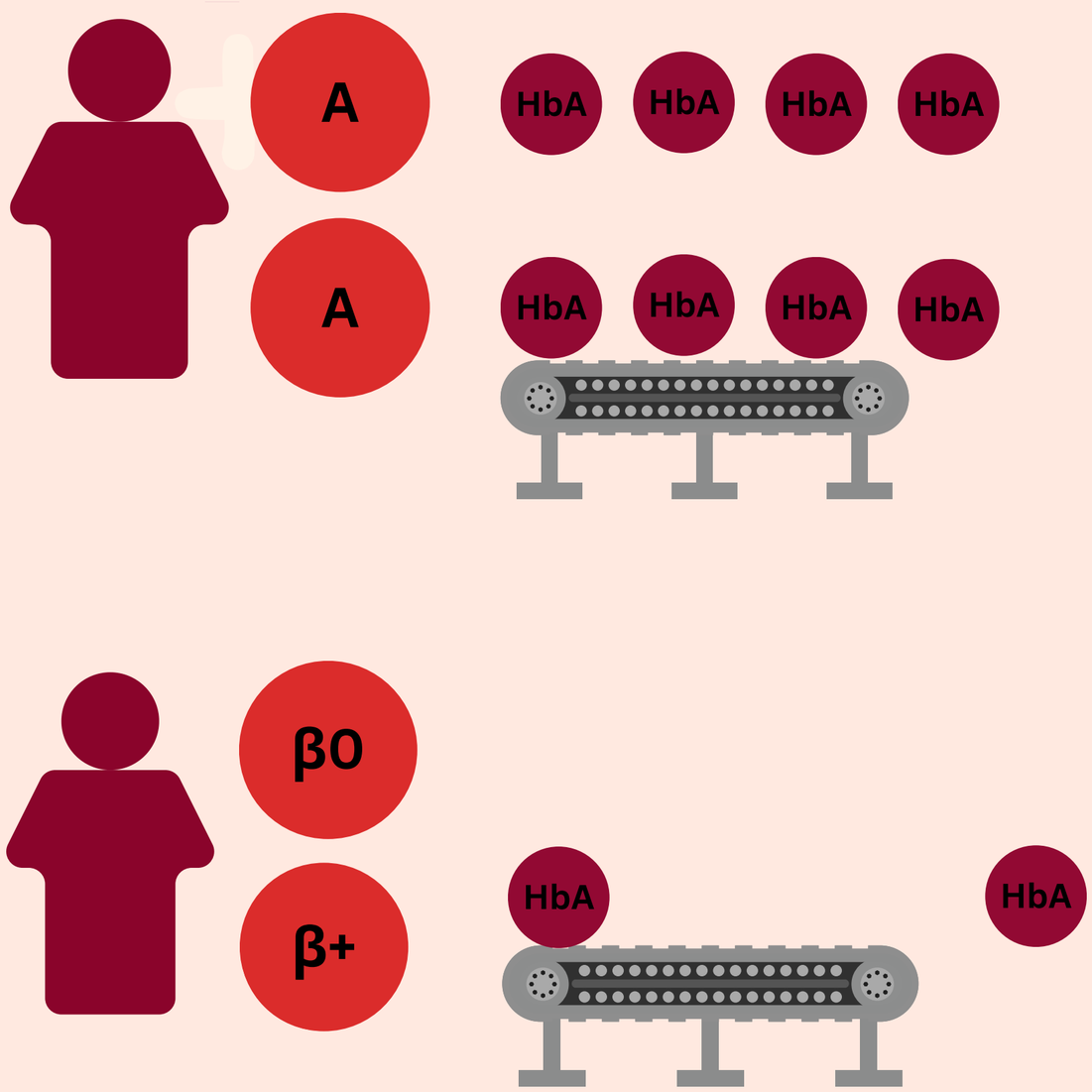
Haemoglobinopathy
Coordinating Centre



BETA THALASSAEMIA MAJOR

Chromosome 16

ζ	α	α

Chromosome 16

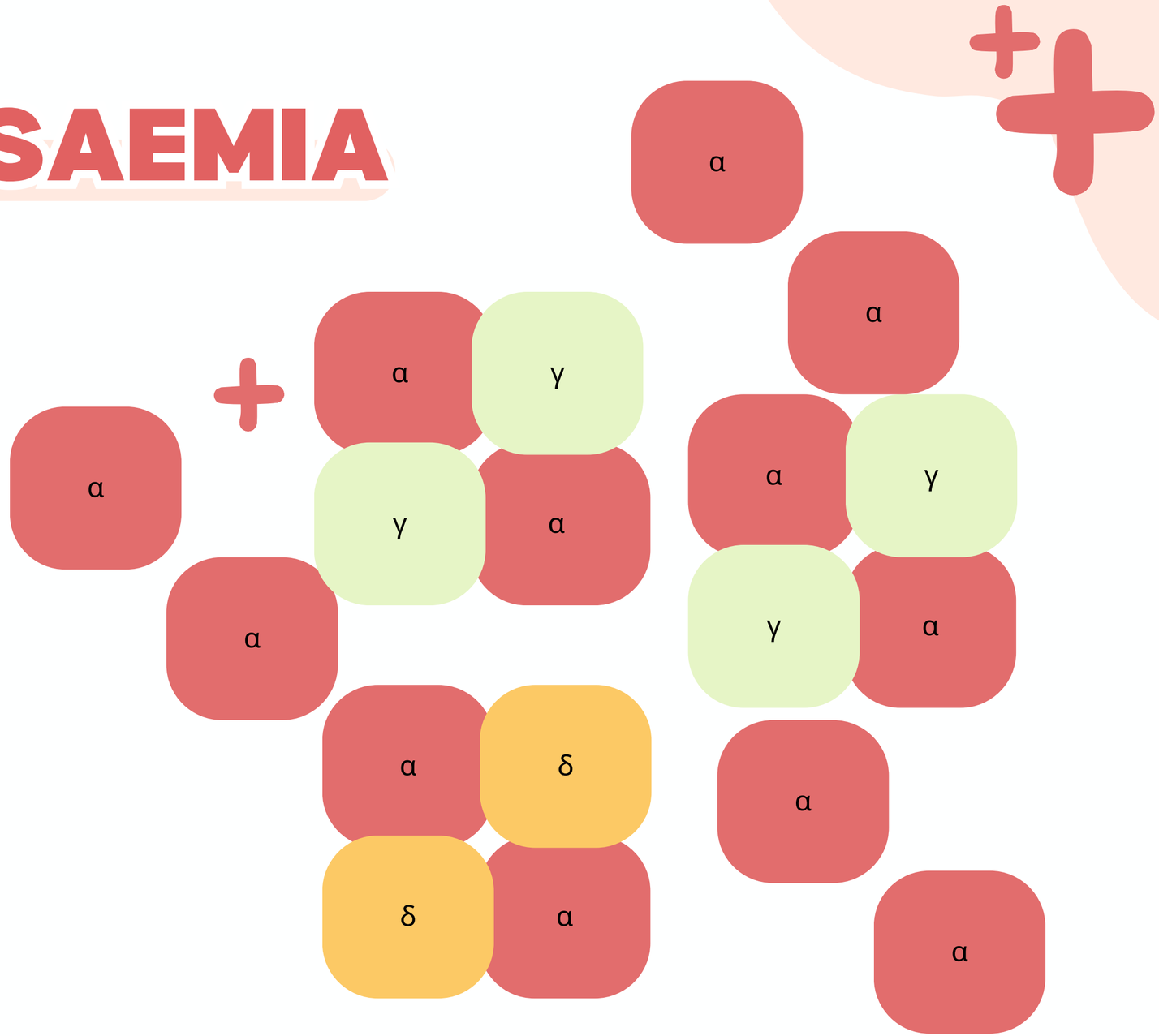
ζ	α	α

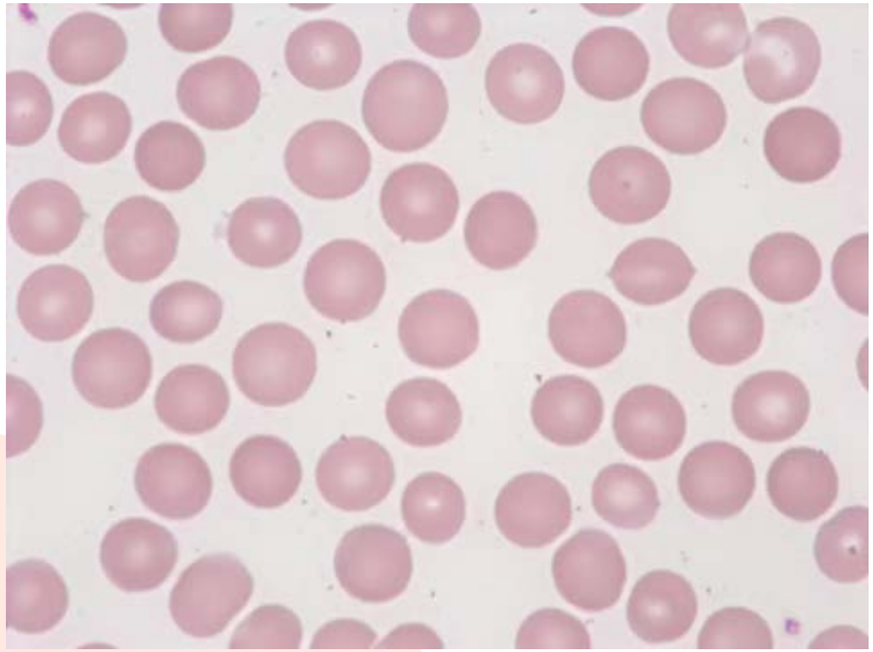
Chromosome 11

ε	γ	δ	~~β0~~

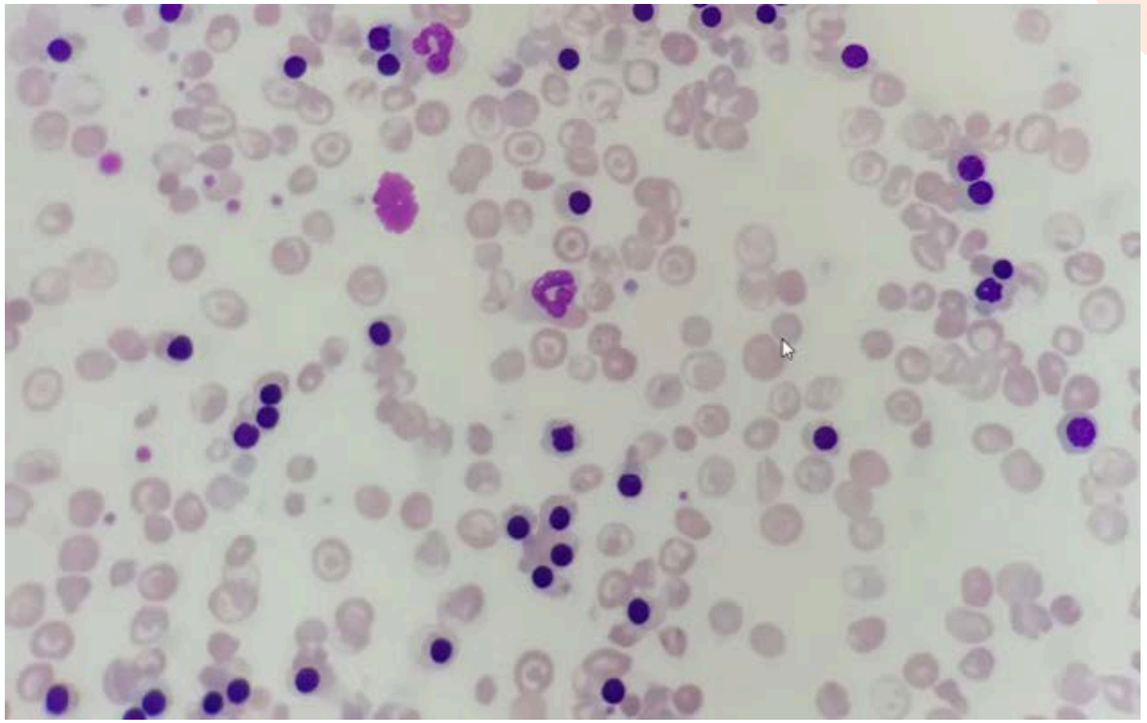
Chromosome 11

ε	γ	δ	~~β0~~



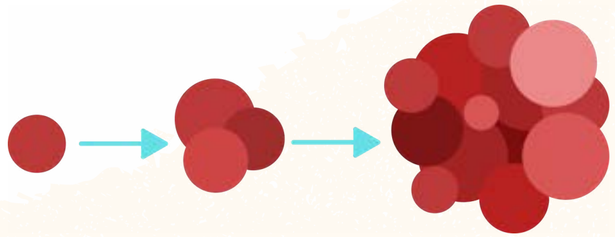


Normal



Thalassaemia major

WHAT HAPPENS IN THALASSAEMIA?



Extramedullary haematopoesis ensues to try to improve anaemia

The body desperately tries to compensate for the anaemia by absorbing more iron, leading to **iron overload.**

Treatment is with regular blood transfusion and iron chelation

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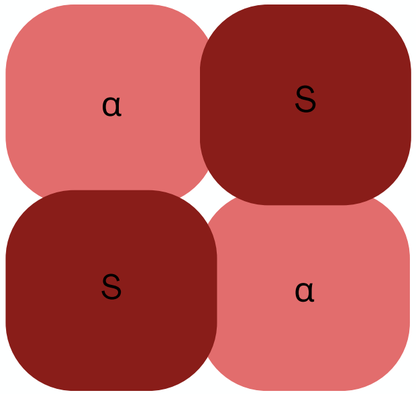


HbS

NO ONE'S LISTENING

Variations in care: "It really is like a lottery"

Specialist v non-specialist variation: "Clinicians had not got a clue or the care was so poor it was negligent"

Lack of compliance with national care standards: "It is life threatening!"

NO ONE'S LISTENING:

AN INQUIRY INTO THE AVOIDABLE DEATHS AND FAILURES OF CARE FOR SICKLE CELL PATIENTS IN SECONDARY CARE

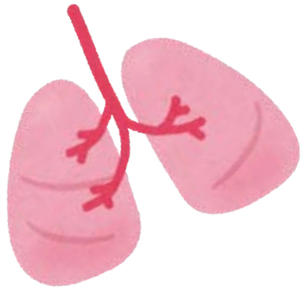
Fear and avoidance of hospitals: 'I do not trust the people who have sworn to protect us, because many times they have failed'

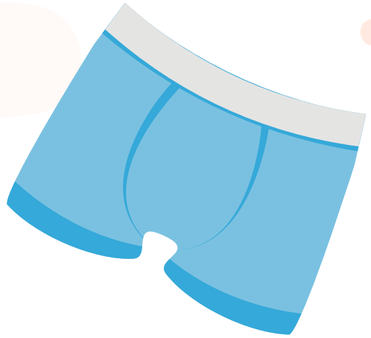
A large number of patients told us that their experiences of sub-standard care meant that they feared accessing secondary care, while others told us that they feel compelled to avoid attending hospital altogether.

"Going into hospital as a sickle cell patient requires you to put on an armour because from the moment you reach A&E it becomes your job to convince everyone you are really in that much pain and are not simply there for medication"

– Sickle cell patient

Racial inequality as a factor in sickle cell care: "Care is clouded by stereotypical perceptions of black people"





ACUTE COMPLICATIONS

This patient with sickle cell disease has come to the ED saying she has 9/10 pain in her right leg after being at the gym yesterday.

What's going on?

Case One

ACUTE PAINFUL CRISIS

Mechanism

An acute insult (e.g. cold, infection, hypoxia, trauma) prompts red cells to sickle and cause vaso-occlusion. This leads to ischaemia and acute **severe** pain.

Most common sites

Can happen in any bone, but most common in limbs, back, ribcage/sternum.

Type of pain

Pain is related to acute ischaemia and is excruciatingly painful. Listen to your patient and treat appropriately. Patients may not show their pain as you would expect.

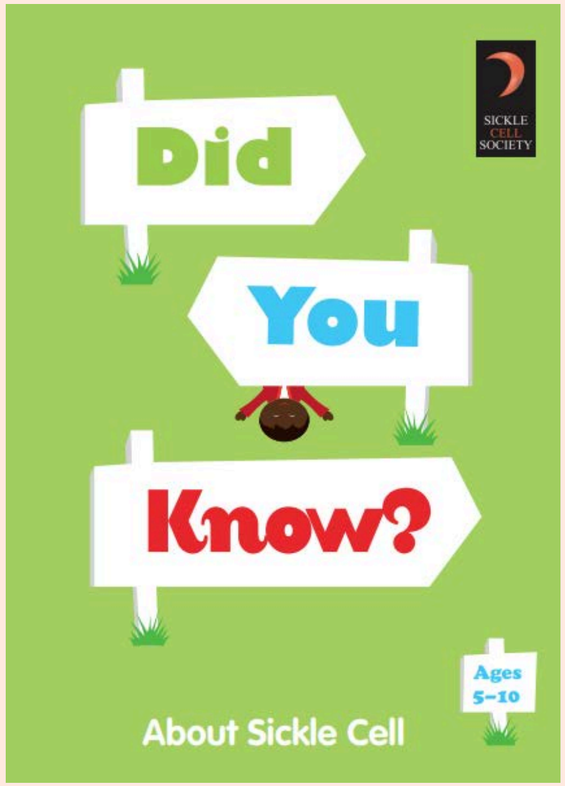
Opioid analgesia **within 15 minutes** of presentation for moderate to severe pain

Closely monitor observations, early warning score and pain score

Regular sedation score while using opiates

Early discussion with haematology team

She’s not in pain....


SICKLE CELL SOCIETY
Did
You
Know?
Ages 5–10
About Sickle Cell

but there are other things you can try too.
You could try:
• Reading
• Listening to music
• Hot water bottle
• Eating food you like
• Phoning a friend
• Watching TV
• Sleeping
• Thinking of a place that makes you feel happy
• Playing computer games
6

ACUTE PAINFUL CRISIS

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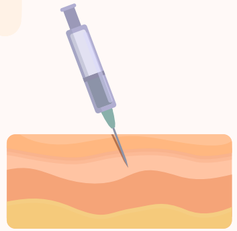

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ANALGESIA CHOICE

Clinical Guideline

SICKLE CELL ACUTE PAIN (VASO-OCCLUSIVE) CRISIS IN THE EMERGENCY DEPARTMENT

1. **For all levels of pain, prescribe:**
   - Diclofenac 50mg PO TDS or ibuprofen 400mg PO TDS (adjust in renal impairment), with PPI cover
   - For opioid naïve patients (not on regular opioids at home):
     - Give Co-codamol 30/500mg PO QDS (Dose adjust if weight <50kg or liver impairment)
     - Codeine alternatives include tramadol & dihydrocodeine. Avoid pethidine.
   - For patients on regular opioids at home:
     - Continue usual background slow-release opiates
     - Give Paracetamol 1g PO QDS (Dose adjust if weight <50kg or liver impairment)

2. **a) For mild to moderate pain:** give oral morphine sulphate 10mg/5ml (Oramorph®) 5-10mg

   b) For severe pain / pain unresponsive to oral analgesia:
   - For opioid naïve patients (not on regular opioids at home):
     - give 0.15mg/kg SC morphine up to every 30 mins until pain improves.
   - For patients on regular opioids at home:
     - Refer to individualised plan if available
     - If unavailable & background intake <200mg/day oral morphine equivalent, give 0.3mg/kg SC morphine up to every 30 mins until pain improves
     - If unavailable & background intake >200mg/day oral morphine equivalent, give 0.45mg/kg SC morphine up to every 30 mins until pain improves

Or PCA?

SUPPORTIVE MEDICATION

Antiemetics

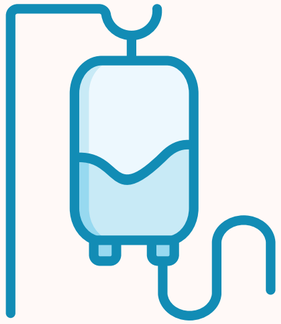
Laxatives

Thromboprophylaxis

Antipruritic

Naloxone

OTHER CONSIDERATIONS



IV fluids and input/output monitoring

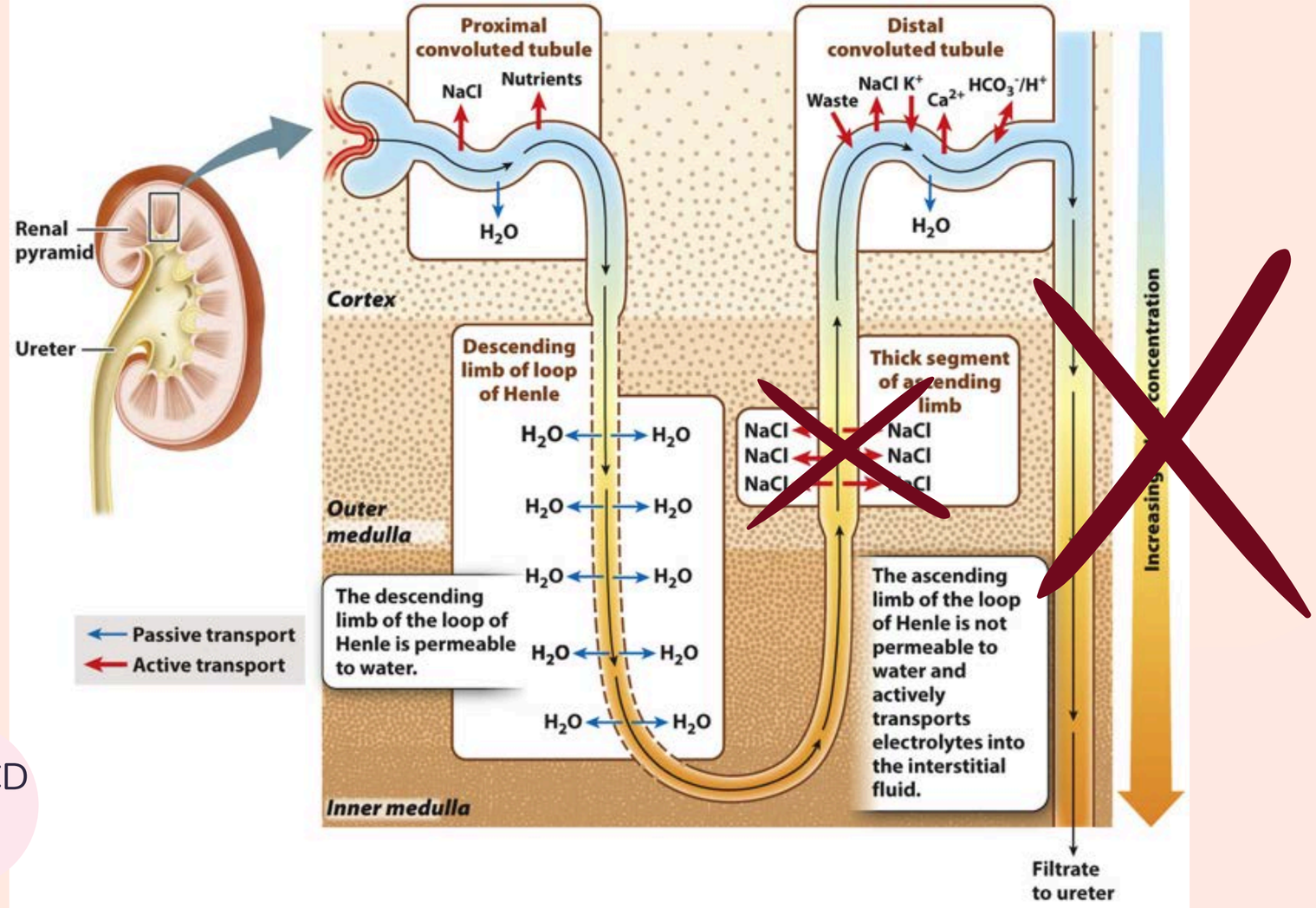
Low threshold for antibiotics to cover encapsulated/atypical organisms and septic screen

Give supplementary oxygen if O2 sats <95%

CXR if chest pain or O2 requirement

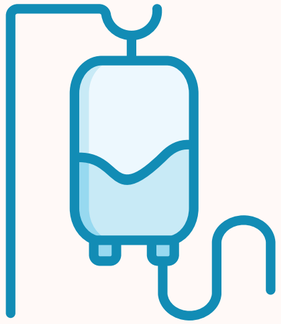
Send bloods including group and screen and haemoglobinopathy screen

URINE CONCENTRATION DEFECTS (HYPOSTHENURIA)



This is near-universal in all SCD patients.

OTHER CONSIDERATIONS



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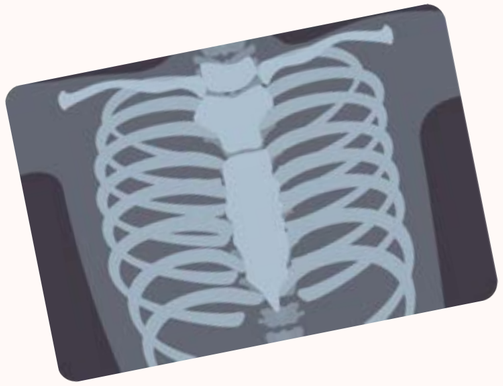
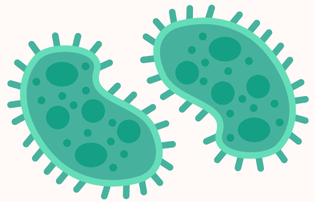


CXR if chest pain or O2 requirement



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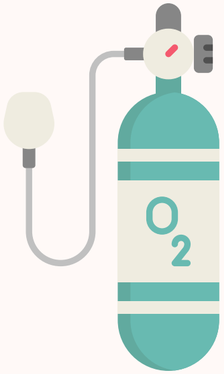

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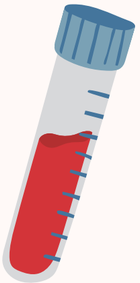


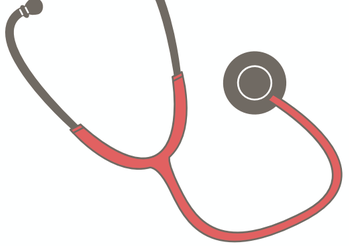
Send bloods including group and screen and haemoglobinopathy screen

OTHER CONSIDERATIONS

"Should I X-ray the painful limb?"

- Not really helpful in diagnosing simple pain crisis
- Consider if clear non-sickle related indication e.g. concern for fracture
- If persistent pain despite analgesia and fever/raised CRP - consider X-ray (but MRI better for osteomyelitis)

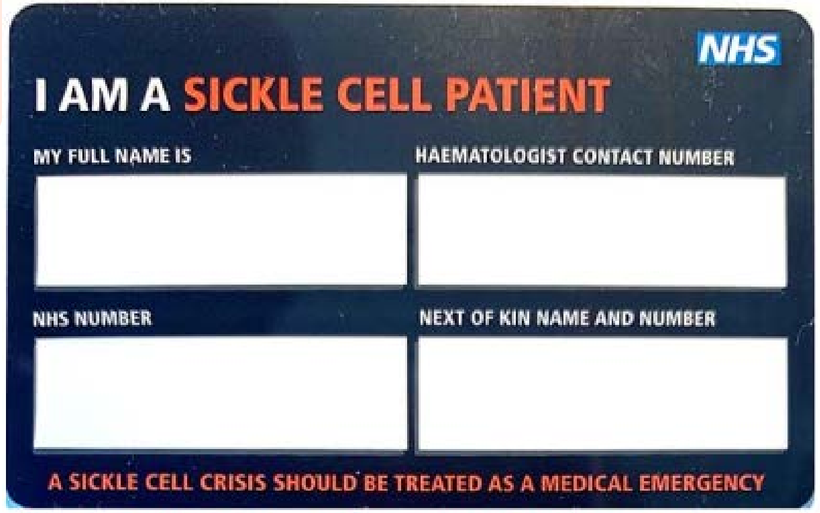
MANAGING ACUTE PAINFUL CRISIS IN SICKLE CELL DISEASE



Sickle Cell Crisis – every second counts

A NALGESIA	**Give analgesia within 30 minutes**, in line with NICE guidance. **Regular assessment of pain score** every 30 minutes until controlled and then every 4 hours. Refer to individualised care plan.
C OMPASSION	**Be compassionate**, Kind, Actively listen, Provide reassurance and keep the patient informed
T EST/TRIGGER	Tests: including transfusion history/previous transfusion reactions. Blood tests (FBC, reticulocyte count, group and save, routine renal, liver & bone biochemistry, CRP), other tests as suggested by history e.g. CXR, MSU. Trigger – what has precipitated the crisis? e.g. infection, dehydration, hypoxia, travel, pregnancy, stress, cold exposure. **Consider IV fluids & antibiotics to treat infection and dehydration.**
N OTIFY	**Notify Specialist Haematology Team** Notify Next of Kin or advocate (when requested or in individual care plan)
O XYGEN	**Offer oxygen supplementation if saturations <95% in room air**; regularly monitor oxygen saturations, including on room air, hourly for the first 6 hours and then 4 hourly if stable as per NICE guidance.
W ATCH	**Watch and keep warm** – regular observations of BP, pulse, respiratory rate, SpO2, temperature. Assess pain every 30 minutes until controlled. **Escalate promptly** (use local scoring e.g. NEWS2 for adults). **Encourage fluids.**

IDENTIFYING PATIENTS AND THEIR PLAN



Acute Personalised Pain Plan For Sickle Cell Disease			
Patient's Name		Date of Birth	
Address		Trust number	
GP Name/Practice		NHS number	
Sex			
Clinical Details			
Sickle Cell Genotype	HbSS		
Medical Surgical History			
Allergies			
Hb	Wbc	Plts	Neut
Medical history			
Analgesia Pain Plan	ED	Assuming patient has taken sufficient analgesia at home, treat as opioid naïve and give initial dose as follows: Pain score 4-7/10: morphine 20mg PO Pain score: 8-10/10: morphine 10mg SC Repeat up to every sixty minutes until pain improves (i.e. any improvement in pain score), then prescribe this dose every 2 hours. See "Urgent management of a sickle cell crisis" guideline for further guidance. Seek senior help if pain not under control in 2 hours.	
	Day Unit	As above.	
	Inpatient	As above.	
	Outpatients	As above.	
Other Medication			

ACUTE MANAGEMENT GUIDELINES

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

Clinical Guideline

SICKLE CELL ACUTE PAIN (VASO-OCCLUSIVE) CRISIS IN THE EMERGENCY DEPARTMENT

SETTING	Emergency department
FOR STAFF	Medical and Nursing staff
PATIENTS	Adult patients diagnosed with sickle cell disease

Guidance

Sickle Cell Disease (SCD) is an inherited disorder of haemoglobin characterised by chronic haemolysis leading to multisystem complications. This is often punctuated by acute crises of varying frequency and severity, which may be life-threatening, and require additional considerations alongside standard patient assessment. The most common is vaso-occlusive painful crisis, which is a **medical emergency**.

This guideline is intended for emergency department use only. The more detailed '24852 Sickle Cell Disease Management for Adults' guideline can be found on MyStaff App.

Management of Acute Presentations of Sickle Cell Disease in the Emergency Department

Royal College *of* Emergency Medicine

NICE National Institute for Health and Care Excellence

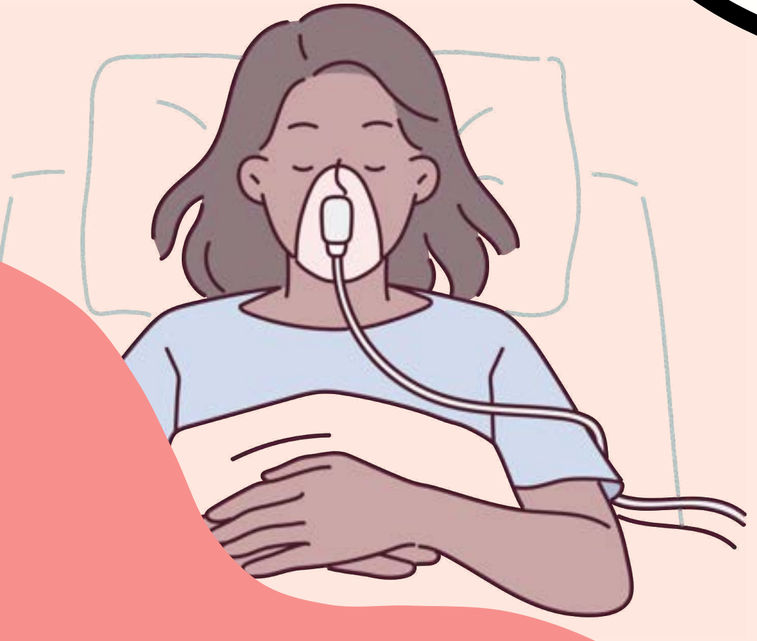
Sickle cell disease: managing acute painful episodes in hospital

DO I NEED TO ADMIT PATIENTS WITH PAINFUL CRISIS?

- If requiring parenteral opiates - yes
- If intercurrent illness - yes
- If not responding as you would expect - yes
- If patient concerns - yes

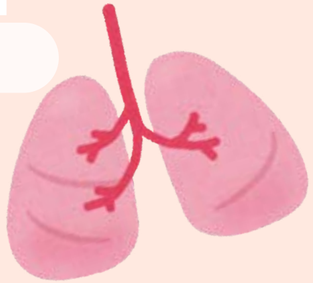
If in doubt, speak to haematology on call

The same patient has been in hospital for two days. Her pain is improving but she has suddenly deteriorated with a new oxygen requirement, cough and fever.



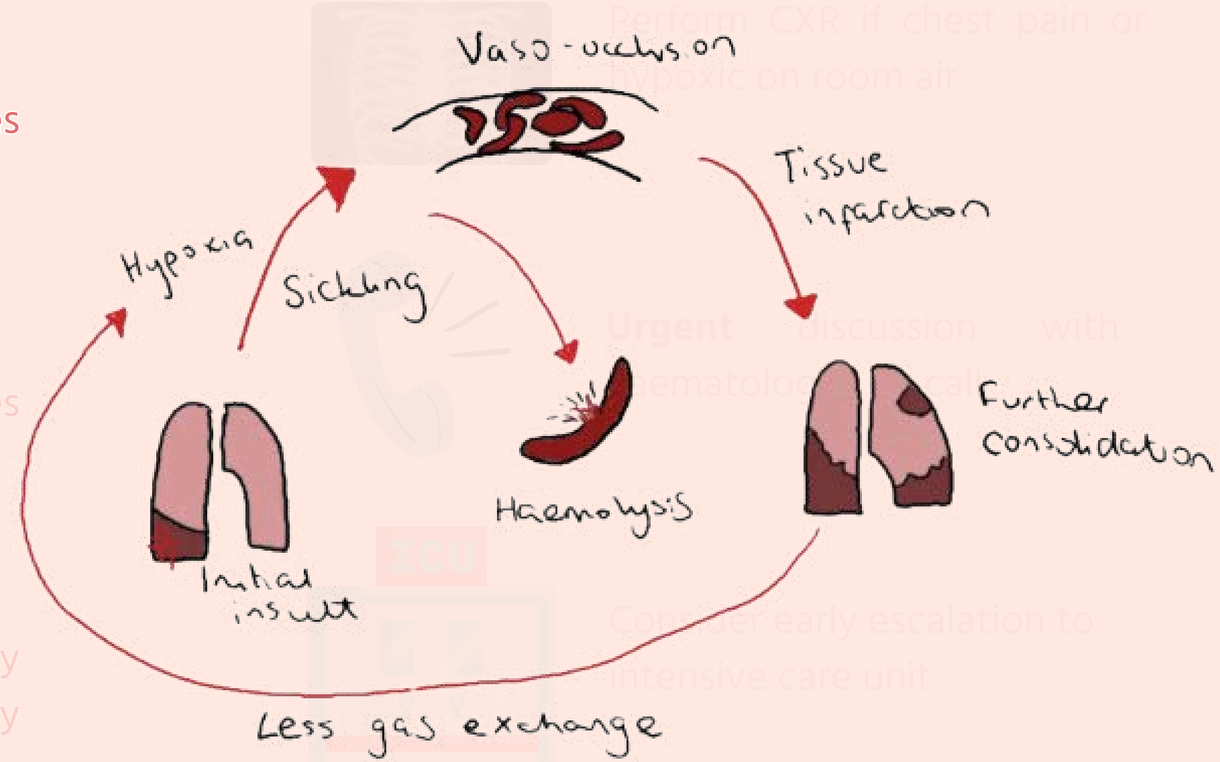
Case Two

ACUTE CHEST SYNDROME



Mechanism

An acute insult on the lung prompts hypoxia, which causes sickling, which leads to more hypoxia, which leads to sickling...



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Clinic

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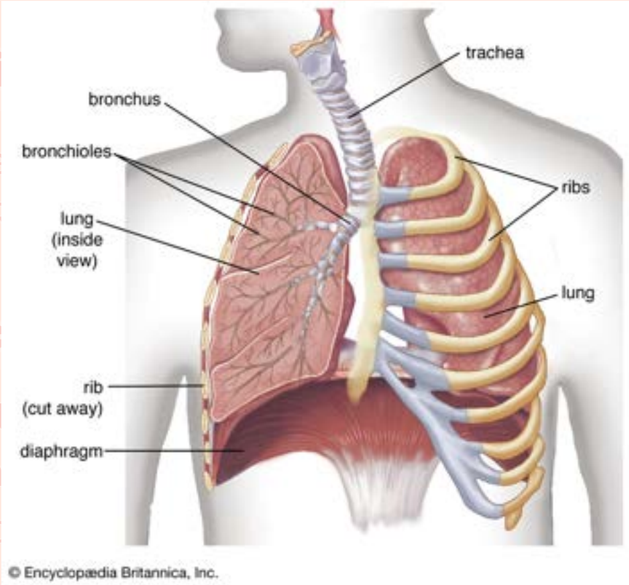


SWRCA

Give supplementary oxygen if oxygen saturations are <95% on air

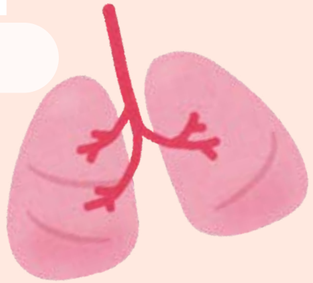
Perform CXR if chest pain or hypoxic on room air

Urgent discussion with haematolo

ICU

Consider early escalation to intensive care unit

ACUTE CHEST SYNDROME



Mechanism

An acute insult on the lung prompts hypoxia, which causes sickling, which leads to more hypoxia, which leads to sickling...

Definition

The definition of acute chest syndrome (ACS) is new infiltrates on CXR with fever and/or respiratory symptoms.

Clinical presentation

Patients may appear well at first but have an escalating early warning score, oxygen requirement or pain. Potential to rapidly deteriorate

Give supplementary oxygen if oxygen saturations are <95% on air

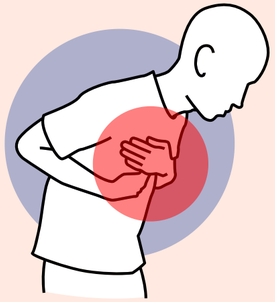
Perform or repeat CXR if chest pain or hypoxic on room air

- Consider CTPA if suspicion of PE

Urgent discussion with haematologist on call

Consider early escalation to intensive care unit

ACUTE CHEST SYNDROME - THE USUAL STORY

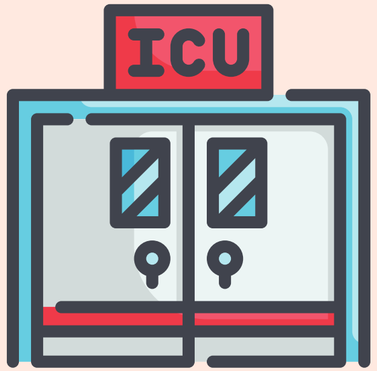


Day 1

Attended ED with back, leg and chest pain
Sats 99% on room air
CXR - clear
Looks very well

Day 2

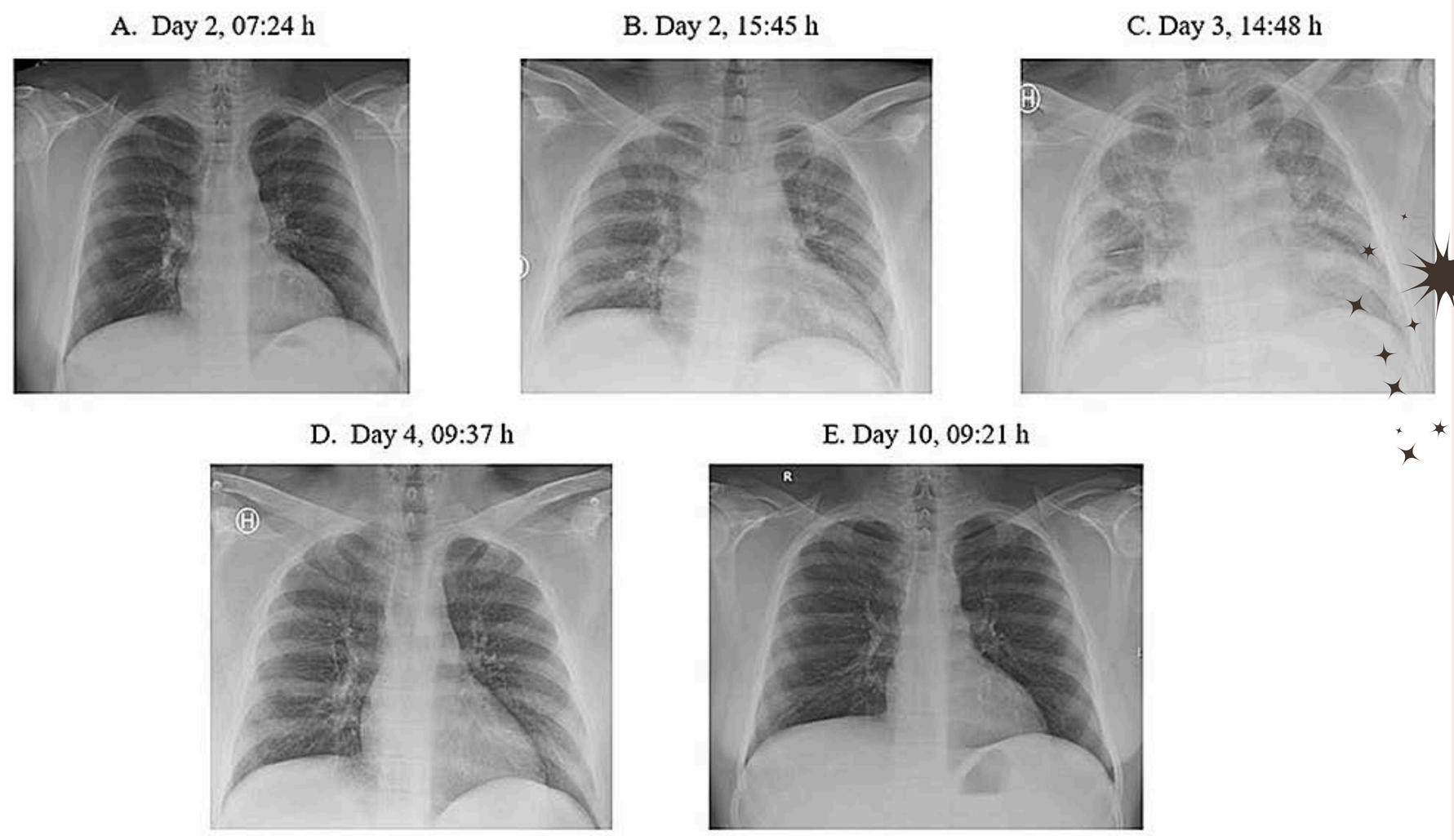
New O2 requirement - 4L nasal cannula
Chest pain settling slightly
New mild cough
Sats 91% on room air, 99% on 4L
CXR - bibasal atelectasis



Day 3

Found with dropped GCS next morning
Sats 85% on 4L O2 - put on 15L non-rebreathe
Transferred to ITU
CXR - left basal consolidation

ACUTE CHEST SYNDROME - THE USUAL STORY



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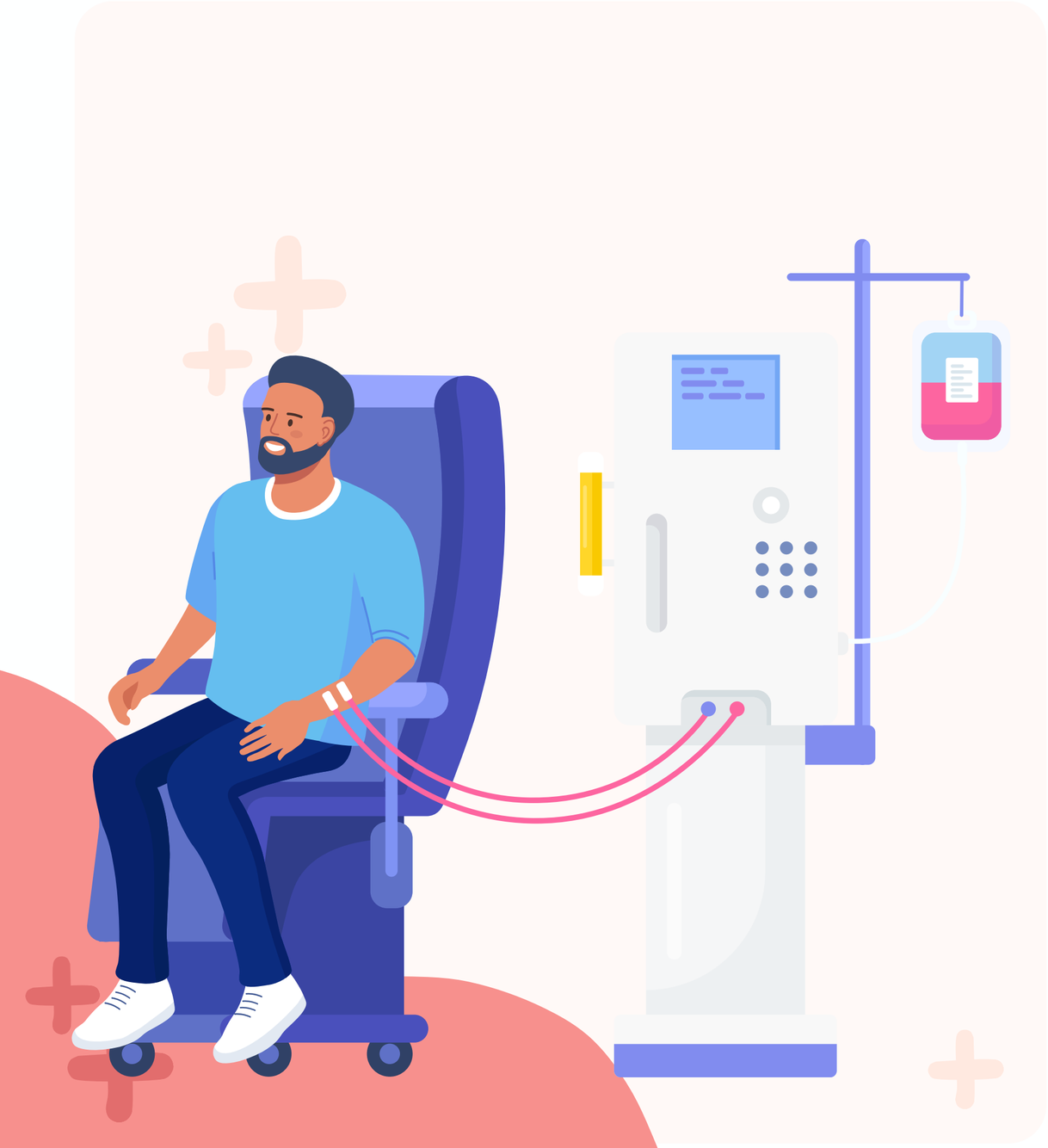


MANAGEMENT OF ACUTE CHEST SYNDROME

Initially:

- Supplementary oxygen
- Adequate analgesia but avoiding sedation
- Incentive spirometry
- Treatment of underlying cause (e.g. antibiotics)

If deteriorating or very unwell:

- Likely to consider blood transfusion - top up or exchange
  - This is a **HAEMATOLOGY CONSULTANT DECISION**

This 21 year old man has attended the emergency department with an unwanted, sustained and painful erection.

Case Three

PRIAPISM

Mechanism

The venous drainage from the penis becomes dysfunctional due to nitric oxide depletion and sickling. Trapped blood causes pain like compartment syndrome. This is a very common complication in adolescent and young adult males.

Types of priapism

Stuttering priapism: recurrent episodes last for less than 4 hours and self-resolve. Penis may not be fully erect. Can precede fulminant priapism

Fulminant priapism: Fully erect penis with soft glans. Severely painful and lasting >4 hours.

Aims of treatment

Treatment aims to preserve erectile function. Significant damage can start to occur at around 6 hours.

Patient will have already tried conservative measures - warm bath, exercise, simple analgesia

Urgent discussion with both haematology and **urology** teams

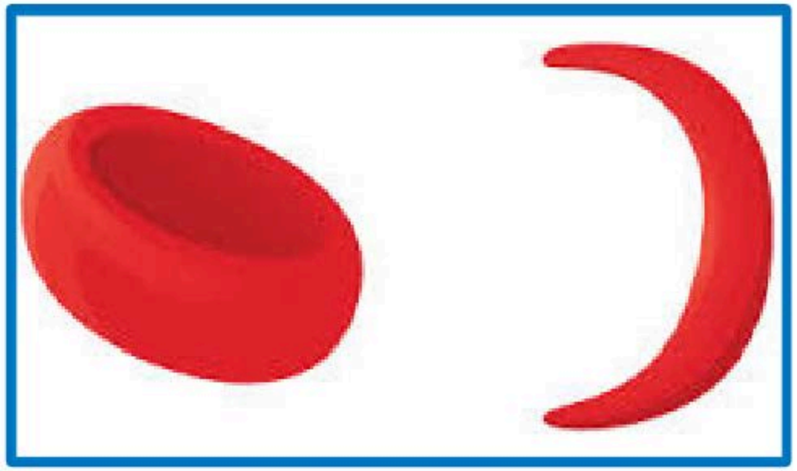
Hyper-hydration can be helpful as a conservative measure

Needle drainage may be required to achieve resolution

NHS
University Hospitals
Bristol and Weston
NHS Foundation Trust

Patient information service
Bristol Haematology and Oncology Centre

Priapism in adults with sickle cell anaemia



What can I do if I get a priapism?

Do the following things immediately:

- Drink lots of fluids
- Take simple painkillers such as paracetamol
- Try to pass urine
- Take a warm bath

- Some people also find that jogging, doing squats or other types of exercise help

These should help to stop the episode within an hour. It is important that you report it to the haematology team caring for you in the next few days.

Do NOT:

- Apply ice or cold water to the penis as it may make it worse
- Engage in sexual activity during priapism. Remember priapism will not be resolved by sex or masturbation
- Take lots of painkillers to manage your priapism; find out about other treatment options
- Use alcohol/cannabis/tobacco/Viagra® as these can potentially worsen or trigger priapism

If the priapism does not go away, you must go to the Emergency Department (A&E) immediately. There is a risk of permanent damage if priapism lasts longer than four hours.

PRIAPISM

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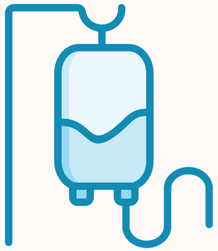

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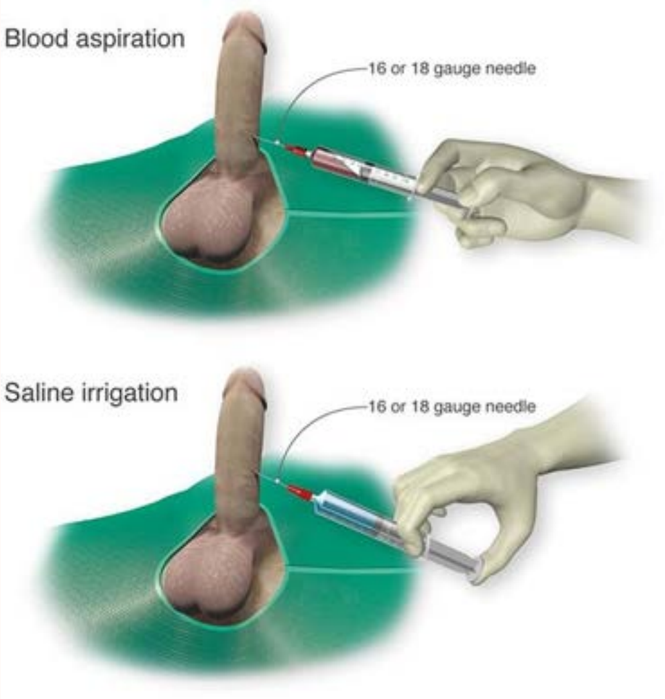
PRIAPISM - MANAGEMENT

Medical management



Needle aspiration +/- irrigation

T shunt procedure

My patient with sickle cell disease has presented with a history of new onset aphasia this morning.

What do I need to do?

What would your immediate management be?

STROKE

Pathophysiology

Haemolysis causes local inflammation, increased endothelial adhesion, vasoconstriction, hypoxia, sickling and eventually ischaemic stroke

The odds are high

- 24% of patients with sickle cell disease have a stroke by age 45
- Children with SCD are 333 times more likely to develop a stroke
- Around half of patients with stroke will get a recurrent episode within 1-2 years without appropriate management

Ischaemic vs haemorrhagic

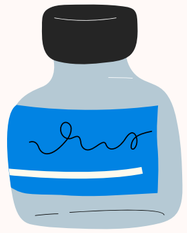
- Majority of strokes are ischaemic, but haemorrhagic more prevalent in 20-30s

There are many other - less common - neurological complications of sickle cell disease

Urgent discussion with haematologist and stroke/neurology clinician on call

Urgent CT imaging to rule out haemorrhagic stroke

Red cell exchange transfusion can terminate the episode

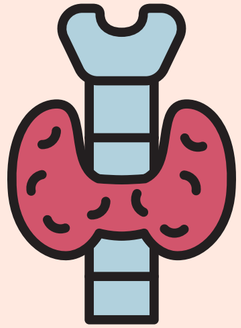


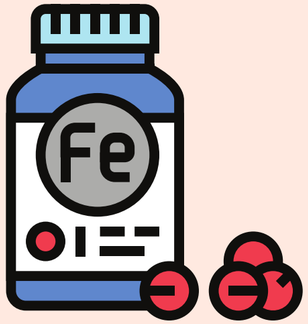
Adult patients with stroke symptoms may be considered for thrombolysis as per stroke pathways (specialist decision)

ACUTE (ON CHRONIC) ANAEMIA

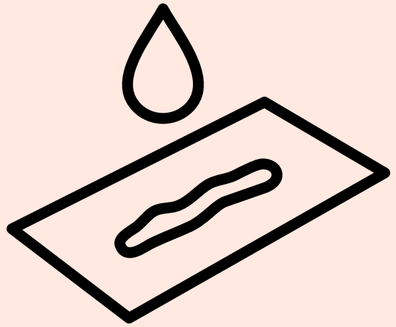
What should we look for?

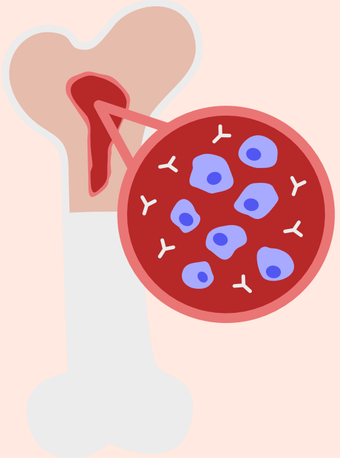
ACUTE (ON CHRONIC) ANAEMIA





Shall I think of the usual culprits?

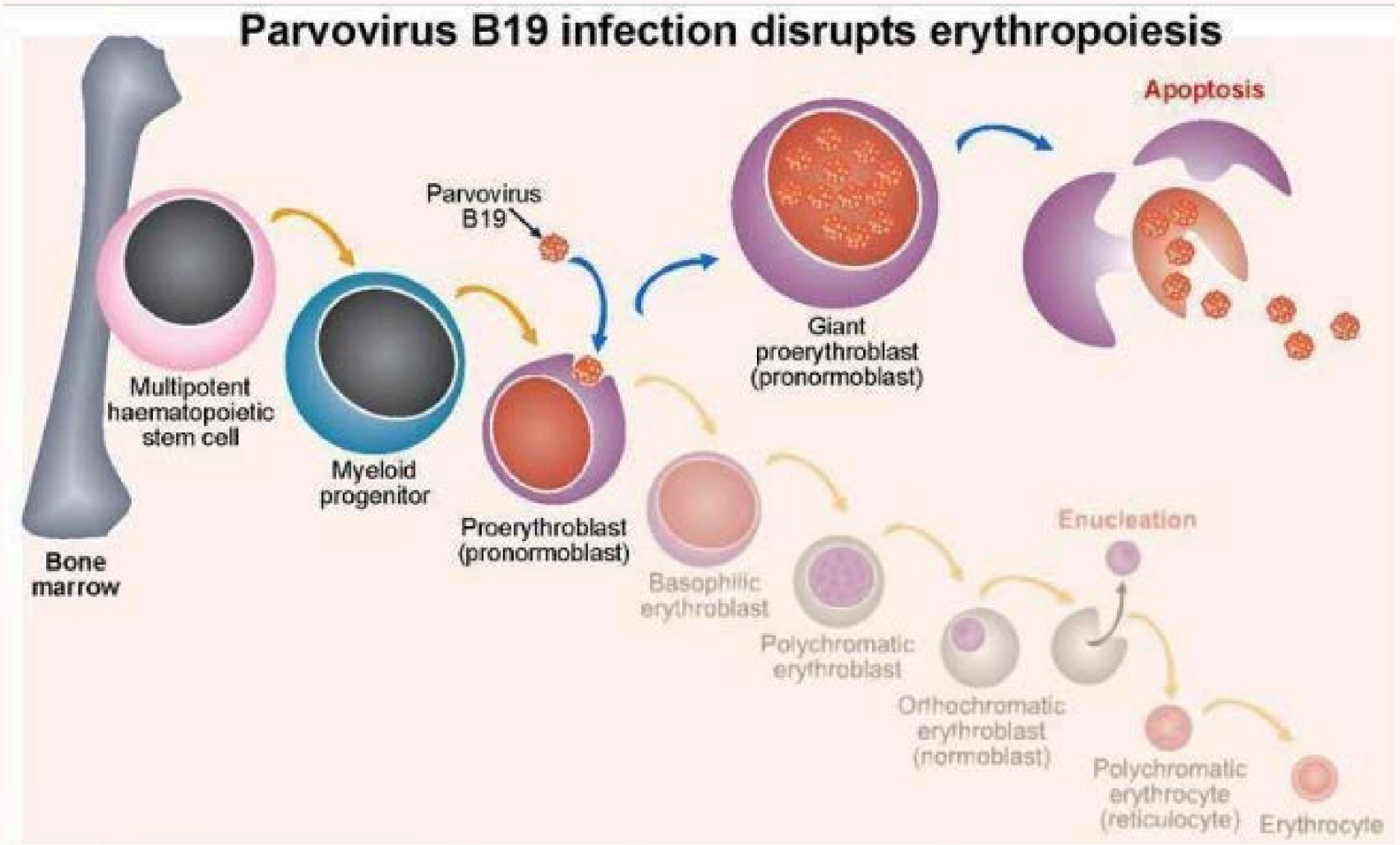




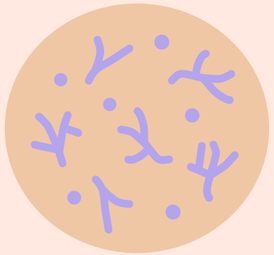
ACUTE (ON CHRONIC) ANAEMIA

Well yes... but we also need to think outside of the box!

APLASTIC CRISIS - PARVOVIRUS



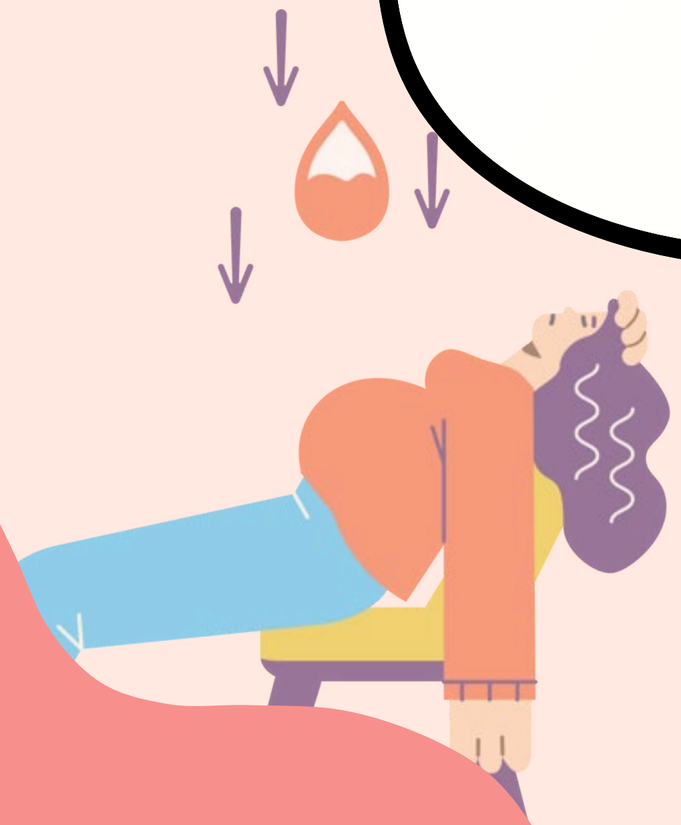
Check the **reticulocyte count**!



Management - transfusion (on haematology advice)

This patient had a transfusion for parvovirus 3 days ago, their Hb was 36

They have presented today with a Hb of 37, fevers and jaundice.



DELAYED HAEMOLYTIC TRANSFUSION REACTION

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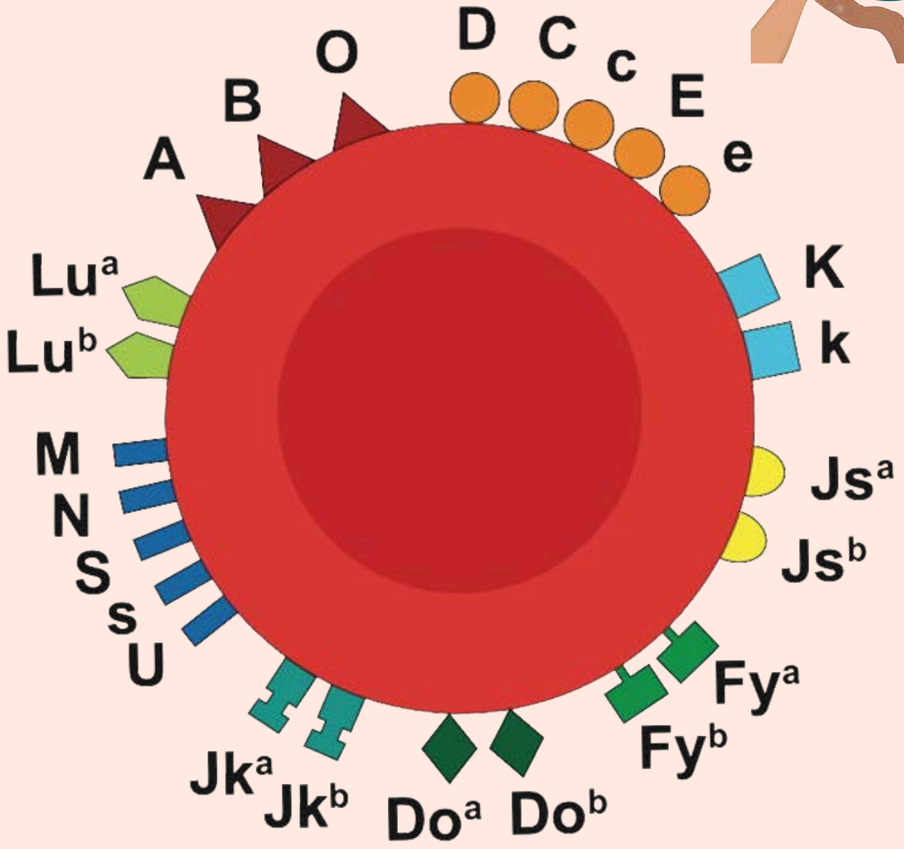

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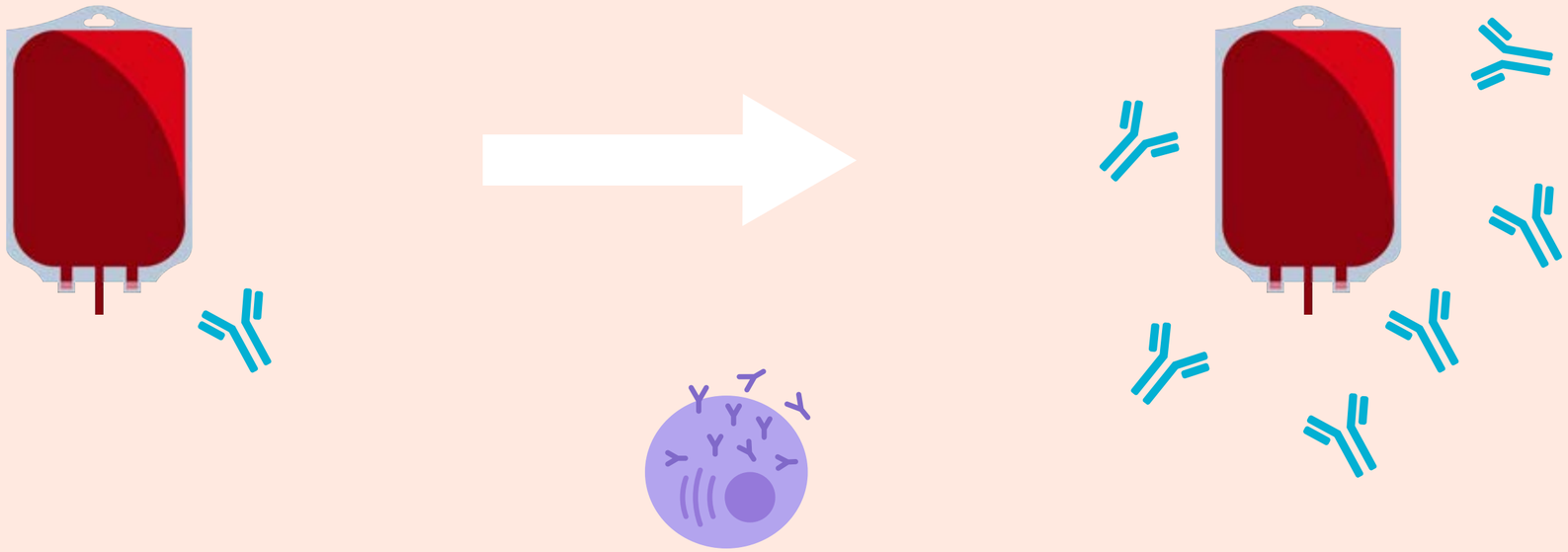

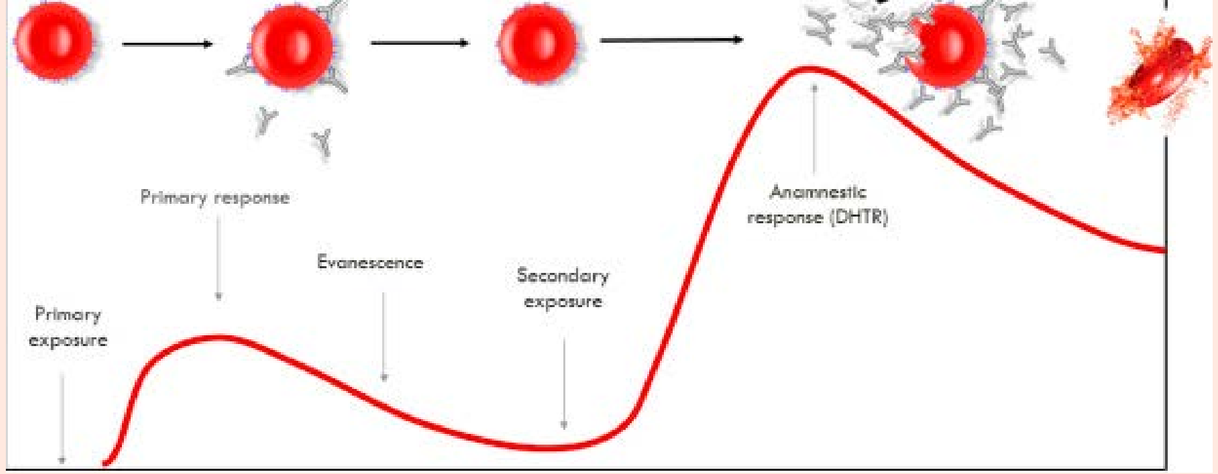

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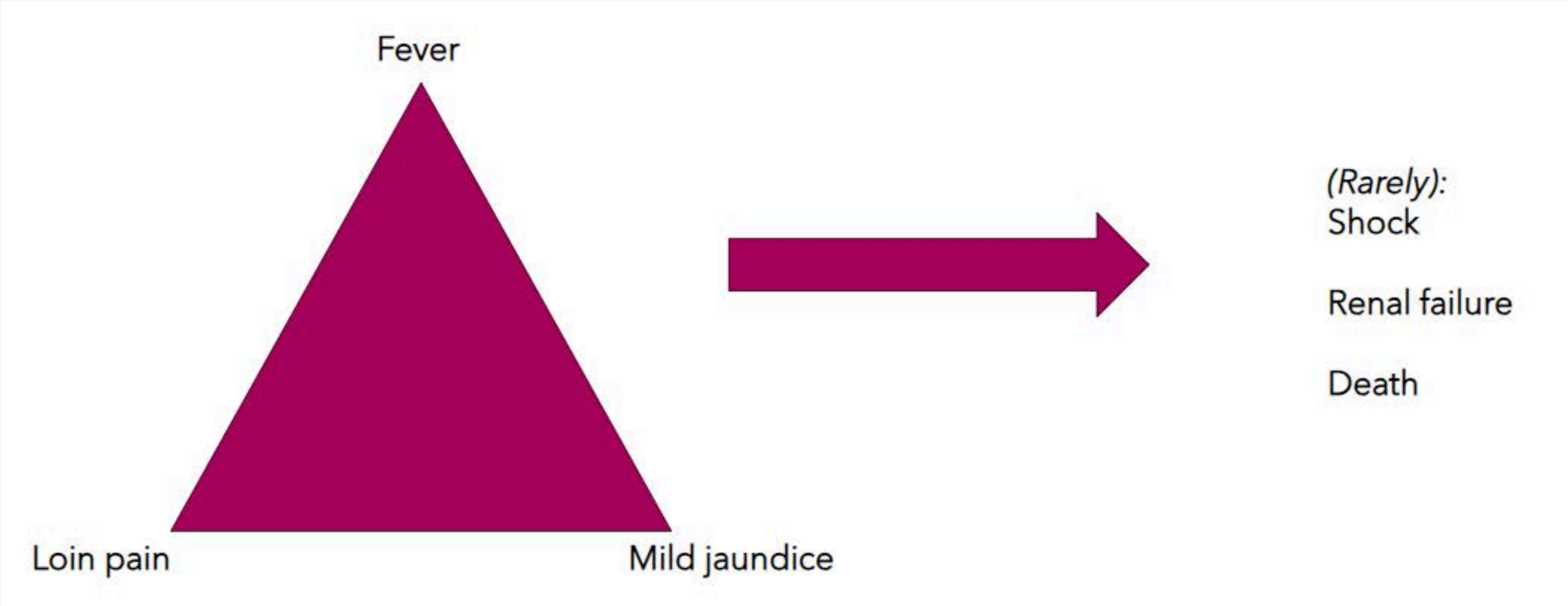
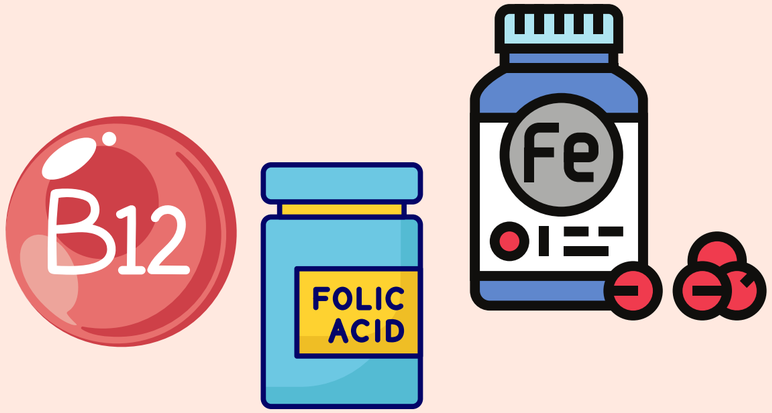
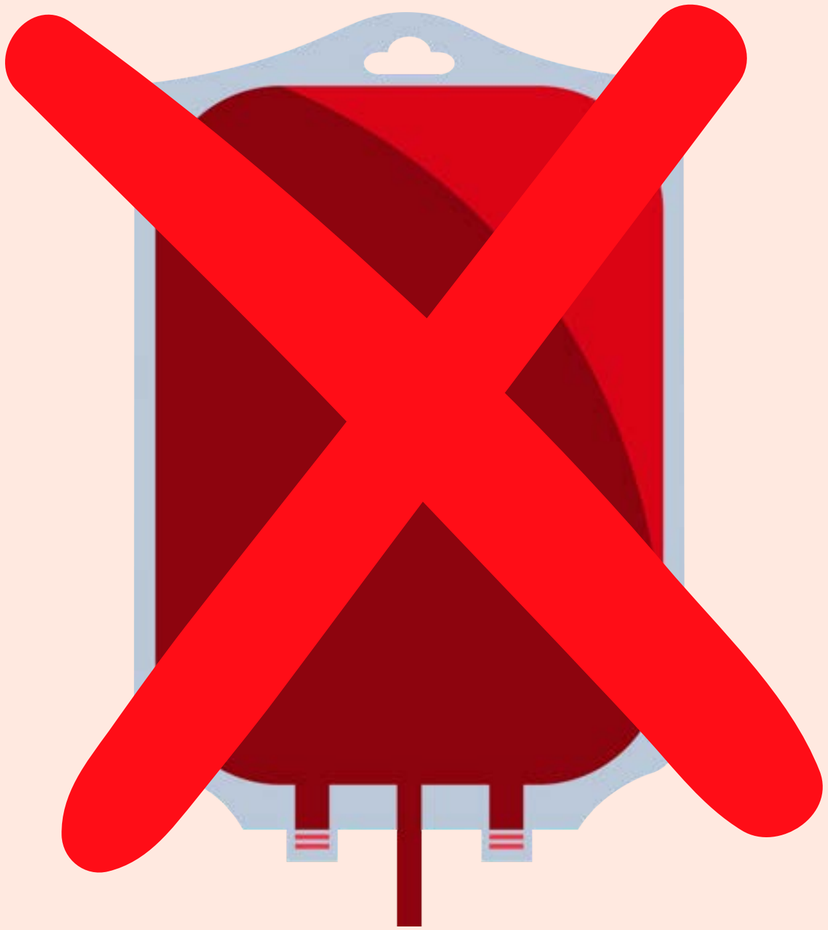


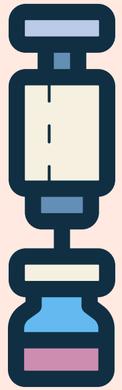
DHTR - MANAGEMENT



Haematinic support



AVOID FURTHER TRANSFUSION!



IV steroids and other medications

IVIG

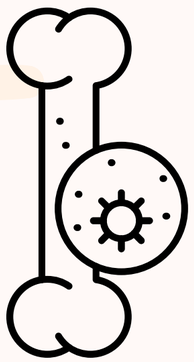
INFECTION

Mechanism

Patients with sickle cell disease become functionally asplenic in the first year of life, before becoming radiologically asplenic. This increases the risk of encapsulated organisms

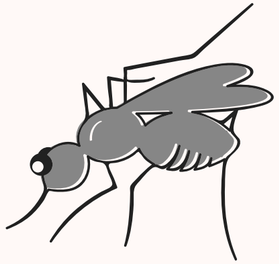
Prevention

Patients are offered lifelong penicillin V prophylaxis and recommended to keep up to date with vaccinations (meningitis, pneumococcal vaccination).



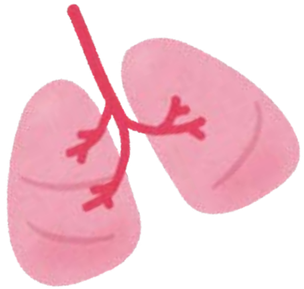
Risk of osteomyelitis caused by encapsulated organisms

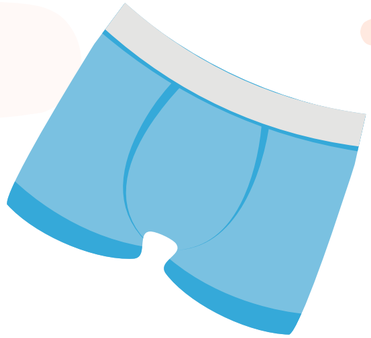
Pneumococcus or haemophilus infection



Consider malaria if appropriate travel history

Yersinia enterocolitica if on iron chelation therapy





THANK YOU!