ARISE

African Research And Innovative Initiative For Sickle Cell Education

PAEDIATRIC PROBLEMS in Sickle Cell Disease

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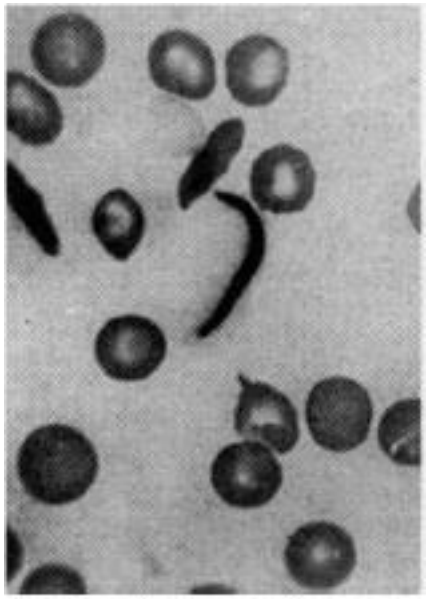
AZIENDA OSPEDALIERA UNIVERSITA' PADOVA

Program

- What is Sickle Cell Disease?
- Why is it important to know about Sickle Cell Disease now?
- Discuss health disease management and comprehensive care in children
- Present some acute clinical complications



Peculiar Elongated and Sickle-shaped Red Blood Corpuscles in a Case of Severe Anemia[a]

James B. Herrick, M.D.

1013 State Street, Chicago, Illinois

This case is reported because of the unusual blood findings, no duplicate of which I have ever seen described. Whether the blood picture represents merely a freakish poikilocytosis or is dependent on some peculiar physical or chemical condition of the blood, or is characteristic of some particular disease, I cannot at present answer. I report some details that may seem non-essential, thinking that if a similar blood condition is found in some other case a comparison of clinical conditions may help in solving the problem.

HISTORY

The patient was an intelligent negro of 20, who had been in the United States three months, during which time he was a student in one of the professional schools in Chicago. His former residence had been Grenada, West Indies, where he had been born and brought up, one of a family of four children, all living, and all well with the exception of himself. His mother was living and in good health; his father had died of accident. At the age of 10 the patient had had yaws. This was a common disease in the locality where he lived. The lesions, as he described them, had been pustular, with formation of ulcers and scabs. On healing, scars, many of which he pointed out, were left. Some of the ulcers had been as large as a silver quarter of a dollar. The disease lasted about one year and during this time he had felt somewhat weak and indisposed. Most of the ulcers had been on the legs and the patient him-

Arch Intern Med 5: 517, **1910**

SCD Short Timeline (1)

1910 – Dr. James B. Herrick publishes a description of sickled cells present in 20-year-old Grenadian dental student Walter Clement Noel.

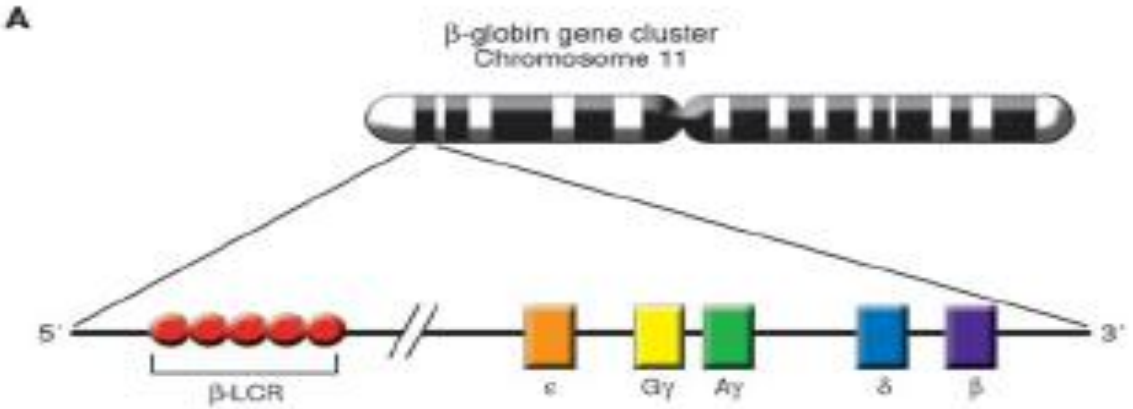
1949 – Dr. Linus Pauling and others reveal the molecular nature of SCD.

1954 – Sickle cell trait is found to protect against malaria, explaining the prevalence of SCD in regions where malaria is a leading cause of death.

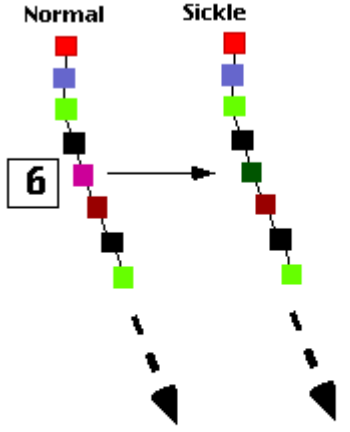
1972 – The National Sickle Cell Anemia Control Act, establishes voluntary SCD screening, counseling, public and professional education, and other key public health measures.

1982 – 5-azacytidine is shown to elevate fetal hemoglobin levels.

1984 – Hydroxyurea demonstrates the ability to increase fetal hemoglobin levels.



SCD is a recessive genetic disorder of hemoglobin due to a single base mutation in codon 6 of the β globin gene on chromosome 11 (HbS/HbS)



HbSS , HbSC, HbSβ° , HbSβ+, HbS/HbE, HbS/HbPunjab

Extreme phenotypic variability
Systemic disorder

2006 The **World Health Organization** released the *"Sickle Cell Anemia" A59/9 Report*, inviting Governments and Health Ministries:

"to design, implement, reinforce in a systematic, equitable and effective manner, comprehensive national integrated programs for the prevention and management of SCD reducing morbidity and mortality"

www.who.int/gb/ebwha/pdf_files/WHA59-REC1/e/WHA59_2006_REC1-en.pdf

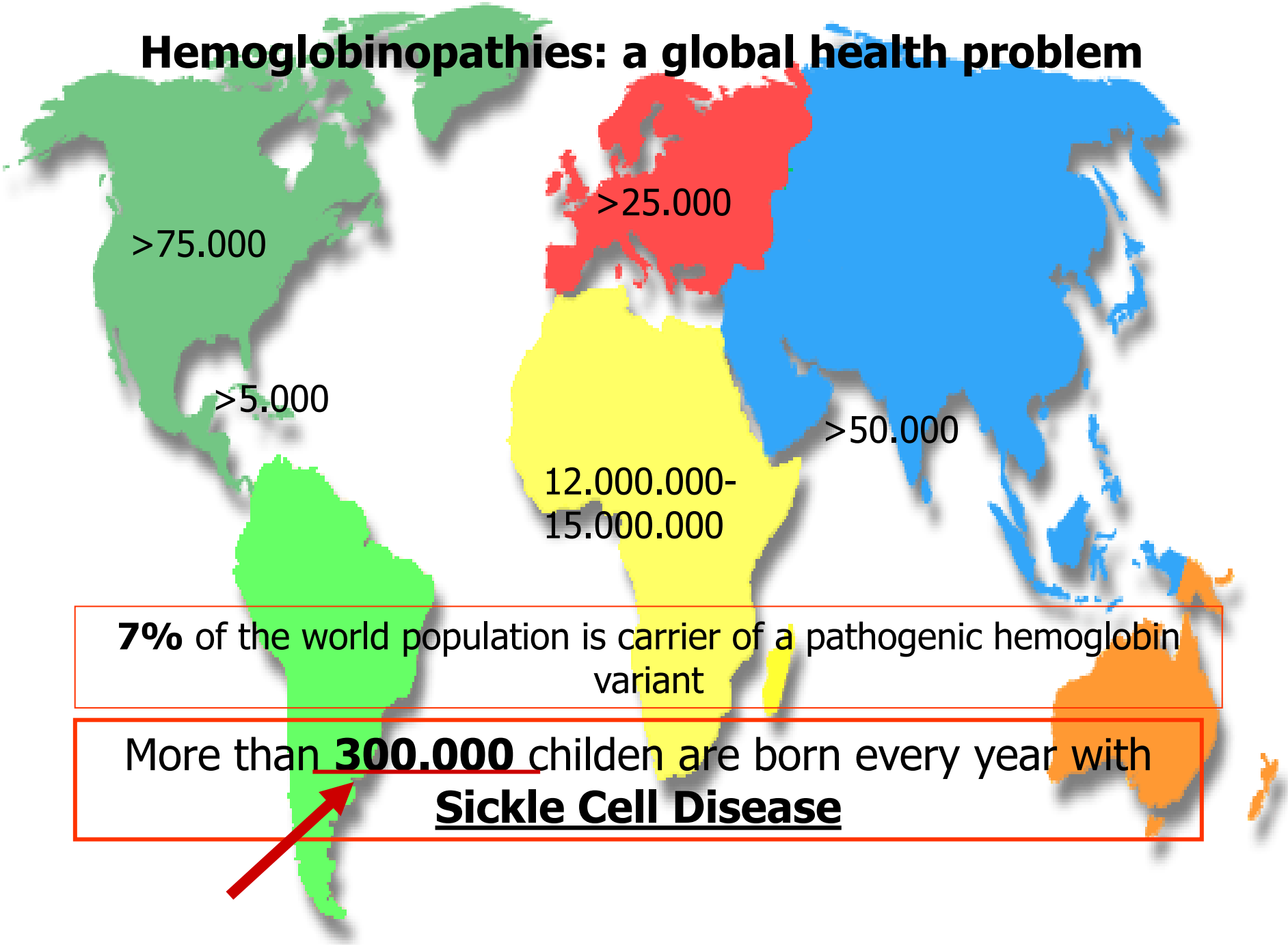
2008 The **General Assembly of the United Nations** approved the Resolution "Recognition of sickle-cell anaemia as a public health problem" (resolution A/63/L.63):

- inviting all States to "**raise global awareness on SCD**"

- defined the **19th of June** of every year as the "Sickle Cell Day"

www.un.org/News/Press/docs/2008/ga10803.doc.htm

Hemoglobinopathies: a global health problem

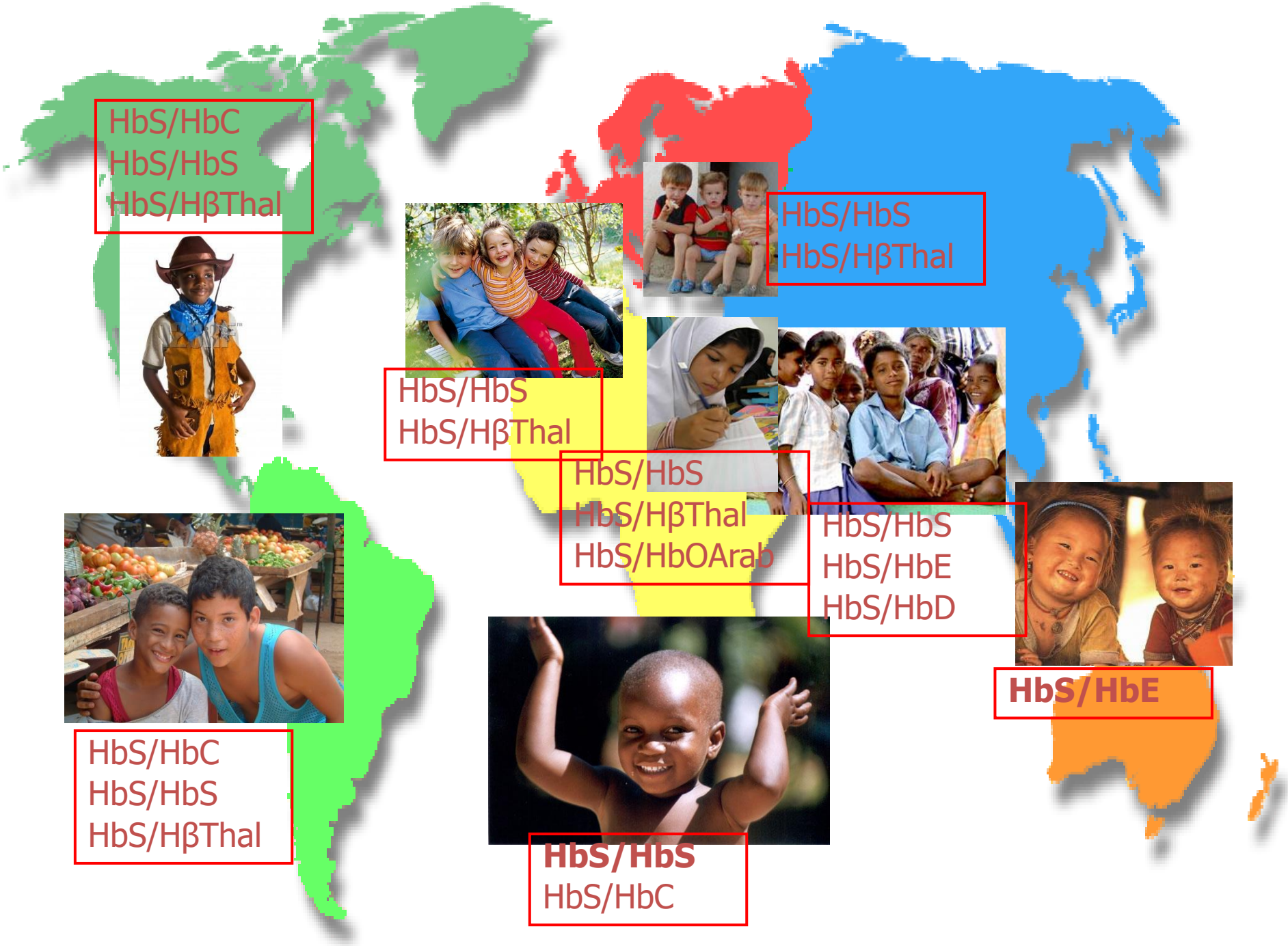


7% of the world population is carrier of a pathogenic hemoglobin variant

More than **300.000** childen are born every year with **Sickle Cell Disease**

Aliyu ZY, et al. Am J Hematol 2007

Modella B et al. Bulletin of the World Health Organization 2008;86:480–487


HbS/HbC
HbS/HbS
HbS/HβThal
HbS/HbS
HbS/HβThal
HbS/HbS
HbS/HβThal
HbS/HbS
HbS/HβThal
HbS/HbOArab
HbS/HbS
HbS/HbE
HbS/HbD
HbS/HbE
HbS/HbC
HbS/HbS
HbS/HβThal
HbS/HbS
HbS/HbC

Global increase of migrants with the Sickle cell gene

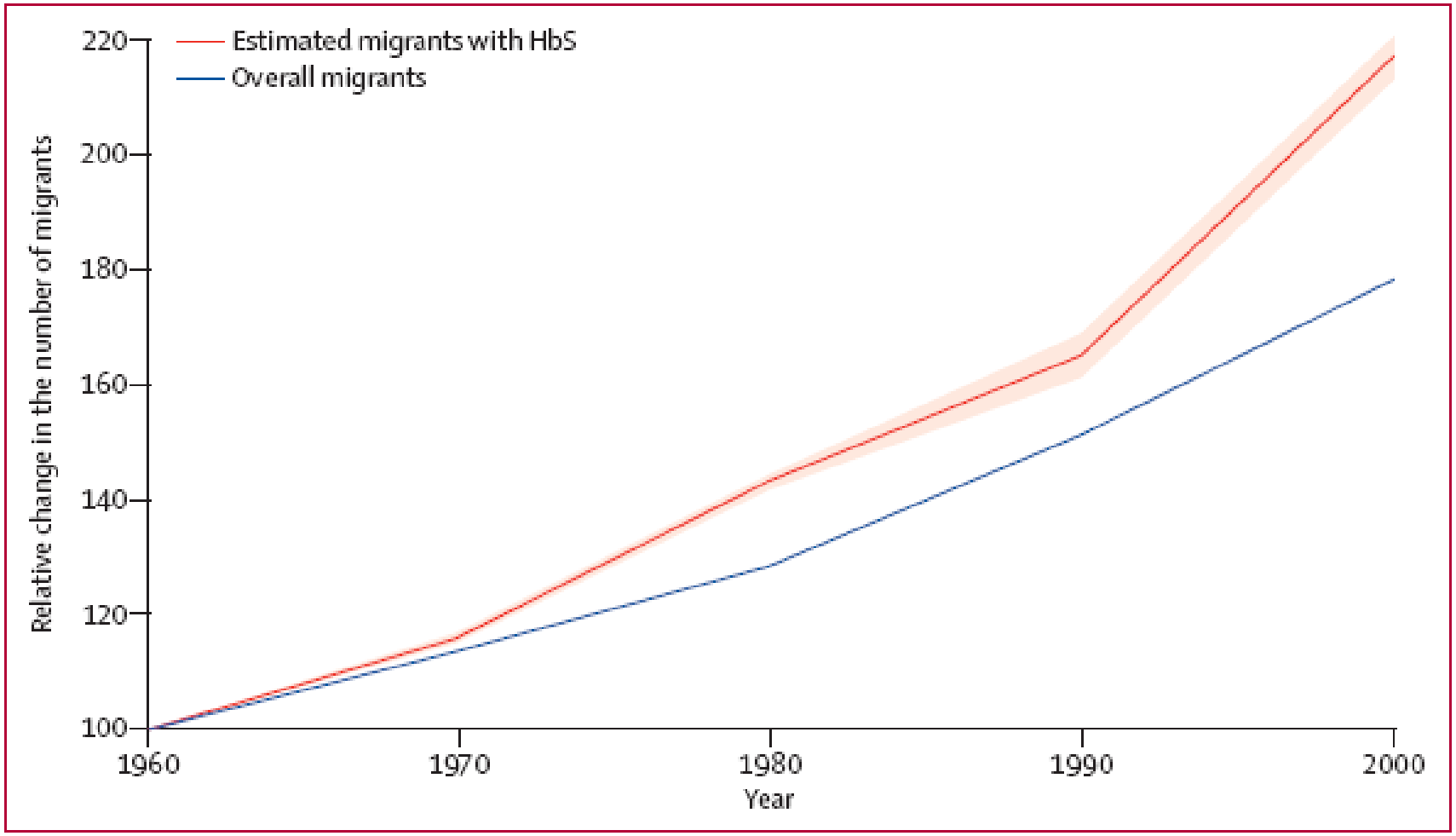
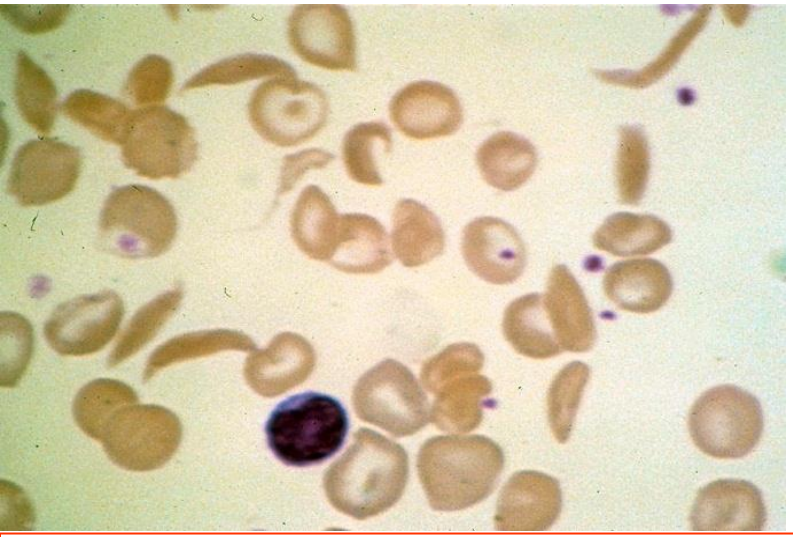


Figure 1: Global trends in the number of international migrants and estimated migrants with HbS compared with the 1960s level

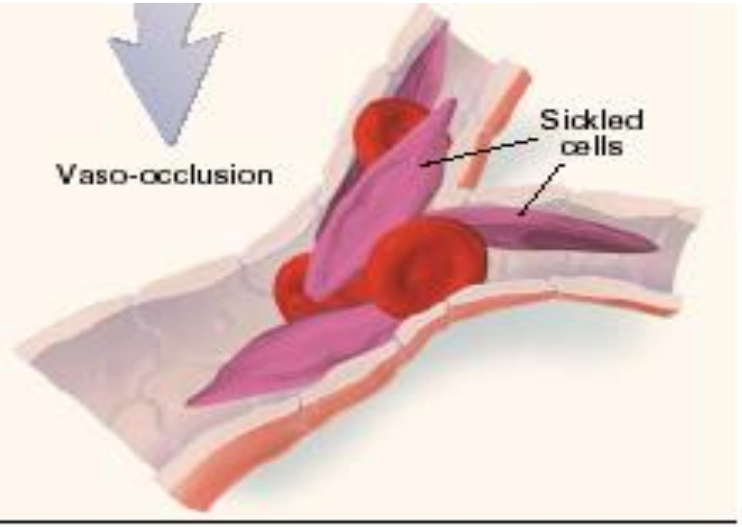
Global migration and the changing distribution of sickle haemoglobin: a quantitative study of temporal trends between 1960 and 2000

Lancet 2014

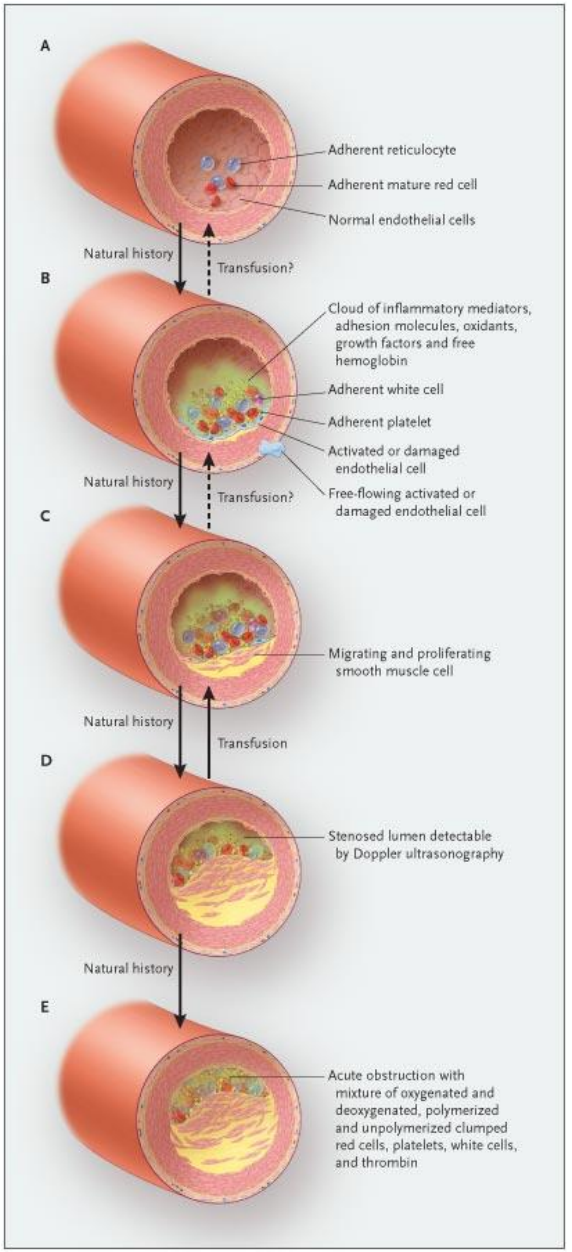
SCD: pathophysiology



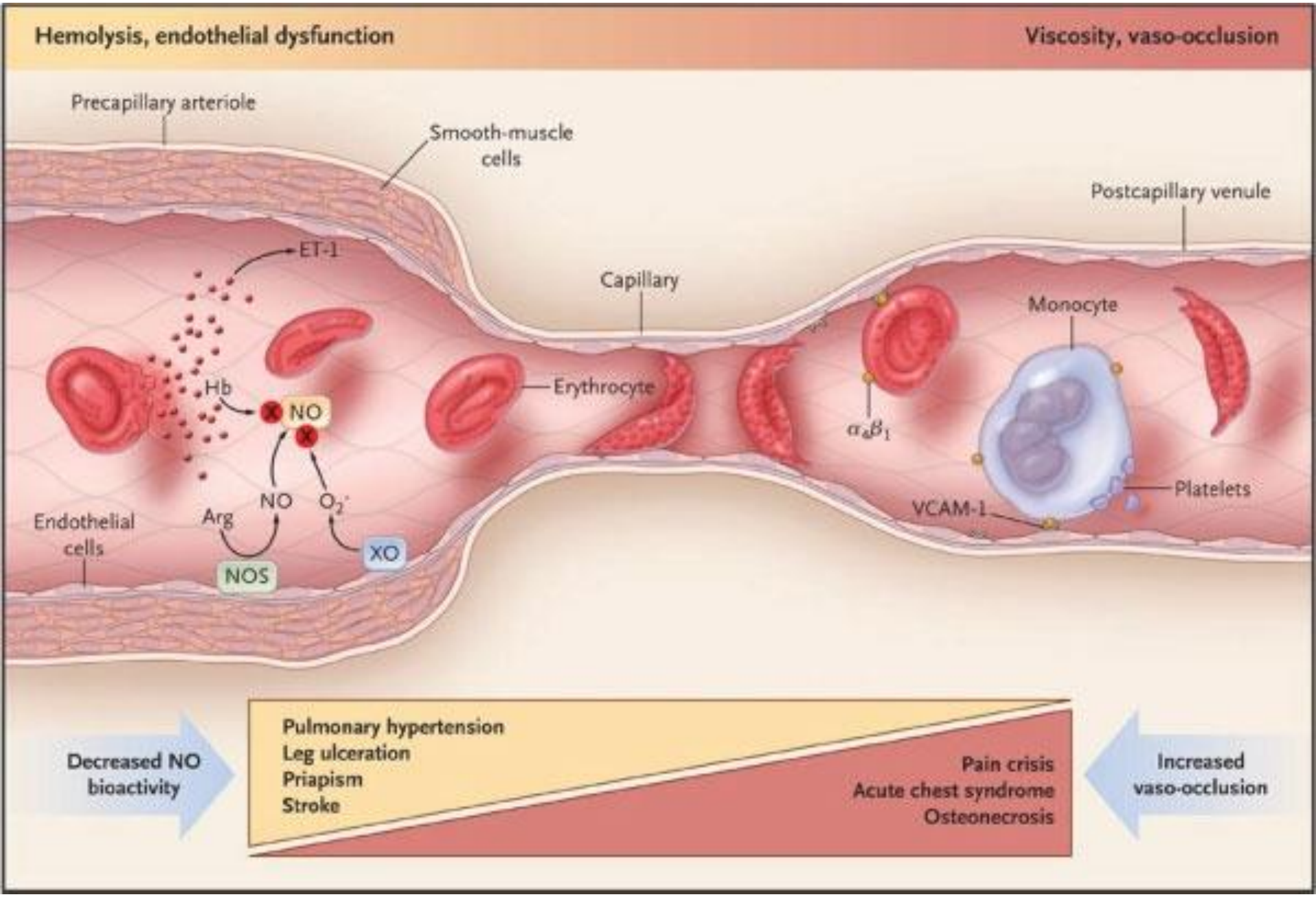
Chronic hemolytic anemia

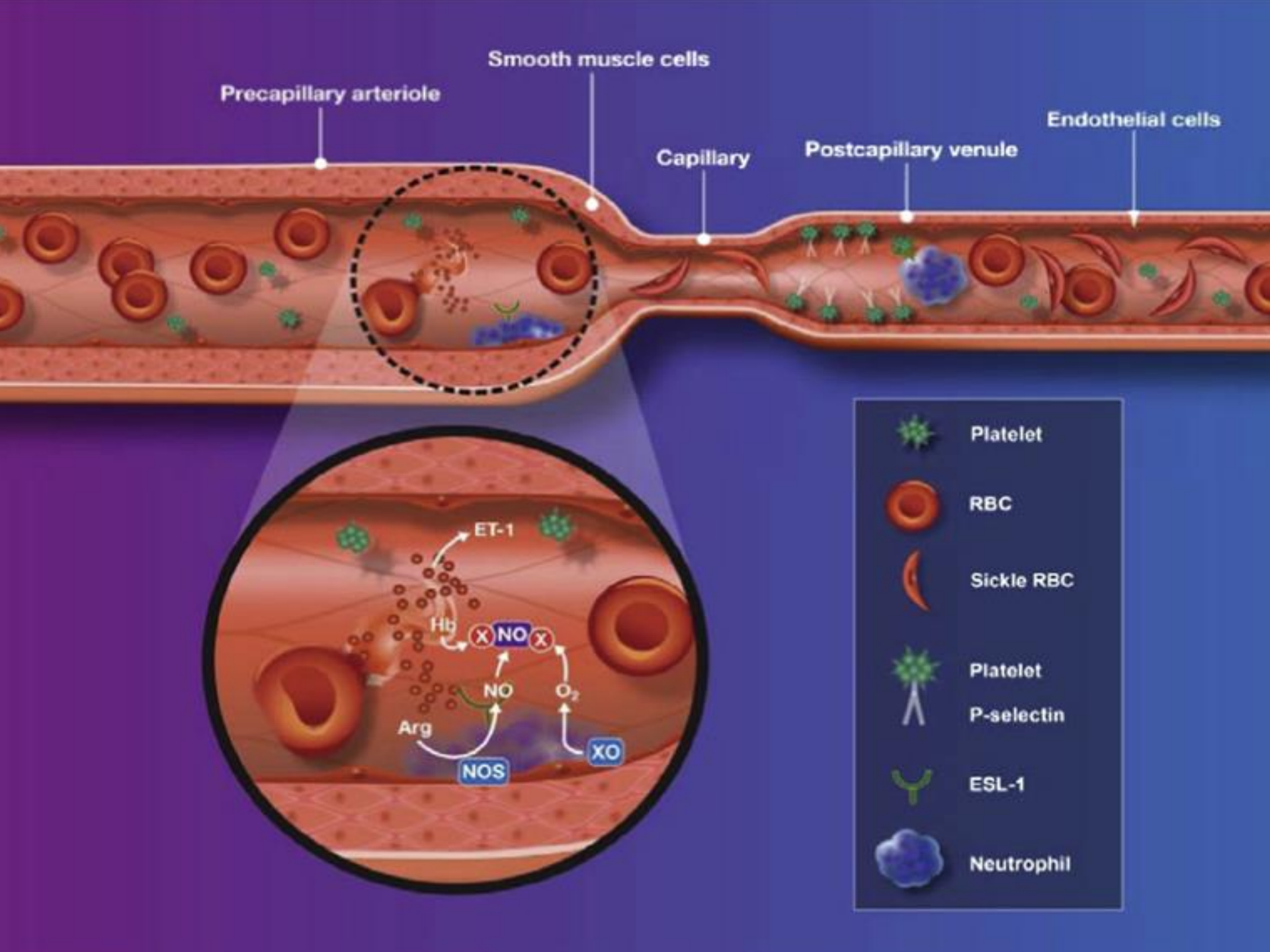


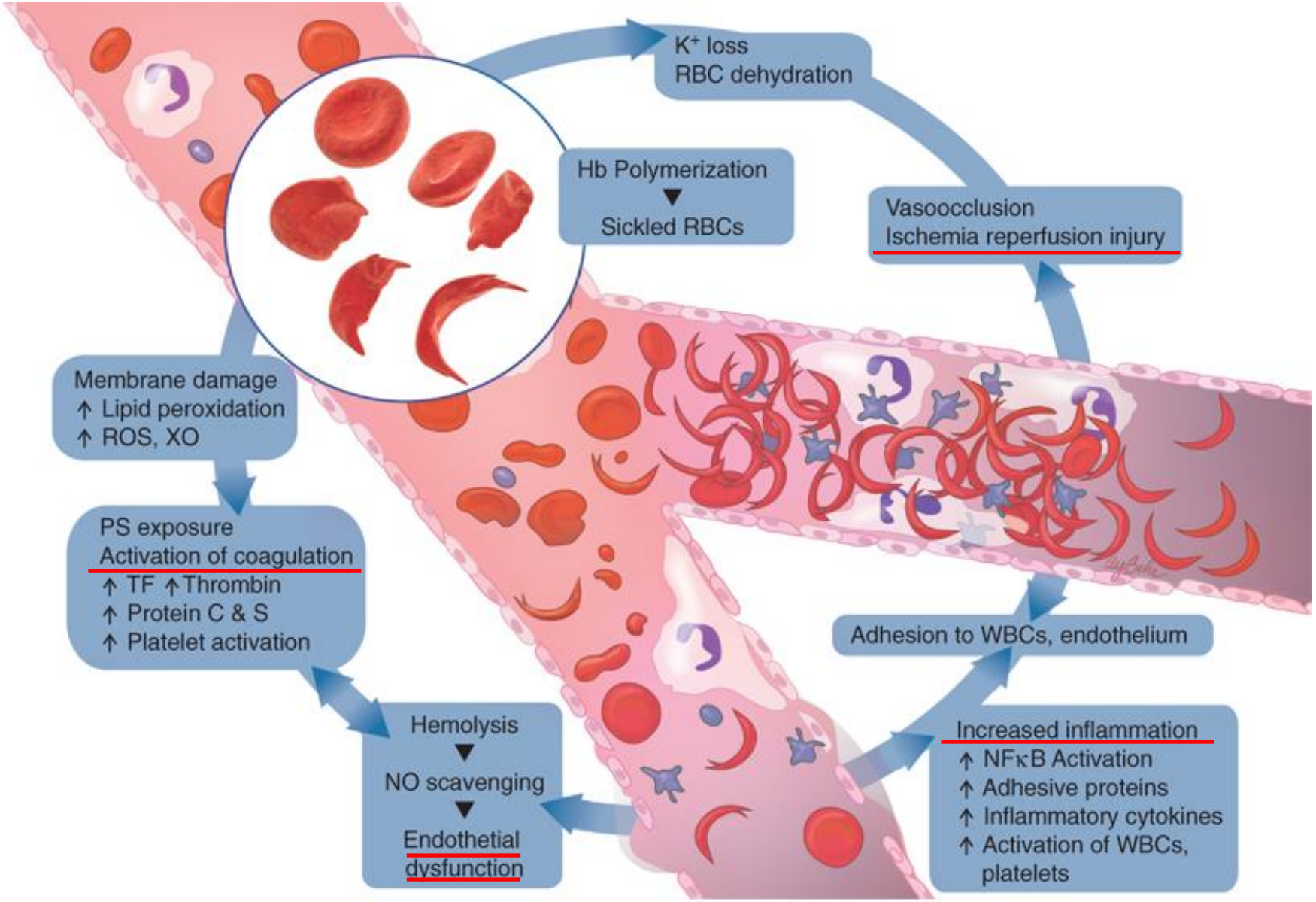
Vaso-occlusion



Vasculopathy


Hemolysis, endothelial dysfunction
Viscosity, vaso-occlusion
Precapillary arteriole
Smooth-muscle cells
Postcapillary venule
ET-1
Capillary
Monocyte
Hb
NO
Erythrocyte
$\alpha_4\beta_1$
Platelets
VCAM-1
Endothelial cells
Arg
NO
O_2^-
XO
NOS
Decreased NO bioactivity
Pulmonary hypertension
Leg ulceration
Priapism
Stroke
Pain crisis
Acute chest syndrome
Osteonecrosis
Increased vaso-occlusion


Smooth muscle cells
Precapillary arteriole
Endothelial cells
Capillary
Postcapillary venule
ET-1
Hb
X NO X
NO
O2
Arg
NOS
XO
Platelet
RBC
Sickle RBC
Platelet
P-selectin
ESL-1
Neutrophil



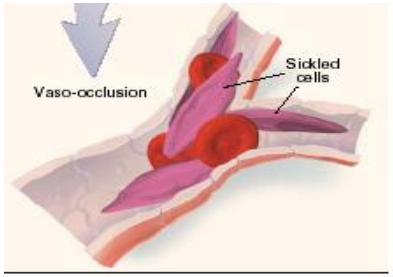
Source: K. Kaushansky, M.A. Lichtman, J.T. Prchal, M.M. Levi, O.W. Press, L.J. Burns, M. Caligiuri: Williams Hematology, 9th edition
www.accessmedicine.com

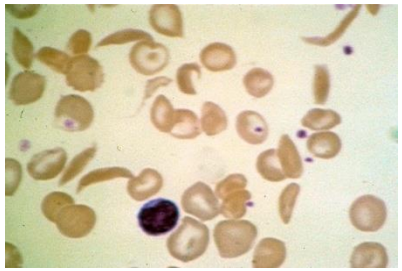
What happens in children?

Vasculopathy,

chronic inflammation,

coagulation activation





- Chronic organ damage (all organs)
- Risk of infections and sepsis (functional asplenia)
- Vaso-occlusive painful crisis

TABLE III. Complications Affecting Major Organs

- Neurologic complications
  - Cerebrovascular accident [stroke] [18]
    - Aneurysm [131,132]
    - Hemorrhagic stroke [133–135]
    - Ischemic or infarctive stroke [133–135]
    - Moyamoya [136,137]
    - Silent cerebral infarct [20,133–135]
  - Transient ischemic attack [19,134]
    - Elevated transcranial Doppler velocity [18,125–127]
    - Seizure [128–130]
- Ophthalmologic complications
  - Angioid streaks [139]
  - Black sunburst lesion [140–142,169]
  - Conjunctival comma sign [143–145]
  - Glaucoma [146–152]
  - Hyphema [146–153]
  - Proliferative sickle retinopathy [154–162]
  - Vitreous hemorrhage [170]
  - Retinal detachment [163–167]
  - Salmon patch hemorrhage [142,168]
- Cardiac complications
  - Cardiomegaly [50–55]
  - Cardiomyopathy [56–64]
  - Congestive heart failure [55,65]
  - Mitral valve prolapse [71,72]
  - Hypertension [66–70]
- Pulmonary complications
  - Acute chest syndrome [31–35,190–194]
  - Pulmonary hypertension [36–41,209–211]
- Gastrointestinal/hepatobiliary complications
  - Cholecystitis [80–85]
  - Cholelithiasis/sludge [86–90]
  - Hepatic sequestration [15–17,88,91]
  - Intrahepatic cholestasis [17,91–95]
  - Viral hepatitis [101,102]
- Renal/genitourinary complications
  - Acute renal failure [212–216]
  - Chronic renal insufficiency [216–219]
  - Hematuria [220]
  - Priapism [221–223]
  - Proteinuria / nephrotic syndrome [220,224–228]
  - Pyelonephritis [229,230]
- Splenic complications
  - Acute splenic infarction [231–233]
  - Functional asplenia [234,235]
  - Hypersplenism [23,43,236]
  - Acute splenic sequestration [3–12,42,43]
- Muscular/skeletal/skin complications
  - Avascular necrosis [103–107]
  - Dactilytis (hand-foot syndrome) [108–110]
  - Leg ulcers [111–114]
  - Myositis/myonecrosis/fasciitis [115–117]
  - Osteomyelitis [108,118]
  - Osteopenia/osteoporosis [108,119–124]
- Disturbances of growth and development
  - Growth retardation [14,78,79]

HbS/HbC

Am J Hematol 2010

TABLE 1. Important Clinical Manifestations of SCD During Childhood and Adolescence

Acute Manifestations
Bacterial sepsis or meningitis*
Recurrent vaso-occlusive pain (dactylitis, musculoskeletal or abdominal pain)
Splenic sequestration*
Aplastic crisis*
Acute chest syndrome*
Stroke*
Priapism
Hematuria, including papillary necrosis

* Potential cause of mortality.

AAP, Pediatrics 2002

Chronic manifestations

- Anemia
- Jaundice
- Splenomegaly
- Functional asplenia
- Cardiomegaly and functional murmurs
- Hyposthenuria and enuresis
- Proteinuria
- Cholelithiasis
- Delayed growth and sexual maturation
- Restrictive lung disease* ⇐
- Pulmonary hypertension* ⇐
- Avascular necrosis
- Proliferative retinopathy
- Leg ulcers
- Transfusional hemosiderosis*

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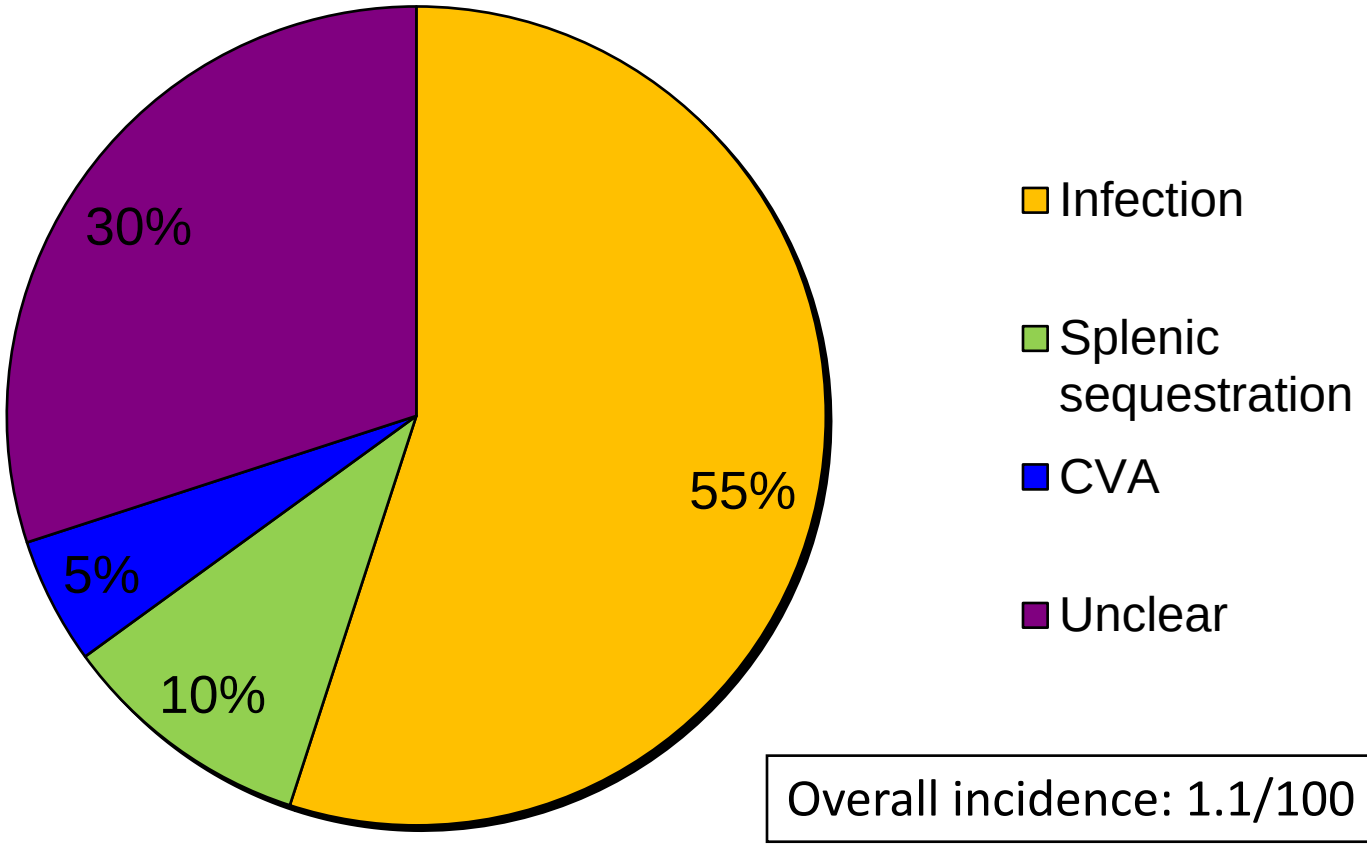
* Potential cause of mortality.

AAP, Pediatrics 2002

Causes of death in SCD-SS (0-10 aa)

In **USA** life expectancy for children with SCD (Hb SS) was 7 years in 1974 and is now 53 years.

CSSCD Infant Cohort Deaths - SCD-SS



Overall incidence: 1.1/100 person-yrs

(Gill FM, et al, CSSCD: 1995)

SCD Short Timeline (2)

1986 – Penicillin is noted as a preventive measure in children with SCD, to vastly reduce *Streptococcus pneumonia* infection.

1994 **The STOP TRIAL proves that Transcranial Doppler can be used to predict stoke risk**

1997 – Blood transfusions demonstrate a 90 percent reduction in stroke in high-risk patients.

1998 – The FDA approves hydroxyurea for treatment of adults with SCD.

2009 – Study shows that blood stem cell transplantation can reverse SCD in adult patients.

2017 – β globin gene therapy demonstrates curative success; crizanlizumab decreases pain crises in patients; L-glutamine is approved.

Infections: Reduce the early mortality

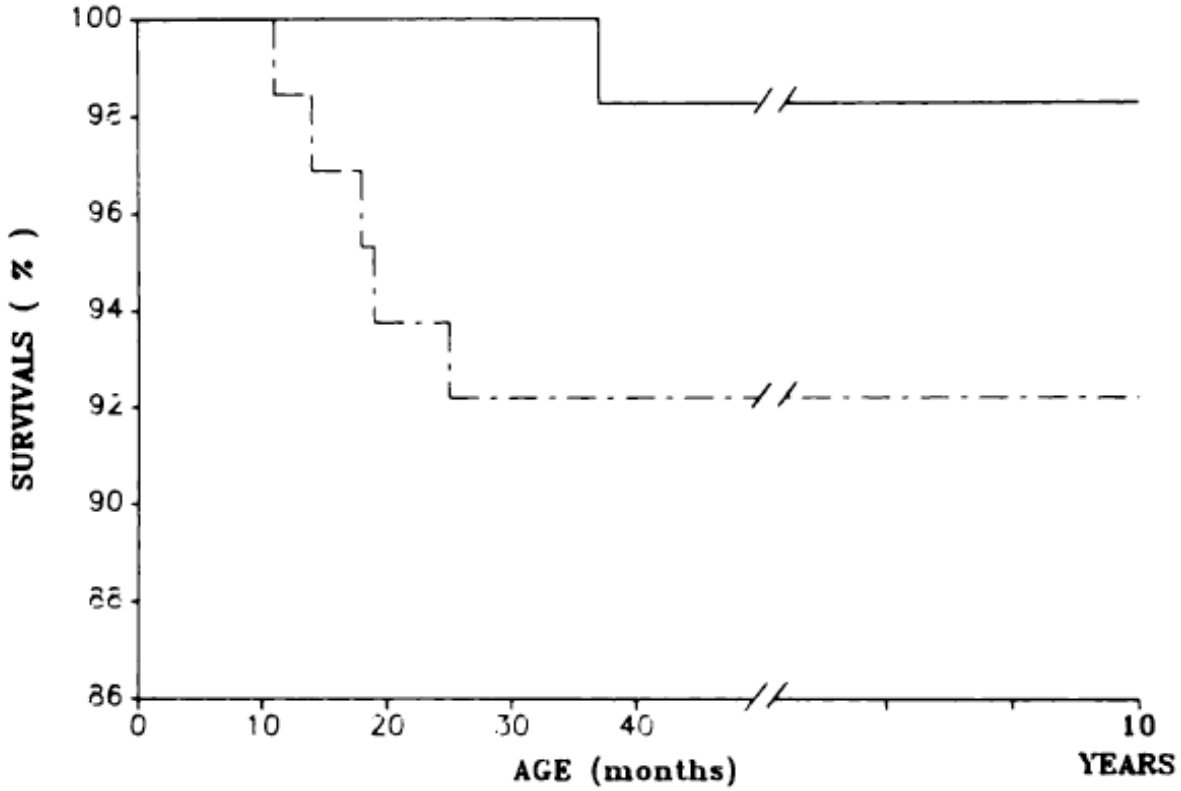
Penicillin Prophylaxis Study (PROPS-I), CSSCD
Children 3-36 months

	Penicillin	Placebo
No. of pts	105	11
Pneumovax	67%	71.6%
Sepsis	2	13
Incidence/10^5 pz-ys	1,524	9,455
Deaths	0	3

Reduction of frequency of bacterial infections by 84%
In children 3-36m

(Gaston, et al.; NEJM 1986)

Infections: Newborn Screening for SCD and Effect on mortality



81 Newborn screened

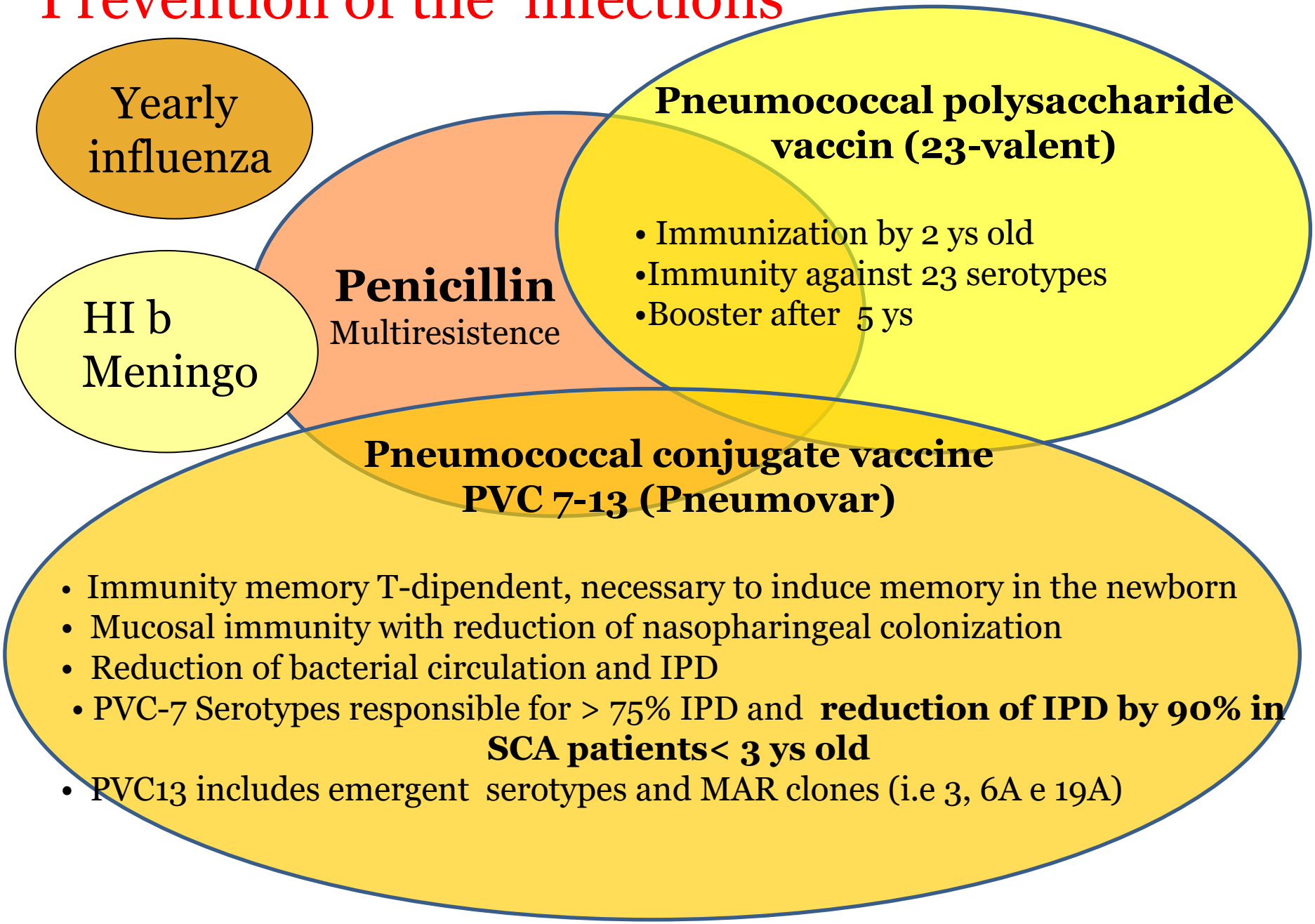
OM 1,8%

64 Diagnosed clinically

OM 8%

Vichinsky et al, Pediatr 1988;81

Prevention of the infections



Infections solved?

- Nowadays for pts of western countries early mortality for infections wouldn't be a problem

Bansil NH Clinical Pediatrics 2013
Baskin MN Pediatrics 2013

Is it true???

Preention of infection: aggressive treatment of child with fever

1. **High risk of sepsis: < 12 months, previous sepsis or splenectomy**

   - Prompt medical evaluation
   - Blood tests and colture and others (if warrented)
   - Prompt Ab ev treatment
   - 24-48 hours observation in hospital

2. **Low risk of sepsis**

   - Blood tests and coltures and 4-6 hrs observation
   - Prompt Ab ev treatment
   - Ab treatment at home, daily control for not septic pts
   - Admission for others

A.I.E.O.P.
Associazione Italiana Ematologia Oncologia Pediatrica

Linee Guida AIEOP 2012

Management of SCD in Children

Prevention of Death Due to Bacterial Infection

The predominant feature in the management of young children with SCD

Management of SCD in Children

What reduces mortality in young children with SCD?

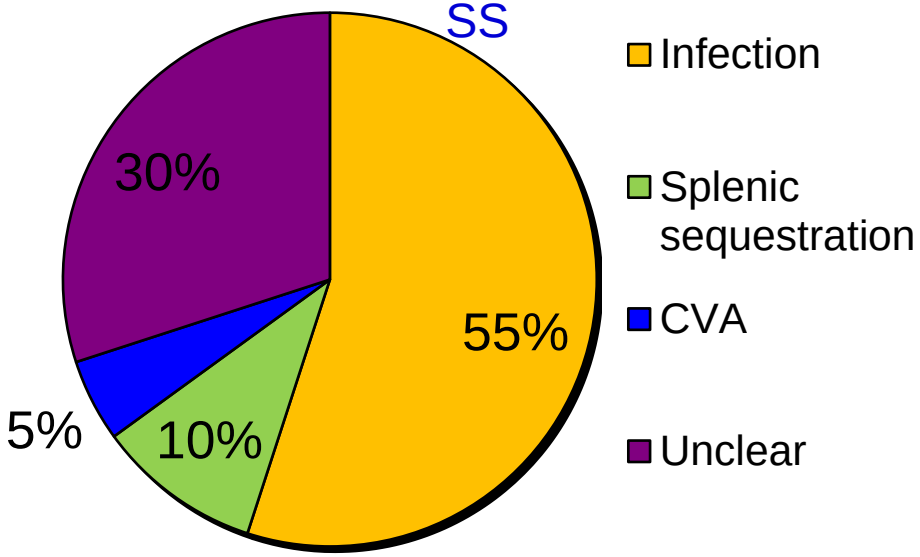
Prevention of Pneumococcal Infection

Penicillin prophylaxis - starting in infancy for 5 yr (?)

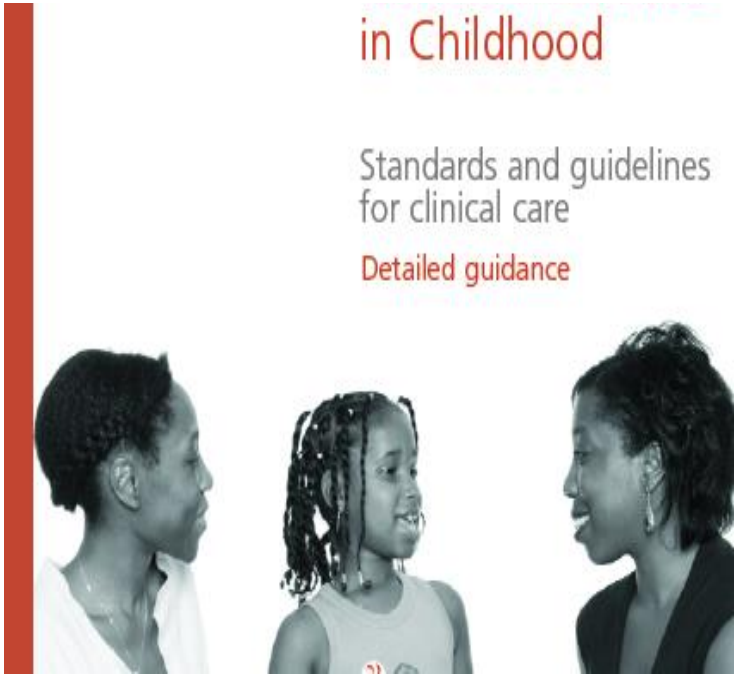
Pneumococcal Vaccination

Newborn screening (followed by comprehensive management including parental health education, penicillin prophylaxis, close follow-up)

“Aggressive” management of fever



tandards of care (1)

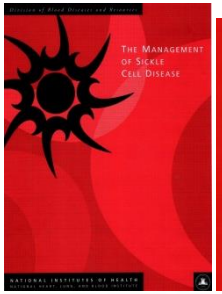


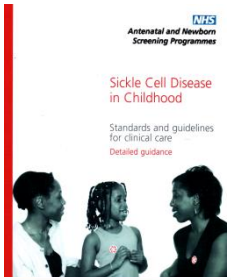
NHS 2009

rn Screening

- **Antibiotic prophylaxis**
- **Vaccinations**
- **Transcanial Doppler Starting at age 2 (with RBC transfusion)**
- **Comprehensive care**
- **Use of hydroxyurea**

Minimal Standards of care (2)





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Neonatal Screening

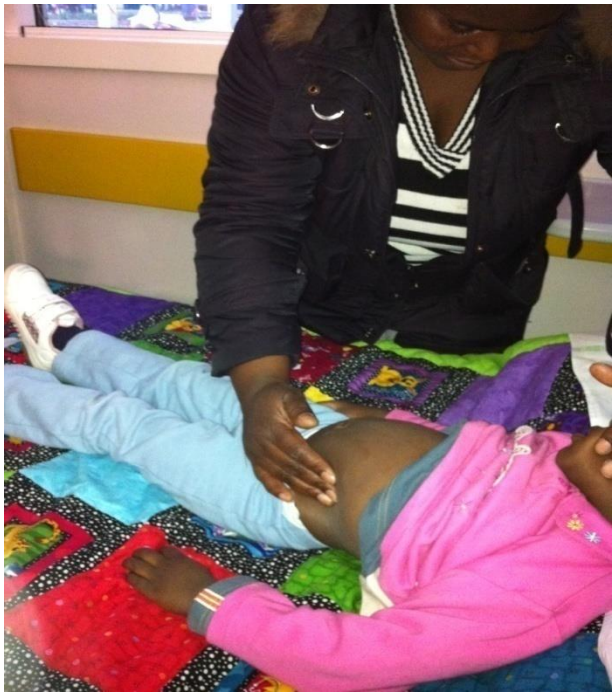
Antibiotic prophylaxis
(3 months-6 years)

Complete Immunization

TCD scanning and long term transfusion regimen for high risk patients (TAMM> 200)

Information and education, Sickle cell centers →

Transition to adult

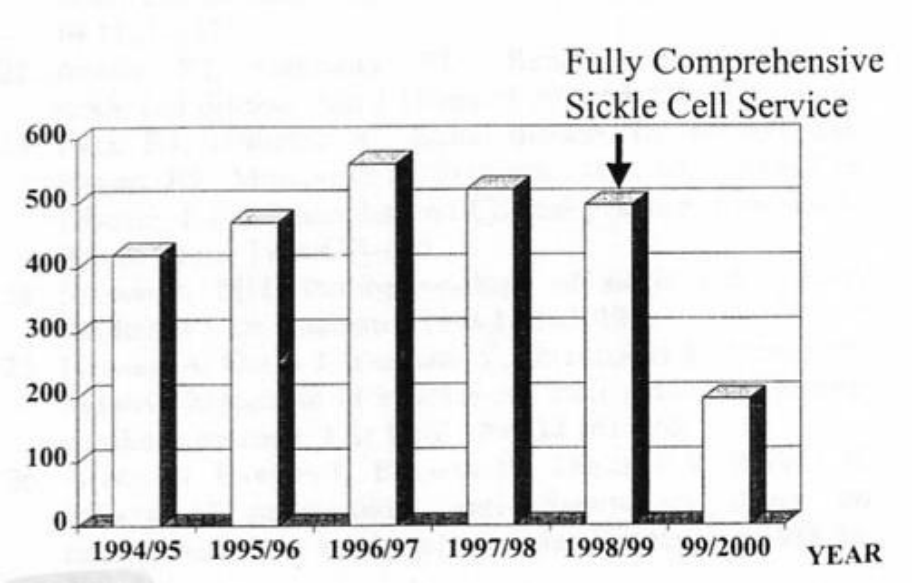


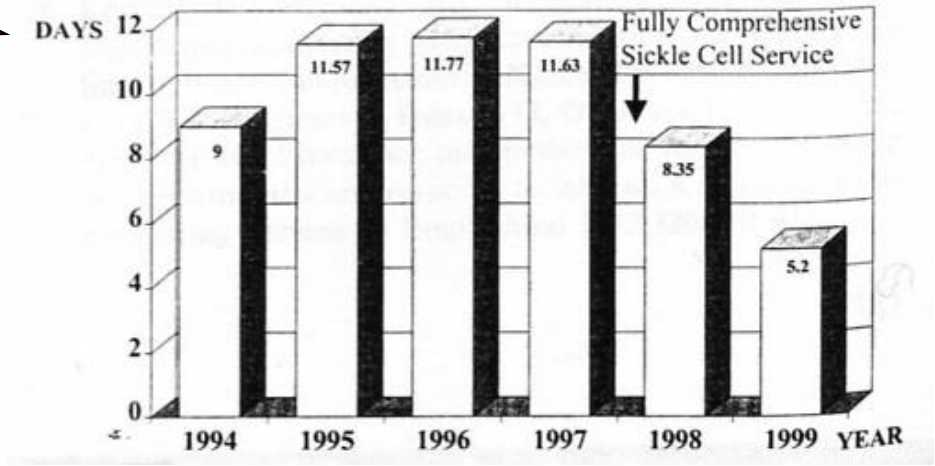
Organization of a comprehensive care Center in London

Decrease the admissions number

«prevention»
Education of families
Dedicated follow up
schedule

Decrease the lengh of admissions





Okpala I et al. Eur J Haematol. 2002; 68 (3)

Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London

Paul Telfer, Pietro Coen, Subarna Chakravorty, Olu Wilkey, Jane Evans, Heather Newell, Beverley Smalling, Roger Amos, Adrian Stephens, David Rogers, Fenella Kirkham

- 252 children (180 SS, 64 HbSC, 8 HbSβ), neonatal screening 1983-2005
- Enrolled in Comprehensive program (hospital and community-based)
- penicillin since 3 months of life Pneumocccic immunization
- Screening TCD since 1993

- 2158 year/patien observation Age 7.8 ys (range 3.3-13.0)
- Sepsis (Pneumo) 0.3 events/ 100 patient-year.
- Stroke risk 4.3%, further reduction after the TCD screening
- No death for stroke or sepsis in HbSC o HbSβ$^+$
- Overall survival HbSS at 16 years 99.0%
- Reduce mortality compare to other studies

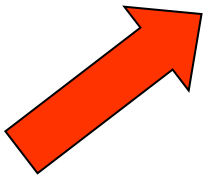
Haematologica 2007

Pediatr Blood Cancer 2011;56:1005–1008

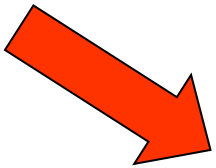
COMMENTARY

Translating Scientific Advances to Improved Outcomes for Children With Sickle Cell Disease: A Timely Opportunity

- Newborn screening,
- Prophylactic penycillin and vaccinations,
- Comprehensive care,
- TCD screening



IMPROVED SURVIVAL



IMPROVED Quality Of Life

Do advances in research really mean improved care for ALL patients?

Quinn 2010, Telfer 2007

Pediatr Blood Cancer 2012;59:1275–1279

Comprehensive Care for Sickle Cell Disease Immigrant Patients: A Reproducible Model Achieving High Adherence to Minimum Standards of Care

Raffaella Colombatti, MD, PhD,[1]* Maria Montanaro, PhD,[1] Fabiola Guasti, PhD,[2] Patrizia Rampazzo, PhD,[3] Giorgio Meneghetti, MD,[3] Marco Giordan, PhD,[1] Giuseppe Basso, MD,[1] and Laura Sainati, MD[1]

TABLE II. Adherence to Specific Elements of Care Before (2006) and After (2010) the Implementation of Sickle Cell Comprehensive Care.

	2006	2010	*P*-value
Pneumococcus immunization coverage	80%	92%	0.11
Influenza vaccination coverage	26%	96%	0.0006
Amoxicillin prophylaxis prescription	40%	100%	0.0005
TCD evaluation above two years of age	27.4%	100%	0.0002
Adherence to FUP hematology visits	nr	99%	—
Adherence to FUP visits with TCD	nr	100%	—

Organize a Specialized Comprehensive care focused on the needs of **immigrant patients**

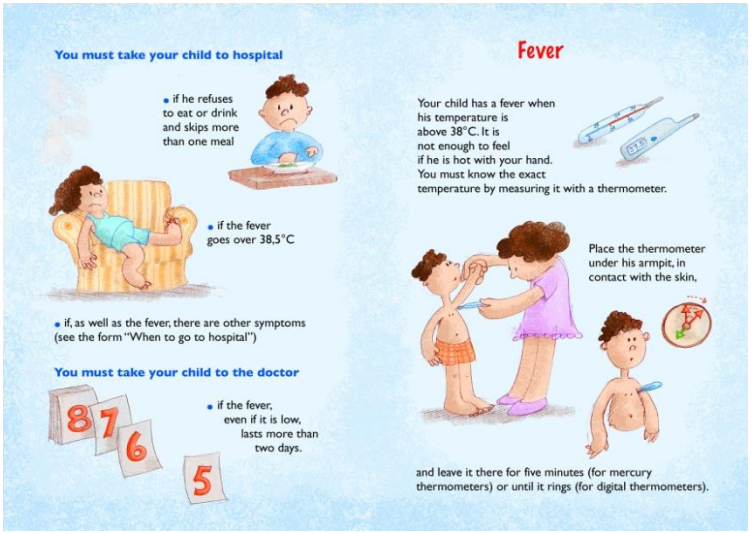
LINGUISTIC, **SOCIAL** **CULTURAL** ISSUES as PRIORITY

- Parental Health Education
- Flexible Schedule
- Continuous Social Support
- Assistance via telephone 24 h/day
- Reminders (tel. calls, letters)

Parental Health Education in their own language

1. A **three-language** (English, French, Italian), image rich **educational book** on SCD (including a pain diary) was given to every family at diagnosis

2. **Repeated health education** at every visit (in Italian, English or French) on: <u>pain</u> and <u>fever</u> management; on the need for <u>vaccination</u> and <u>TCD screening</u>



Continuous Social Support

5 – Your rights

A child with sickle cell disease does not have to pay for the ticket for medical examination, exams or medicines (code RDG 010). To get your exemption, ask at your local clinic. You do not have to pay for the ticket to do the exams when you suspect sickle cell disease, nor for the prenatal exams (code R99999).

If you present a request for a council house, for the renewal of your stay permit or to join any type of waiting list, it may be useful if you also attach the copy of your exemption certificate and the clinical report.

Up to the age of 18, your child has the right to be accompanied on visits, and parents can get extra time off work for this purpose (Law 104.92). You can get more information at the Ufficio Invalidi Civili of your local ULSS.

To obtain disability benefits

To obtain/renew permit of stay

Assistance via telephone 24 h/day

- **Mobile number** of hematologist (SCD);
- **Number** and name of SCD secretary

Reminders (telephone calls, letters)

-**To families** (phone calls as reminders for appointments; letters for vaccinations)

- **To primary care pediatricians** (letters as reminders for vaccinations and amoxacillin prescription)

ADHERENCE effect on Outpatient visits and Admissions

	2006 *29 pts*	**2010** *90 pts*
hematology visits/yr	4	660
DH for transfusion/yr	5	60
hematology visits/pts/yr *	0.13	7.25
ED access/pt/yr *	2.3	0.98
Inpatient admission/pt/yr *	0.30	0.25

**p<0.001*

Colombatti et al. Ped Blood Cancer 2012

HYDROXYUREA reduces acute events

(MSH-RCT) 299 ADULTS Hb SS

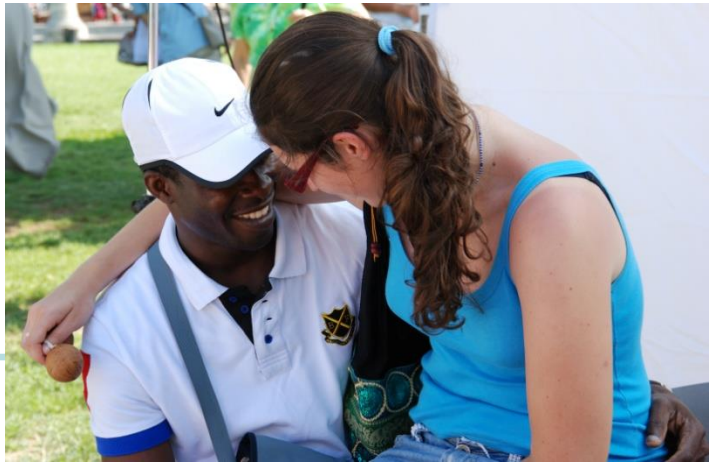
- Reduction vaso-occlusive crisis
- Reduction of ACS
- Reduction of transfusion
- Reduction of inpatient admissions

> 40% reduction

Charake, NEJM 1995

- Improves quality of life

Ballas 2006



HU in children

REVIEW ARTICLE

PEDIATRICS 2008

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Hydroxyurea for Sickle Cell Disease: A Systematic Review for Efficacy and Toxicity in Children

John J. Strouse, MD[a], Sophie La[illegible]ron, MD[a], Mary Catherine Beach, MD, MPH[b], Carlton H[illegible]ood, MS[c], Haeseong Park, MD[a], Catherine Witkop, MD, MPH[d], [illegible]ee F. Wilson, MSc[e], Eric B. Bass, MD, MPH[b], Jodi B. Segal, M[illegible]PH[b]

STRONG EVIDENCE

- ↑HbF and total Hb
- ↓hospitalization

- ↓ frequency of pain crisis

- ↓ neurologic events

Safe | **Well tolerated**

HU IMPROVES SURVIVAL

children HU vs ST

- 1760 pts age 3-18 2000-9 (Hemorio Institute Rio)
- 267 SCD pts in HU (MTD)
- > 60% good response
- 37 deaths related to SCD

INCREASED SURVIVAL of PATIENTS in HU
(99.5% vs 94.5%)

de Castro Lobo Br J Haemat 2013

Received: 8 June 2017 | Revised: 24 July 2017 | Accepted: 1 August 2017

DOI: 10.1002/pbc.26774

RESEARCH ARTICLE

WIL

Hydroxyurea prescription, availability a with sickle cell disease in Italy: Results Multicenter survey

Raffaella Colombatti[1] | Giovanni Palazzi[2] | Nicolet
Lucia Dora Notarangelo[4] | Elisa Bonetti[5] | Piera Samp
Silverio Perrotta[8] | Elena Facchini[9] | Maurizio Miano[1]
Giovanni Carlo Del Vecchio[11] | Maria Elena Guerzoni[2] |
Federica Menzato[1] | Simone Cesaro[5] | Maddalena Ca
Gian Luca Forni[13] | Giovanna Russo[6] | Laura Sainati[1]
Multicenter Study of Hydroxyurea in Sickle Cell Anemia In

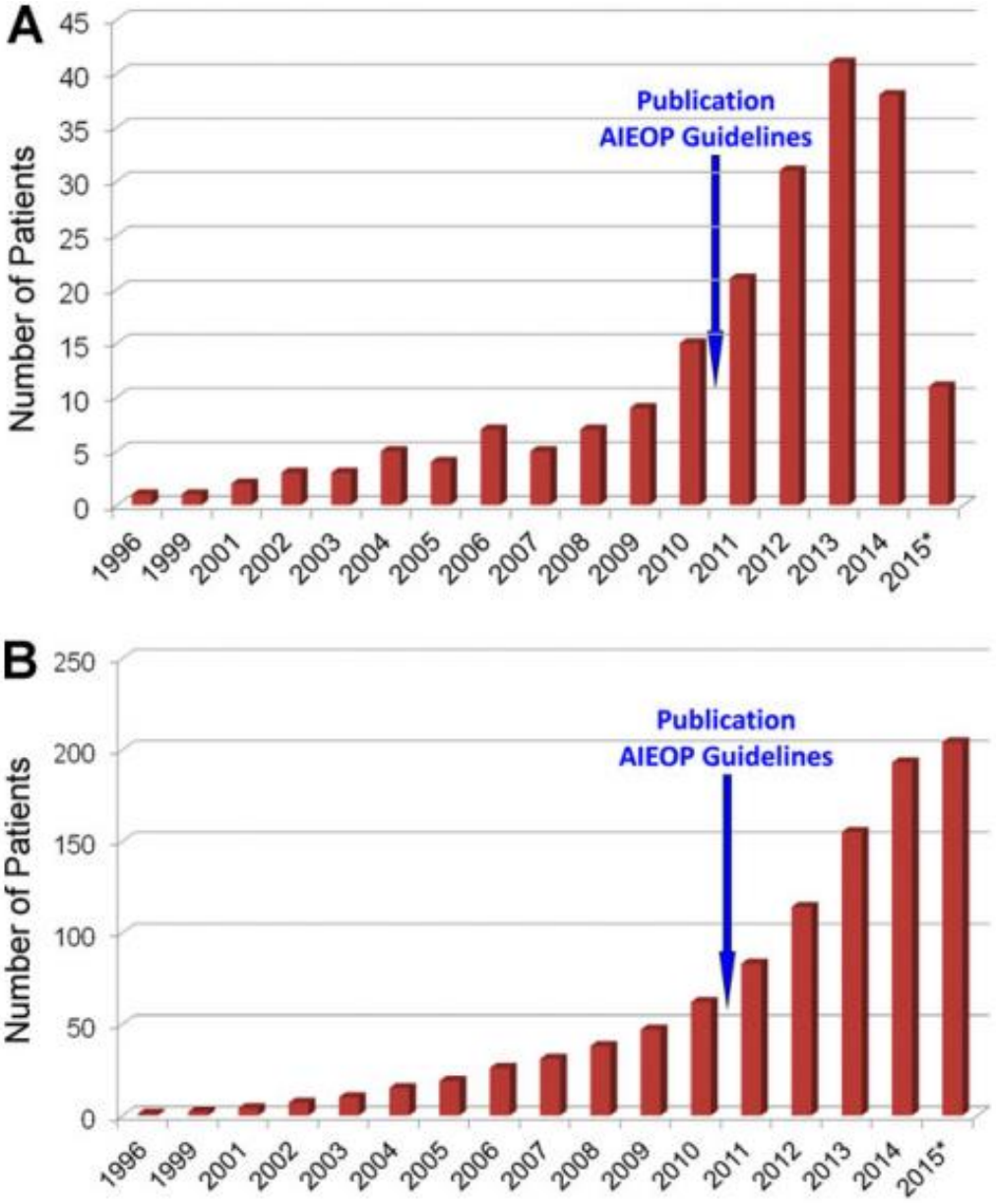


FIGURE 1 Number of patients who start therapy with hydroxyurea (HU) every year (A) and number of patients per year on HU (B). *Data recorded until January 2015

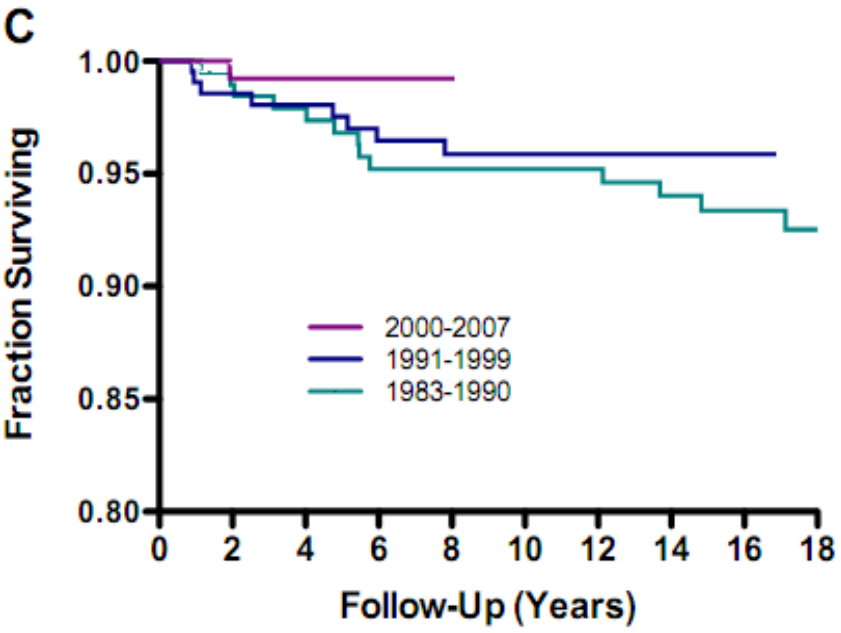
Improved survival of children and adolescents with sickle cell disease

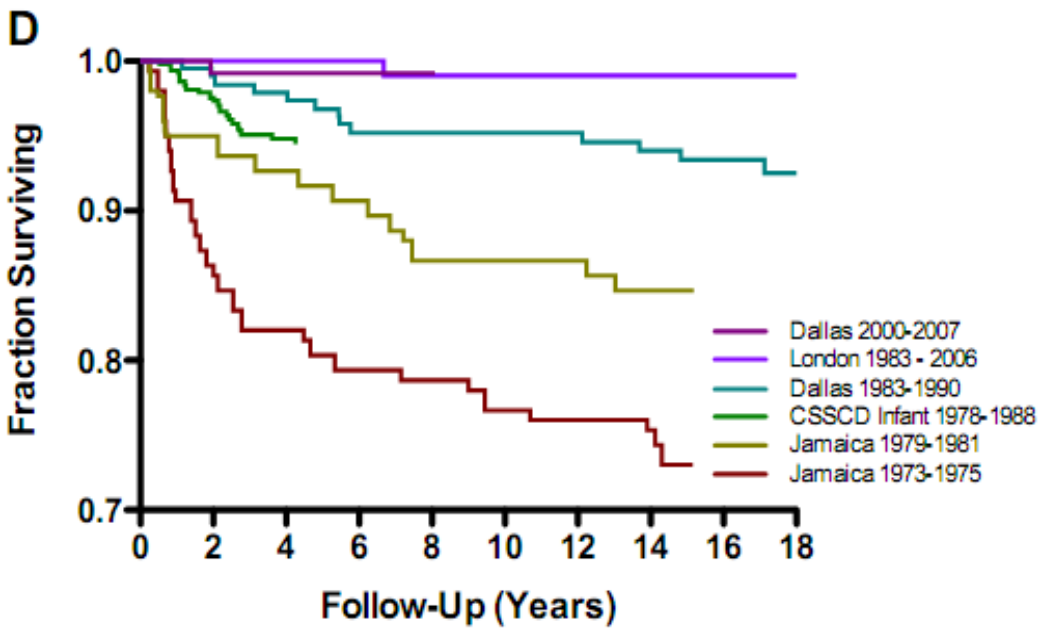
Charles T. Quinn,[1-3] Zora R. Rogers,[1-3] Timothy L. McCavit,[1-3] and George R. Buchanan[1-3]

[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, 29 APRIL 2010 • VOLUME 115, NUMBER 17

The survival of young children with sickle cell disease (SCD) has improved, but less is known about older children and adolescents. We studied the Dallas Newborn Cohort (DNC) to estimate contemporary 18-year survival for newborns with SCD and document changes in the causes and ages of death over time. We also explored whether improvements in the quality of medical care were temporally associated with survival. The DNC now includes 940 subjects with 8857 patient-years of follow-up. Most children with sickle cell anemia (93.9%) and nearly all children with milder forms of SCD (98.4%) now live to become adults. The incidence of death and the pattern of mortality changed over the duration of the cohort. Sepsis is no longer the leading cause of death. All the recent deaths in the cohort occurred in patients 18 years or older, most shortly after the transition to adult care. Quality of care in the DNC has improved over time, with significantly more timely initial visits and preventive interventions for young children. In summary, most children with SCD now survive the childhood years, but young adults who transition to adult medical care are at high risk for early death. (*Blood*. 2010;115(17):3447-3452)





Transition to adult

Pediatr Blood Cancer 2013;60:828–835

Age-Related Treatment Patterns in Sickle Cell Disease Patients and the Associated Sickle Cell Complications and Healthcare Costs

Morey A. Blinder, MD,[1]* Francis Vekeman, MA,[2] Medha Sasane, BPharm, PhD,[3] Alex Trahey, BA,[4] Carole Paley, MD,[3] and Mei Sheng Duh, MPH, ScD[4]

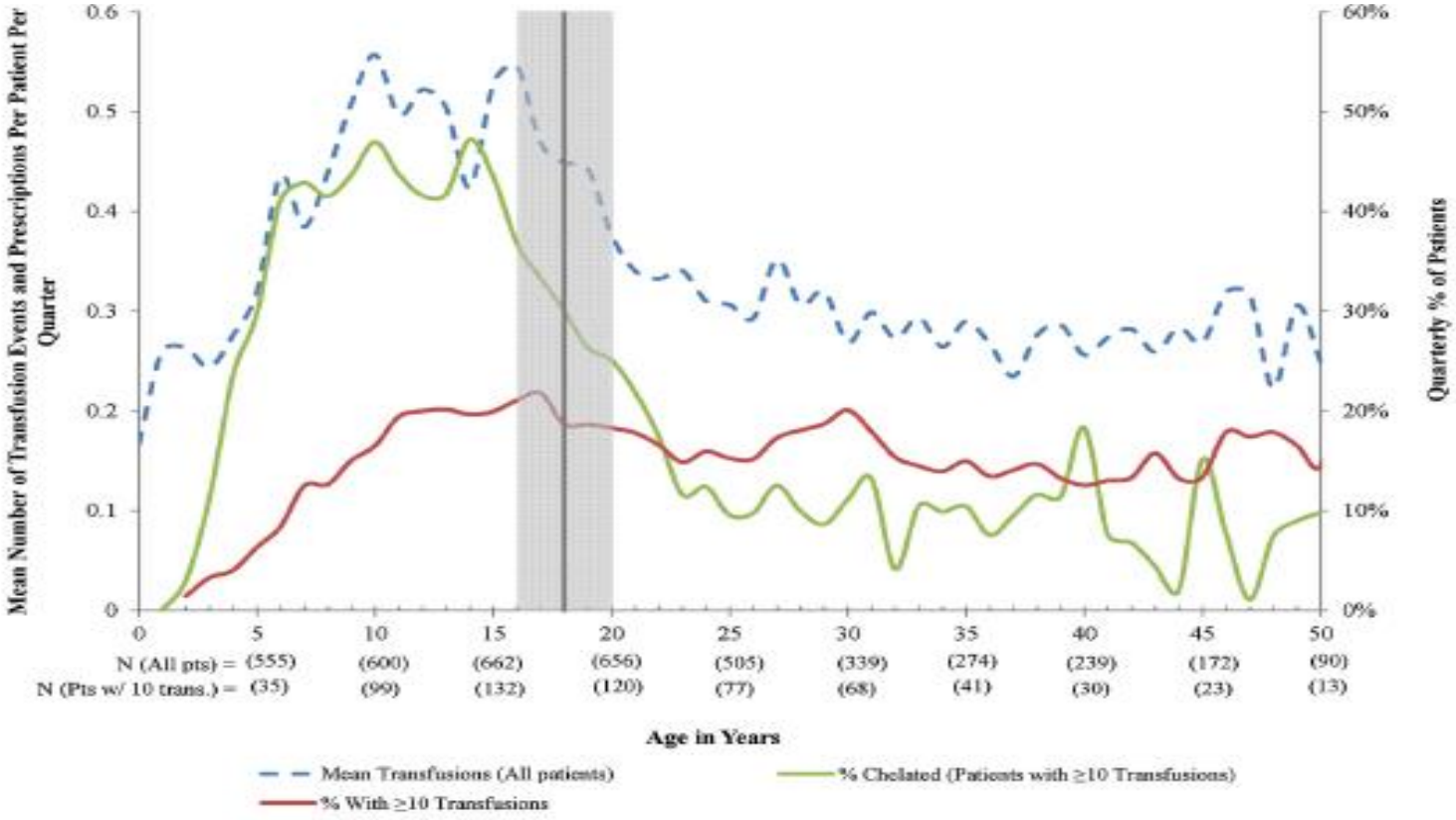


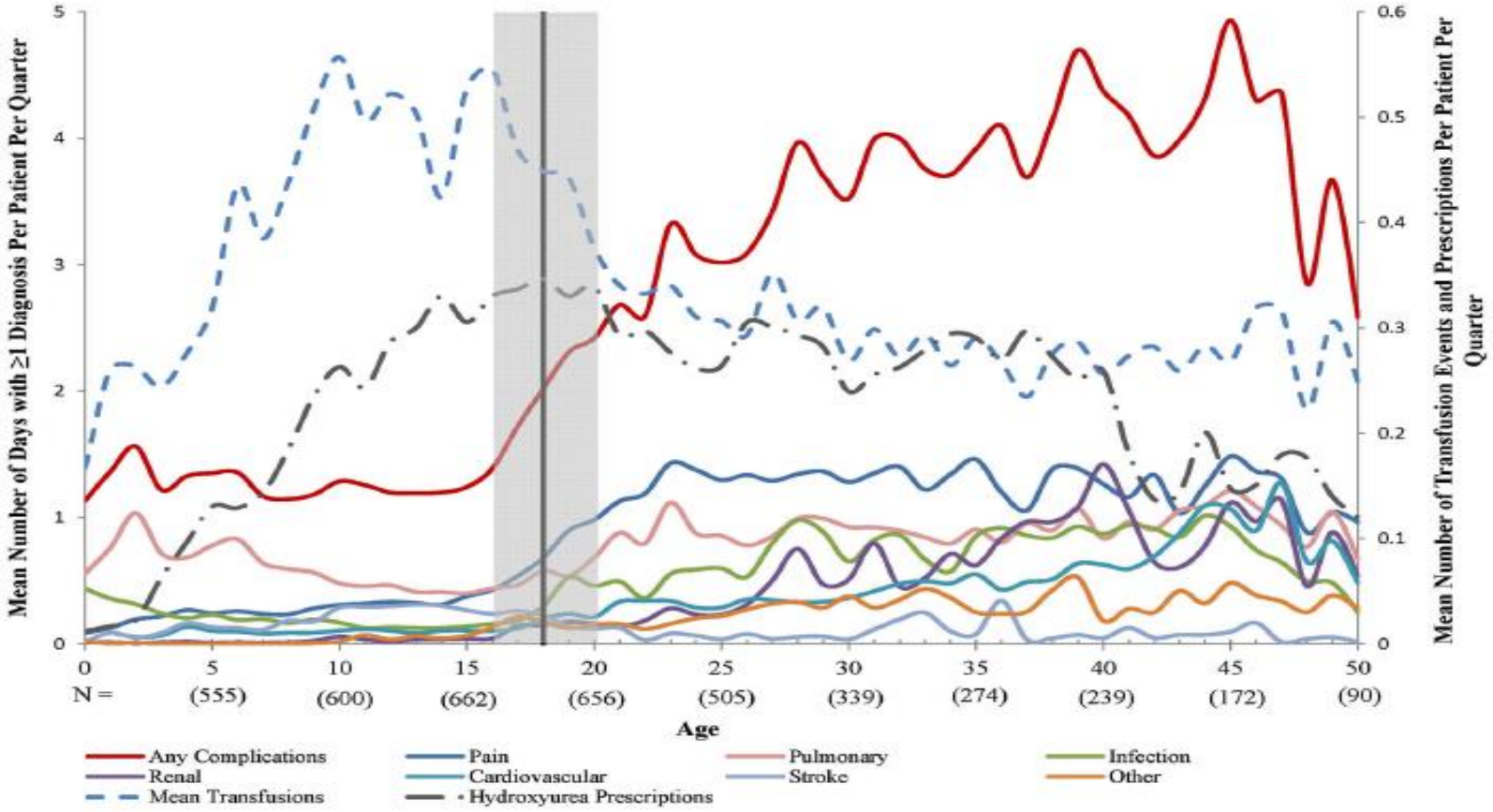
Fig. 1. Treatment patterns by age.

Transition to adult

Pediatr Blood Cancer 2013;60:828–835

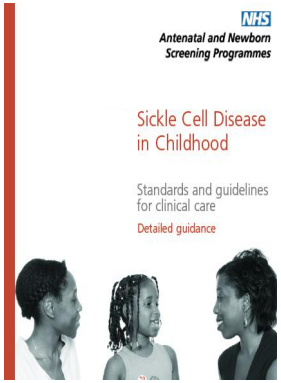
Age-Related Treatment Patterns in Sickle Cell Disease Patients and the Associated Sickle Cell Complications and Healthcare Costs

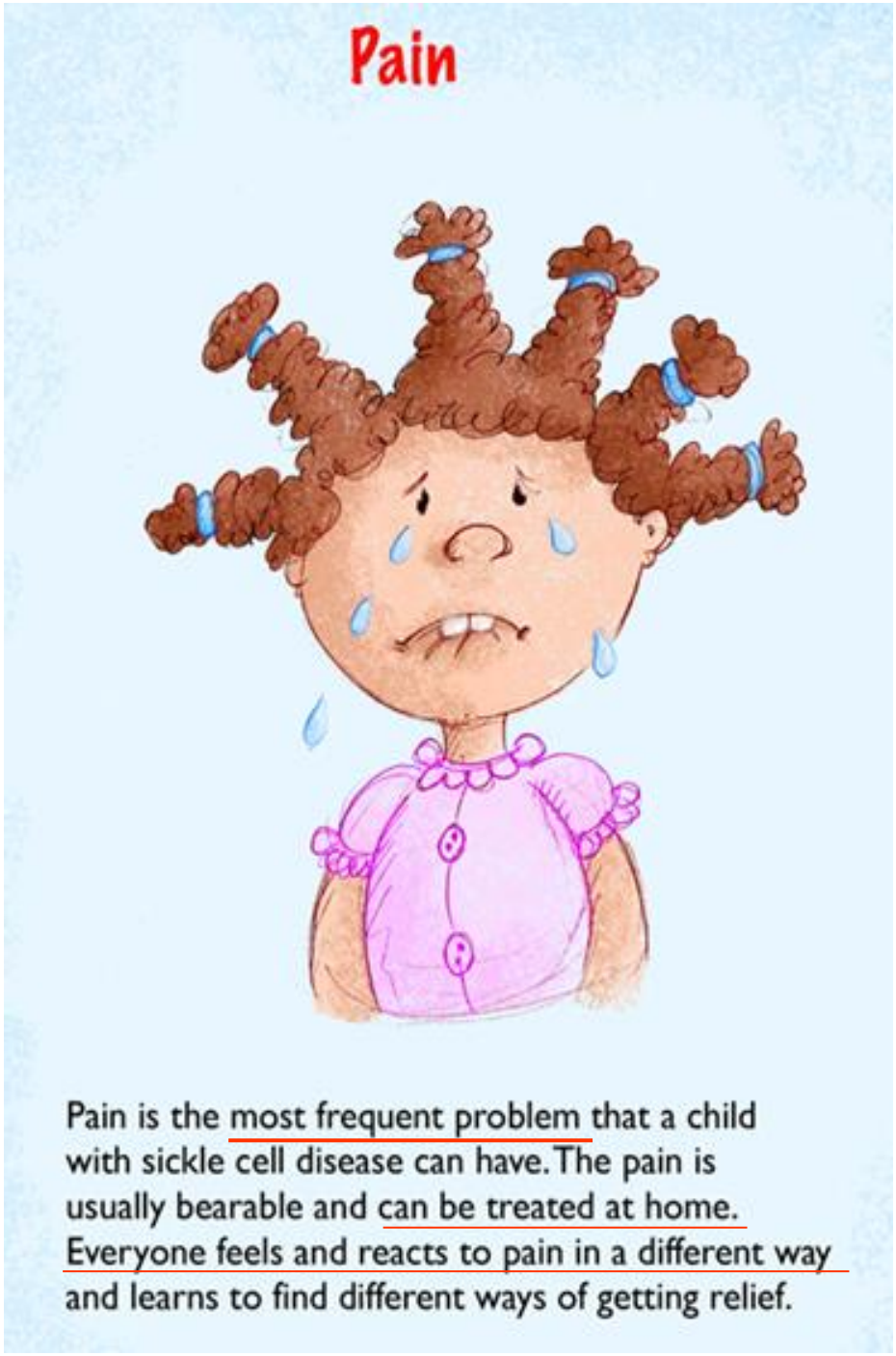
Morey A. Blinder, MD,[1]* Francis Vekeman, MA,[2] Medha Sasane, BPharm, PhD,[3] Alex Trahey, BA,[4] Carole Paley, MD,[3] and Mei Sheng Duh, MPH, ScD[4]



Comprehensive care

- ***Information and education***
- ***Sickle cell centers***
- ***Pathways for the Management of ACUTE COMPLICATIONS (at home and in hospital)***
- ***Follow up schedule for monitoring of CHRONIC COMPLICATIONS***





VOC

- 10% of days of life
- 6-7% days off from school/work
- 25% of patients first symptom
- >90% reason of admission
- 80% of VOC can be treated at home with appropriate education

Vichinsky 1982, Benjamin 2000, Ware 1999, Payne 2009, Aisiku 2009

ACUTE CHEST SYNDROME

Cause	*n*	%
Acute chest syndrome	71	25.27
Cardiac causes	13	4.63
Hemolytic crisis	4	1.42
Hepatic crisis	1	0.36
Infection	82	29.18
Organ damage	30	10.68
Overt stroke	33	11.74
Splenic sequestration	1	0.36
Sudden during painful crisis	26	9.25
Unknown	7	2.49
Unrelated	13	4.63
Total	281	100

2° CAUSE OF DEATH

De Castro Lobo 2018

Conclusions

- Single gene disorders can be complex and with extreme phenotypic variability
- It takes time to find answers and solution to clinical issues
- Minimal standards of care should be provided to ALL children
- Comprehensive care requires a multidisciplinary team and different «skills»

ARISE

African Research And Innovative Initiative For Sickle Cell Education

Neurosonologist

Data Manager

Director

Resident

Biologist

Sickle Cell Group

Psycologist

Biologist

Pediatrician

Neuroradiologist

TCD-TCDi technician

Biologist

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THANK YOU ALL!