Sickle cell disease in the emergency ward: the tip of the iceberg

A.Ferster – HUDERF-ULB

47th Annual Meeting of the Belgian Society of Paediatrics (BVK-SBP)
March 2019

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Introduction

- Wide spectrum of symptoms and complications, dominated by vaso-occlusive crises (VOC), infections, multi-organ dysfunction, poor quality of life and shorter life expectancy.
- > 200.000 newborns/year

- 1000 pts in Belgium?
- 700 registered in Belgian Registry

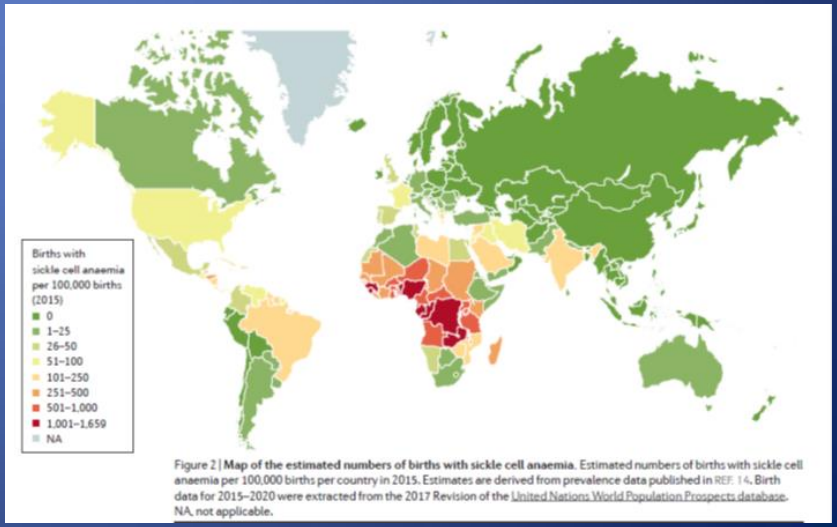


Figure 2 | **Map of the estimated numbers of births with sickle cell anaemia.** Estimated numbers of births with sickle cell anaemia per 100,000 births per country in 2015. Estimates are derived from prevalence data published in REF. 14. Birth data for 2015–2020 were extracted from the 2017 Revision of the United Nations World Population Prospects database. NA, not applicable.

Pathophysiology

Single amino-acid change

The most common sickle cell syndromes	
Sickle cell disease	**Disease severity**
- **Homozygous Hb S**	Moderate to severe
- **Hb SC**	Mild to severe
- **HbS ß°- thalassemia**	Severe
- **HbS ß⁺- thalassemia**	Mild to severe
- **Hb SD^{Punjab}**	Moderate to severe

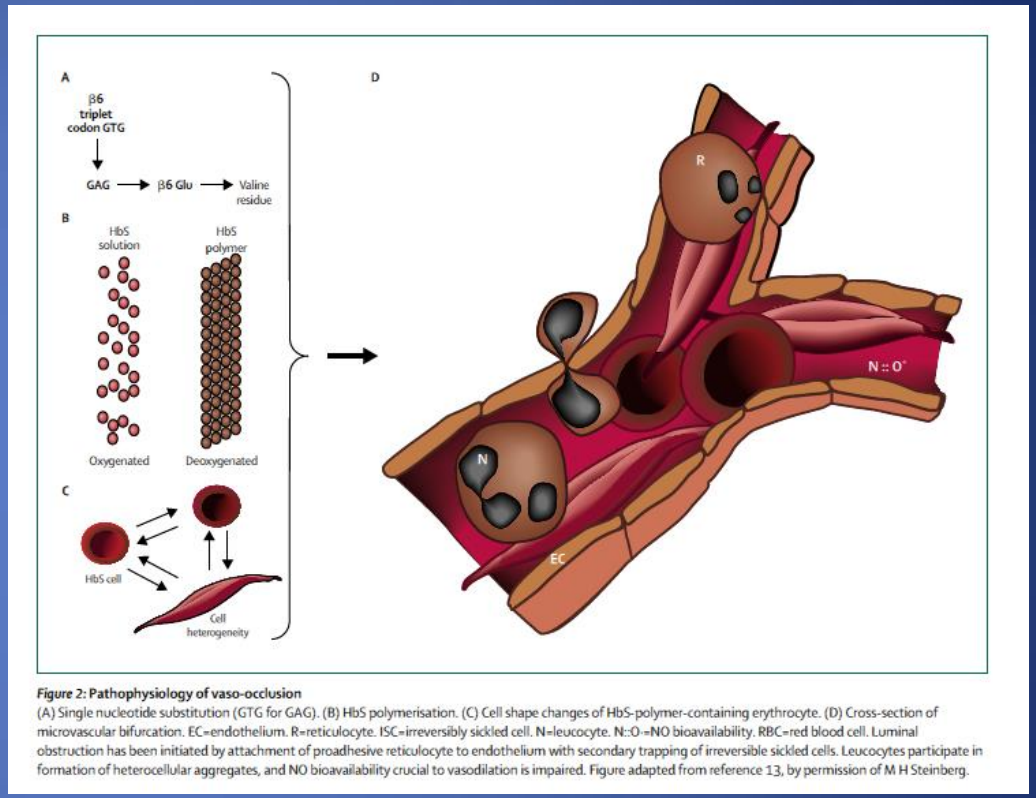


Figure 2: **Pathophysiology of vaso-occlusion**
(A) Single nucleotide substitution (GTG for GAG). (B) HbS polymerisation. (C) Cell shape changes of HbS-polymer-containing erythrocyte. (D) Cross-section of microvascular bifurcation. EC=endothelium. R=reticulocyte. ISC=irreversibly sickled cell. N=leucocyte. N::O=NO bioavailability. RBC=red blood cell. Luminal obstruction has been initiated by attachment of proadhesive reticulocyte to endothelium with secondary trapping of irreversible sickled cells. Leucocytes participate in formation of heterocellular aggregates, and NO bioavailability crucial to vasodilation is impaired. Figure adapted from reference 13, by permission of M H Steinberg.

Hemolysis
Vaso-occlusion/ hyperviscosity

Stuart et al. *Lancet*. 2004

Rees et al. *Lancet*. 2010

Kato. *Blood Reviews*. 2018

Clinical symptoms, complications and survival

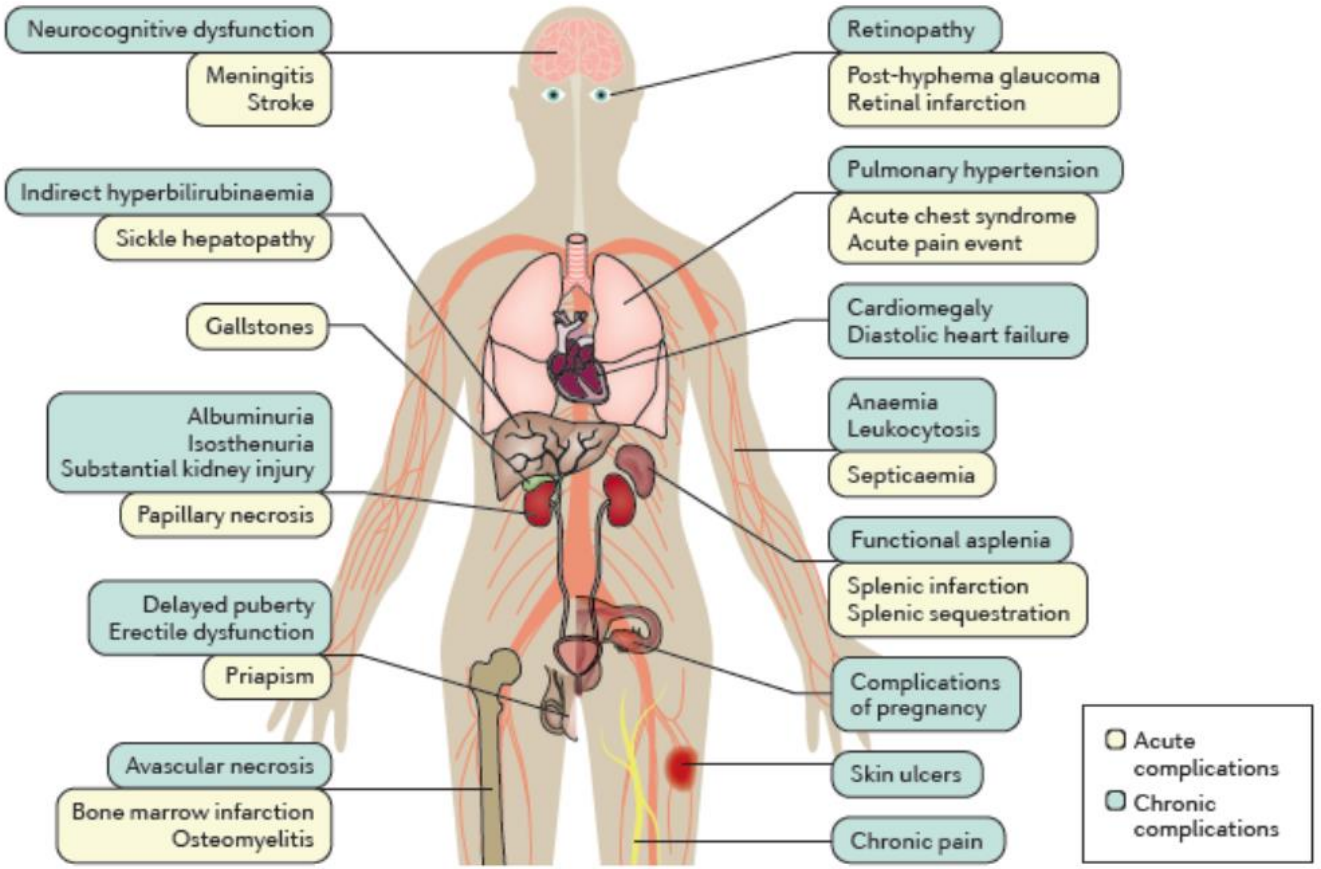
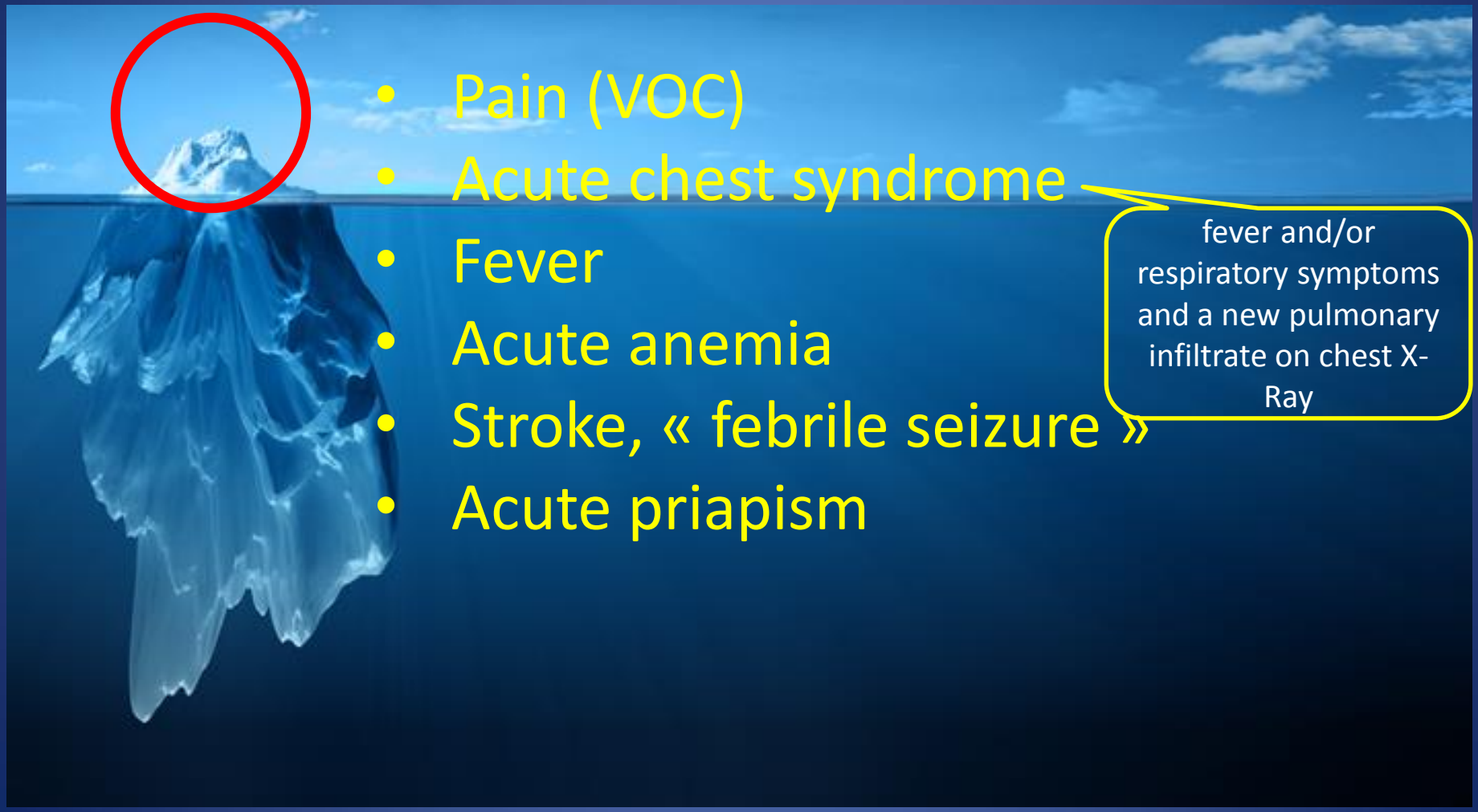


Figure 5 | **Sickle cell disease clinical complications**. Acute complications bring the individual with sickle cell disease (SCD) to immediate medical attention; pain is the most common acute complication. As individuals with SCD age, chronic complications produce organ dysfunction that can contribute to earlier death. Complications of pregnancy include pre-eclampsia, intrauterine growth restriction, preterm delivery and perinatal mortality.

Kato (2018)

Reasons for ED visits



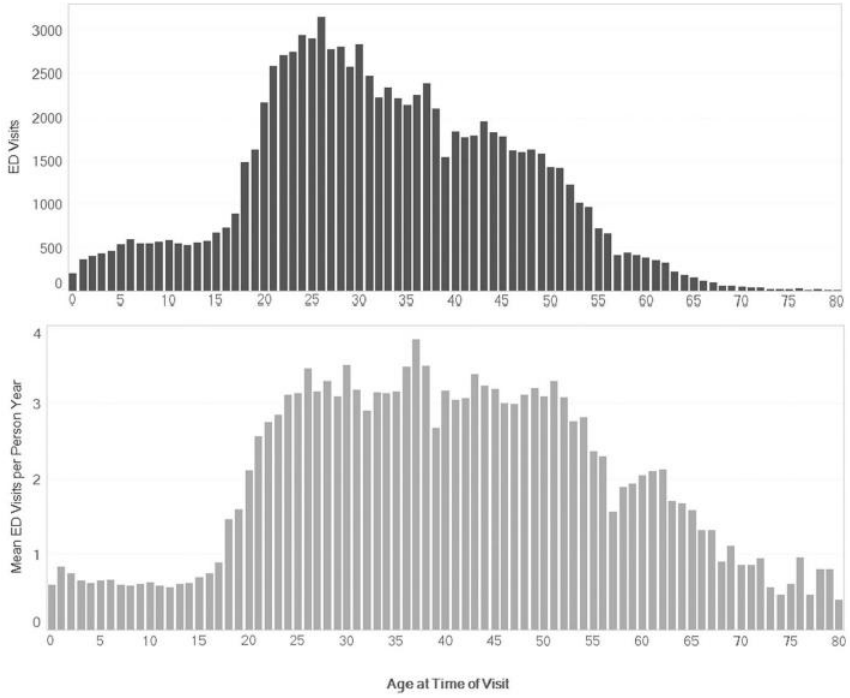
- Pain (VOC)
- Acute chest syndrome
- Fever
- Acute anemia
- Stroke, « febrile seizure »
- Acute priapism

fever and/or respiratory symptoms and a new pulmonary infiltrate on chest X-Ray

Pediatr Blood Cancer. 2017 June ; 64(6): . doi:10.1002/pbc.26390.

Emergency department utilization by Californians with sickle cell disease, 2005–2014

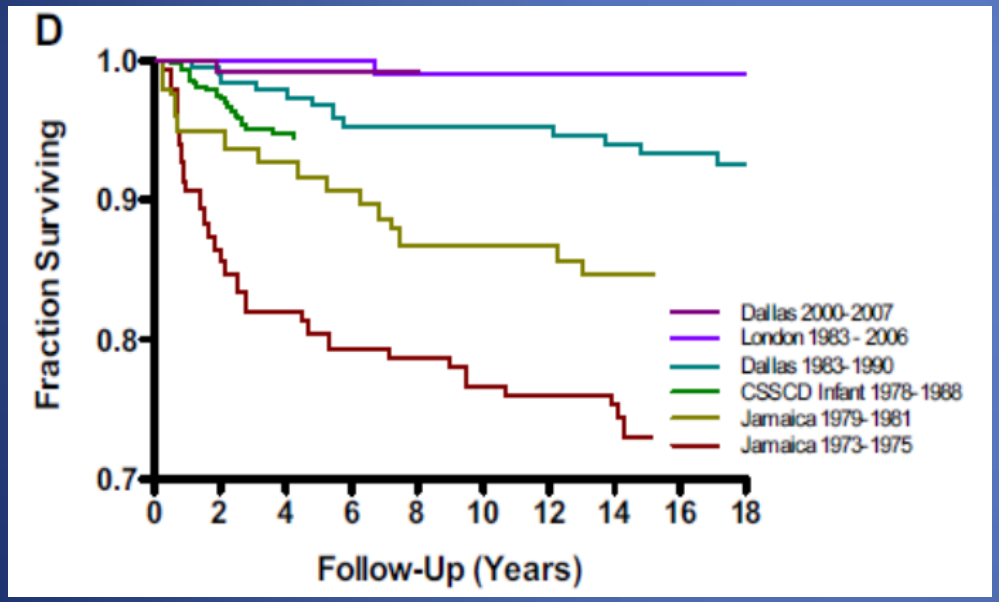
Susan T. Paulukonis[1], **Lisa B. Feuchtbaum**[2], **Thomas D. Coates**[3], **Lynne D. Neumayr**[4], **Marsha J. Treadwell**[4], **Elliott P. Vichinsky**[4], and **Mary M. Hulihan**[5]

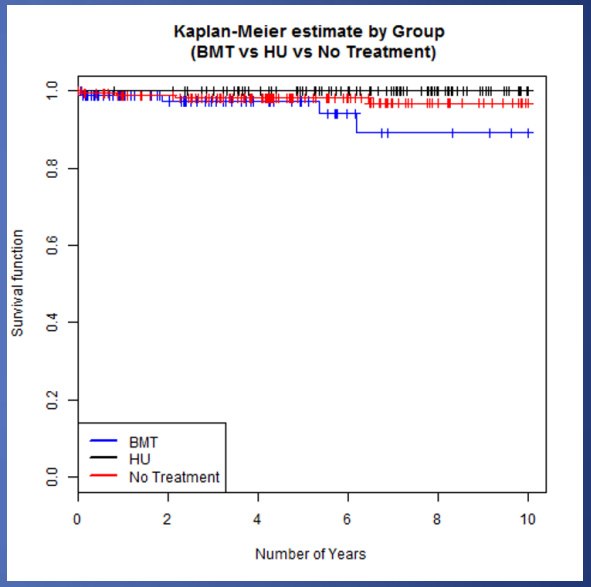


1 ED visit/y
(never for some, many for others)
Much higher in AYA

Survival and causes of deaths

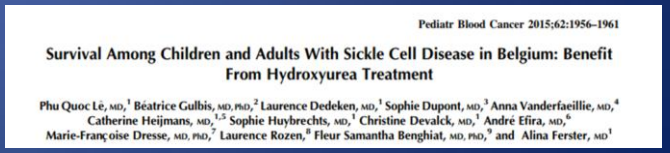
Death rate:
0,20 to 0,60/100 PY





Belgium
470 patients from 6 centres
Follow-up: 3810 pts-years

Dallas cohort
940 subjects with 8857 patient-years of follow-up
Quinn et al (Blood 2010)



Pediatr Blood Cancer 2015;62:1956–1961

Survival Among Children and Adults With Sickle Cell Disease in Belgium: Benefit From Hydroxyurea Treatment

Phu Quoc Lê, MD,[1] Béatrice Gulbis, MD, PhD,[2] Laurence Dedeken, MD,[1] Sophie Dupont, MD,[3] Anna Vanderfaeillie, MD,[4] Catherine Heijmans, MD,[1,5] Sophie Huybrechts, MD,[1] Christine Devalck, MD,[1] André Efira, MD,[6] Marie-Françoise Dresse, MD, PhD,[7] Laurence Rozen,[8] Fleur Samantha Benghiat, MD, PhD,[9] and Alina Ferster, MD[1]

Improved survival of children and adolescents with sickle cell disease

Charles T. Quinn,[1-3] Zora R. Rogers,[1-3] Timothy L. McCavit,[1-3] and George R. Buchanan[1-3]

[1]Division of Hematology-Oncology, Department of Pediatrics, The University of Texas Southwestern Medical Center, Dallas; [2]Southwestern Comprehensive Sickle Cell Center, Dallas, TX; and [3]Children's Medical Center Dallas, TX

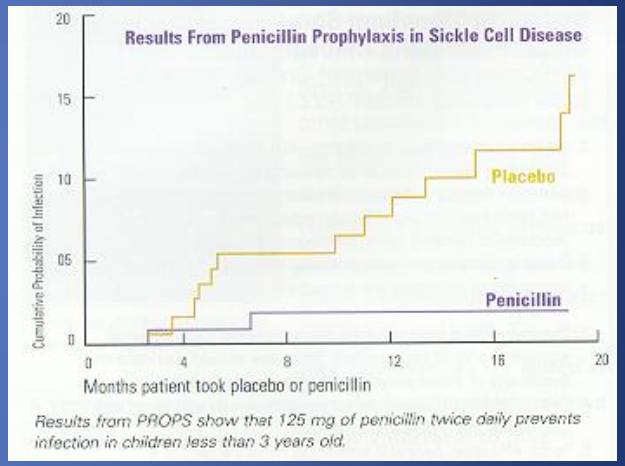
Blood 2010

Deaths in the Dallas Newborn Cohort (n=32)

	No	Age (y)
Related to SCD	**23**	
• **Acute Chest Syndrome**	**5**	**4,5,5,18,19**
• **MOF**	**4**	**4,14,18,19**
• **Pneumococcal/ *H influenzae* sepsis**	**5**	**2,3,5,5**
• **Multifactorial**	**4**	**<1,2,4,20**
• **Stroke/ neurologic event**	**2**	**7,23**
• **Complication of renal failure**	**1**	**18**
• **Cefriaxone-induced hemolysis**	**1**	**2**
• **Myocardial Infarction**	**1**	**13**
Not related to SCD	**9**	**1-17**

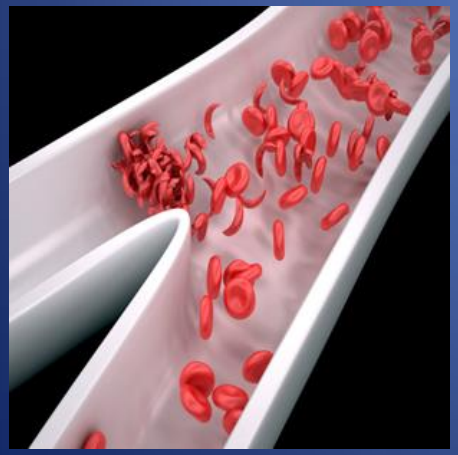
Management

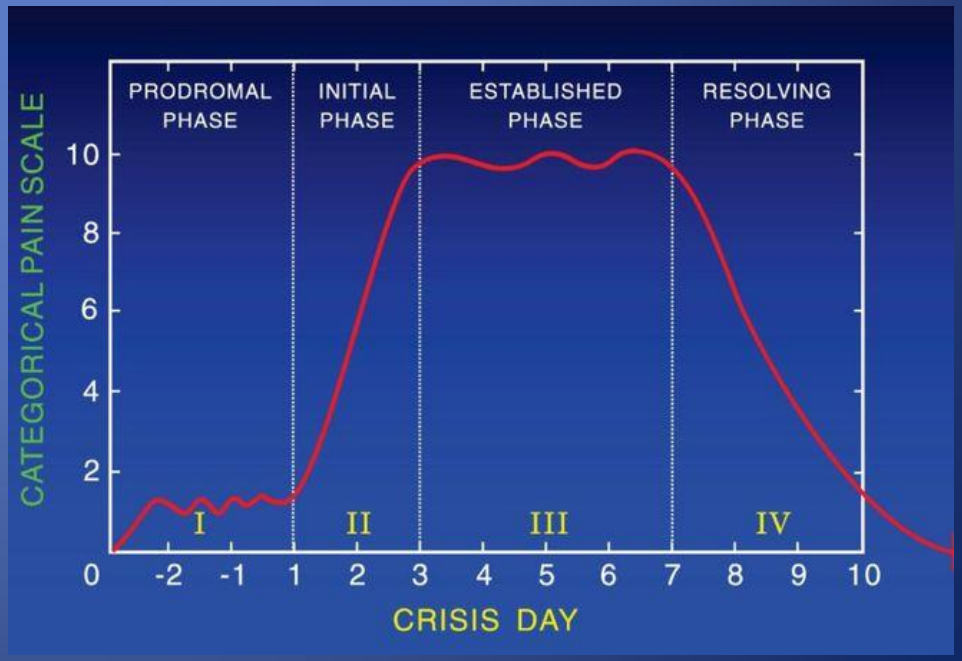
- Education
- Prevention of infections (vaccination, antibiotic prophylaxis)
- Management of acute events
- Prevention of stroke (TCD echo)
- Treatment of complications
- Disease modifying therapy (DMT)
  - Hydroxyurea
  - Chronic transfusion (or exchange)
  - Hematopoietic stem cell transplantation
  - New drugs, gene therapy in the pipeline



Pain crises: the most distinguishing clinical feature of SCD

- Vaso-occlusive pain < obstruction of microcirculation by sickled RBCs, causing ischemic injury
- > 50% patients > 1 episod /y but 1% have more > 10
- VOC rate correlated to the risk of death
- Pain usually multifocal



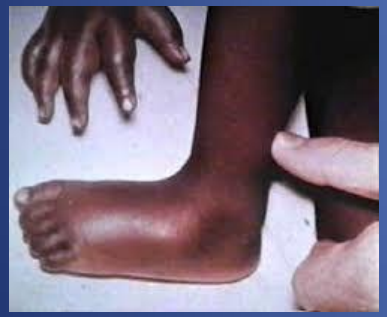


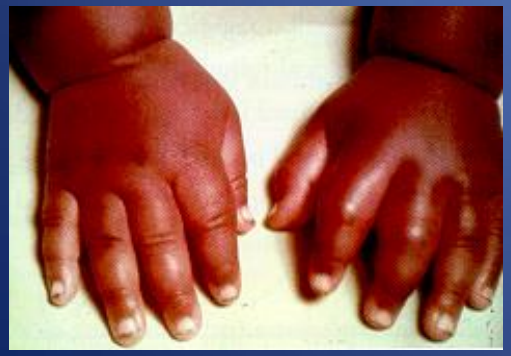
Pain crises: the most distinguishing clinical feature of SCD

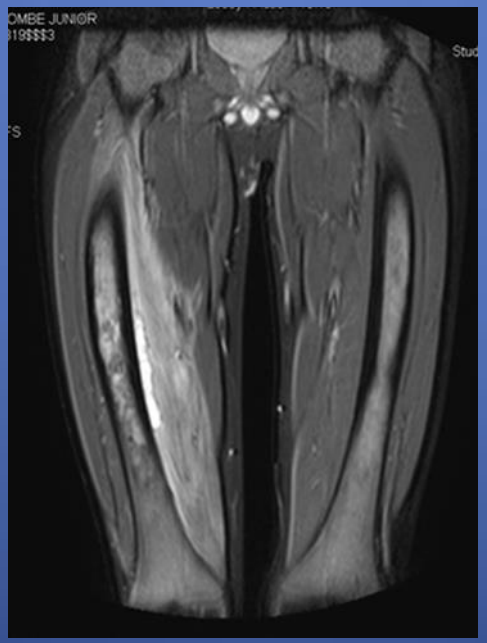
- Pain is a complex phenomenon
  - Central and peripheral sensitization/ Allodynia
  - Nociceptive/neuropathic
- VOC described as comparable to or worse than cancer pain

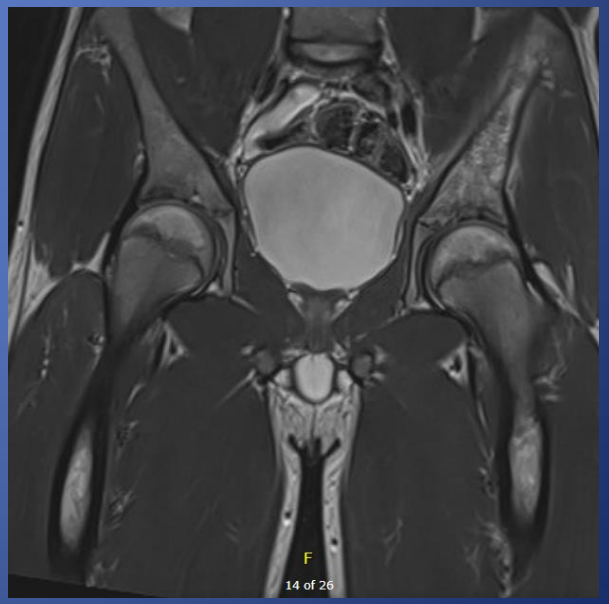
Vaso-occlusive crises

- Dactylitis (< 2 years) Painful swelling of hands and feets
- Muscular Osteo-articular crisis (can mimic osteoarthritis)
- Abdominal pain/ileus (young children) (« appendicitis »)









VOC in the emergency ward

Priority Management

- Evaluation: Pain scale, fever, vital signs, pulse oximetry (≥ 96%)
- Rapid and agressive pain management
- Correct hydration (oral, IV)

- Unfortunately, significant delay to initiate analgesic medication
- Delay in the treatment of pain increases the number of further ED visits
- In AYA, the risk of death increases with the number of ED visits
- Appropriate management will reduce the risk of further addiction and drug abuse

BHS clinical guideline on management of acute complications in sickle cell disease.
Toon Van Genechten et al, in press

Pain management

Start quickly (within 30 min), manage aggressively

Re-evaluate at least every 30 min

Consider strong opioids early in management

Consider the use of N_20 (laughing gas, MEOPA, kalinox)

- Add N_20 (for 20') before opiates can be given

Follow local pain management instruction specifically adapted for sickle cell patients

- Individualize pain management based on patient experience

Consider the use of patient controlled anesthesia (PCA) pumps

- Ensure continuous pain medication administration and not only on demand

Auto and hetero evaluation are mandatory for a good evaluation of pain

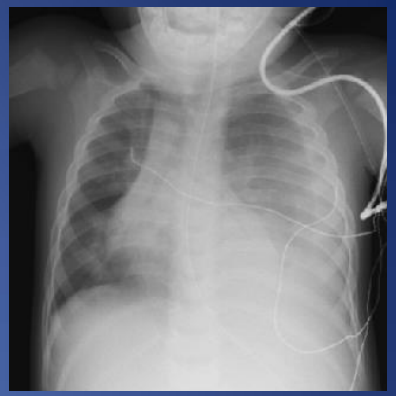
- auto evaluation might be unreliable in patients who experience a lot of pain episodes,

Be aware of neuropathic pain and its specific management

Consider non pharmacological support for pain

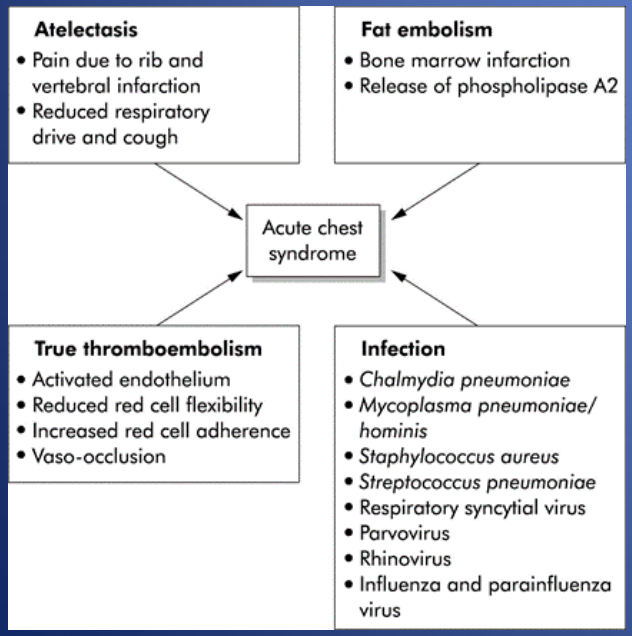
- Refer the patient to his treating hematologist (review compliance, education, DMT)

Acute Chest Syndrome



Complication characterized by fever and/or respiratory symptoms and a new pulmonary infiltrate on chest X-Ray

Life-threatening complication
Chest pain, fever and difficulty breathing may be present a presentation or follow a classical VOC



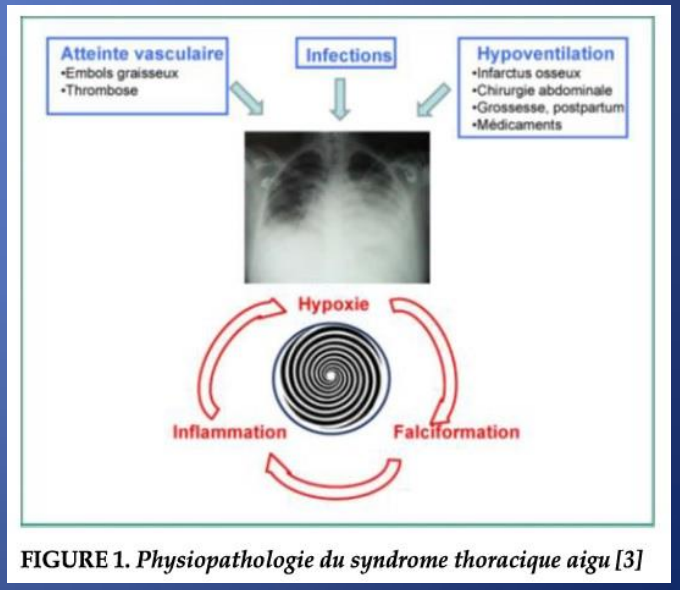


FIGURE 1. *Physiopathologie du syndrome thoracique aigu [3]*

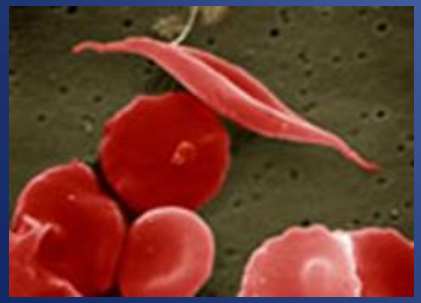
Pulse oxymetry
Caution in interpretation!!

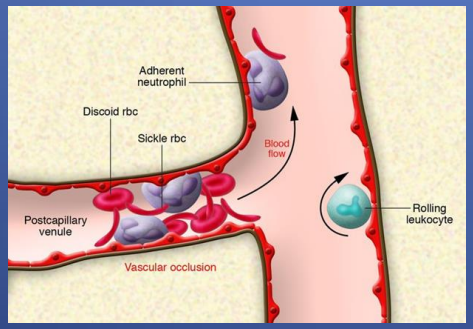
Patients with hemoglobin saturation on pulse oxymetry ≤ 95% may be severely hypoxic!

Eur J Haematol 2005: 74: 309–314
All rights reserved

EUROPEAN
JOURNAL OF HAEMATOLOGY

Hemoglobin oxygen saturation discrepancy using various methods in patients with sickle cell vaso-occlusive painful crisis





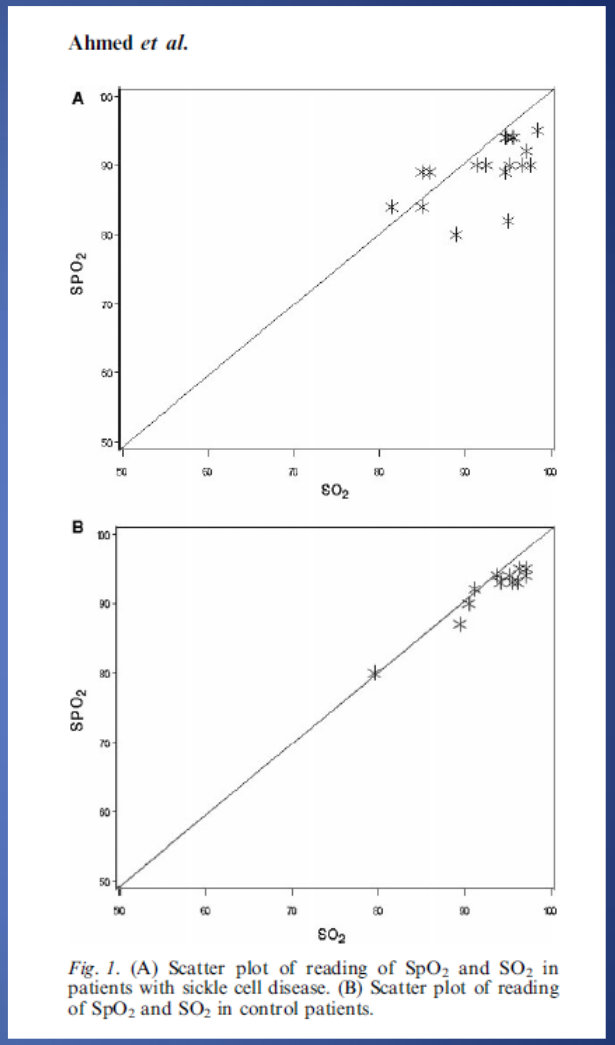


Fig. 1. (A) Scatter plot of reading of SpO_2 and SO_2 in patients with sickle cell disease. (B) Scatter plot of reading of SpO_2 and SO_2 in control patients.

Acute Chest Syndrome management

- Start antibiotics (ceftriaxone and macrolides)
- Avoid fluid overload
- Treat pain aggressively
- Mobilization and spirometry
- If pulse oxymetry indicates saturation ≤ 95%
  - Give oxygen (keep saturation >95%)
  - Refer for specialized care (Hemato + ICU)
  - Transfuse if hypoxemia < 70 mmHg
    - If Hb ≥ 9 g/dL: exchange transfusion (avoid increase blood viscosity)

Fever and infections

- Functional asplenia < 1y
- ↑↑↑ risk of invasive bacterial infection
- Major cause of death
- Fever → Need of aggresive management

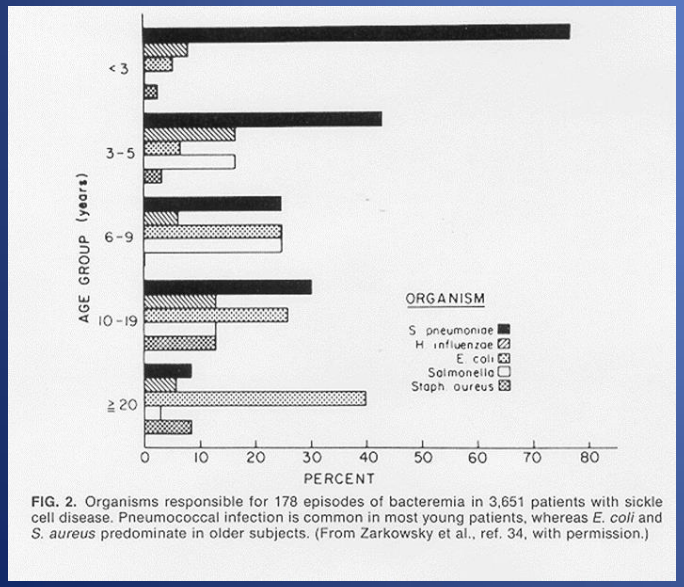
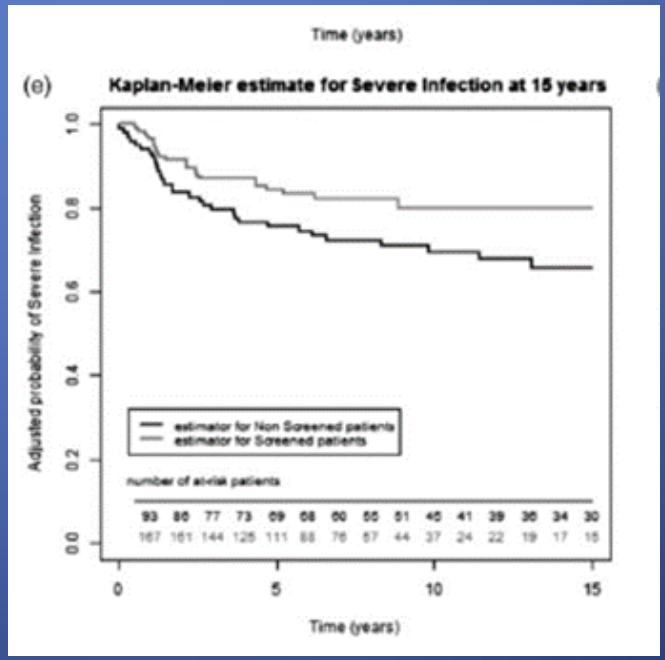


FIG. 2. Organisms responsible for 178 episodes of bacteremia in 3,651 patients with sickle cell disease. Pneumococcal infection is common in most young patients, whereas *E. coli* and *S. aureus* predominate in older subjects. (From Zarkowsky et al., ref. 34, with permission.)



Lê et al, 2017

Severe anemia

Chronic hemolytic anemia

HbSS: steady-state Hb 6-9 g/dl

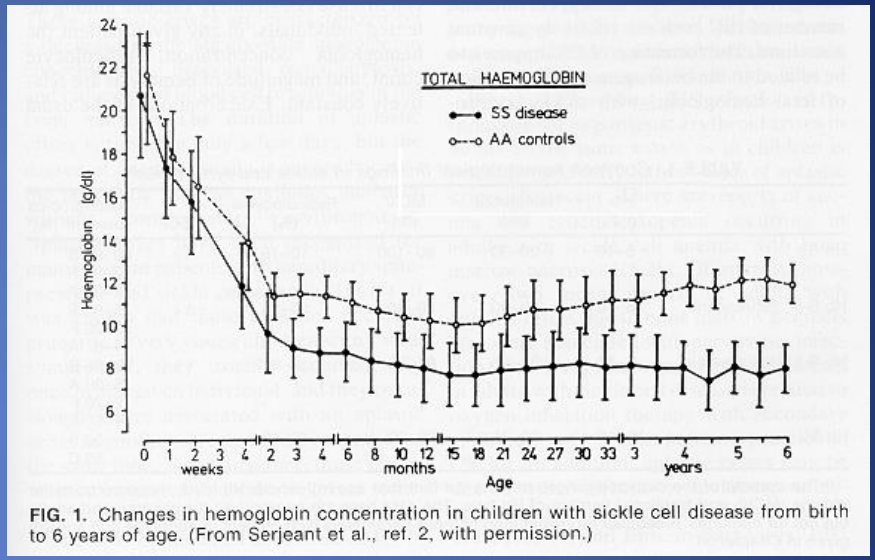
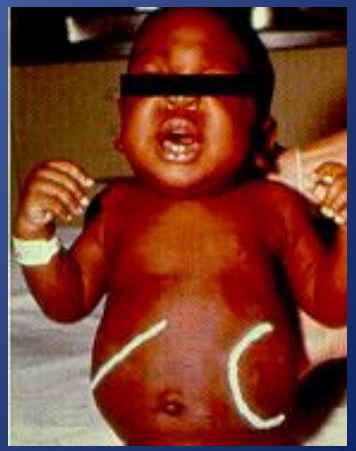


FIG. 1. Changes in hemoglobin concentration in children with sickle cell disease from birth to 6 years of age. (From Serjeant et al., ref. 2, with permission.)

Acute anemia

- Splenic sequestration* (acutely enlarging spleen with a fall of Hb of >2 g/dl)
- Transient erythroblastopenia*
- Infection, malaria
- VOC/hemolysis
- G6PD deficiency

* life-threatening condition/absolute medical emergency



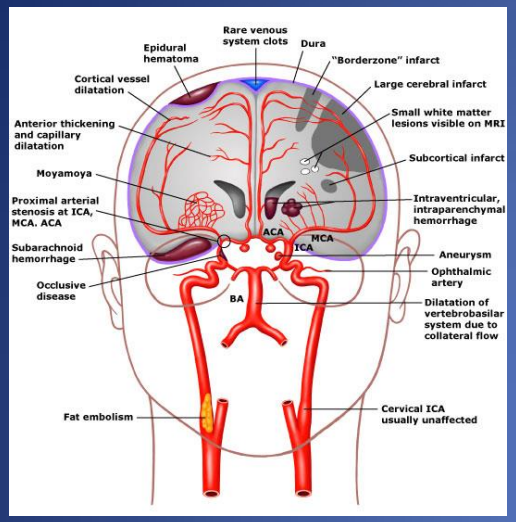
Anemia

- Not so easy to recognize in black children
- Transfusion criteria:
  - < 5g/dl
  - < 6g/dl in case of intolerance or drop Hb >2 g/dl compared to steady-state value

Be aware: specific tranfusion policy!

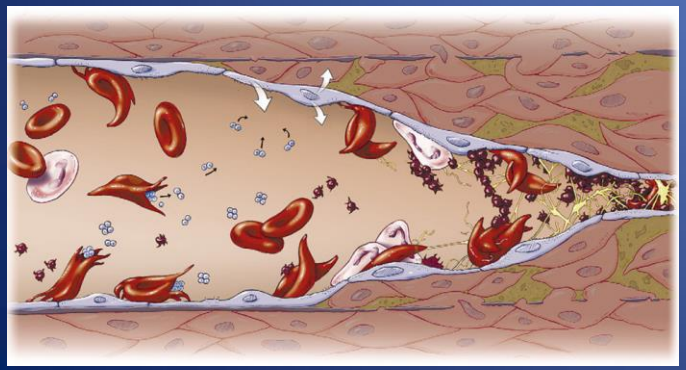
- Post TF Hb level should not exceed 10 g/dL
- Always transfuse with extended RBC phenotype identical blood (perform extended RBC phenotyping + irregular antibodies if unavailable)
- In case of recent transfusion (<2 weeks), do not transfuse unless *delayed hemolytic transfusion reaction* has been excluded (hyperhemolysis, Coombs+, …)

Stroke



- SCD: 1st cause of stroke in children in US
- 11% of patients will have overt stroke <20y

- Cerebral vasculopathy
  - Stroke (Ischemic or hemorragic)
  - Seizures, acute neurologic defect, consciousness disorder
  - Silent infarcts
  - Cognitive disorders



Switzer 2006

Stenosis or occlusion of the internal carotid arteries (ICA), the anterior (ACA) and middle cerebral arteries (MCA)

Stroke management

- Patient preferably at haematological ward (not stroke clinic)
- Exchange transfusion without delay (↓ HbS < 30% and ↓ progression of cerebral ischiemia)
- Oxygenate

- Prevent recurrence (chronic transfusion program)

Transfusion in emergency

Treatment of acute anemia

- Hb level < 5 g/dL
- Drop of Hb level ≥2 g/dL below baseline with Hb < 6 and/or symptoms of anemia (spleen or liver sequestration)

Reverse vaso-occlusion

- Acute chest syndrome (PaO2 < 70 mmHg; if in doubt about severity -> transfuse)
- Multiple organ failure
- Acute neurological symptoms (signs of cerebrovascular accident or seizures)
- Acute priapism

Hb level < 10/dl

Smith-Whitley et al. *Peditr Blood Cancer.* 2012
Adams et al. *N Engl J Med*. 1998
Vichinsky et al. *N Engl J Med*. 2000

Miller. *Blood.* 2011
Brousse et al. *Br J Haematol.* 2012

How to transfuse?

- Top up transfusion

- Exchange transfusion (manual or automated)
  - Acute neurological symptoms
  - Priapism not responding to local therapy
  - Goal: reduction of HbS < 30% on electrophoresis
  - Severe ACS but Hb ≥ 9g/dl

Criteria for hospitalization

Only 1 of these criteria is sufficient

- Fever > 38.5 ° C (< 2 years > 38 ° C)
- Hb < 6gr / dl or drop ≥ 2g/dl
- Pain > 24H despite well-managed anti-pain TT
- Unusual pain syndrome by intensity
- Acute neurological disorders
- Acute Chest Syndrome or VOC with chest/back pain
- Acute Priapism
- Any complication w/o appropriate home surveillance

Thanks to:

- Patients and parents
- Intensive care and emergency department teams
- Colleagues of our Sickle Cell Disease Team
- Members and friends of the BSPHO and Red Blood Cell Committee of the BHS

ULB UNIVERSITÉ LIBRE DE BRUXELLES

BHS

BSPHO