Duke Children's

Sickle Cell Disease Workshop: Breaking Down Myths and Barriers

Pediatric Complications and Treatment

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November 1, 2012

Outline

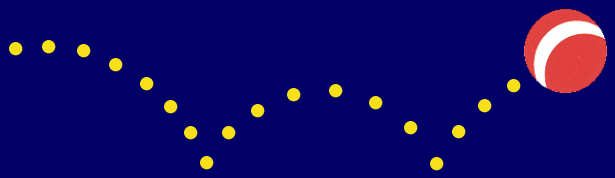
Diagnosis of sickle cell disease

Complications of sickle cell disease in children

Treatment of complications

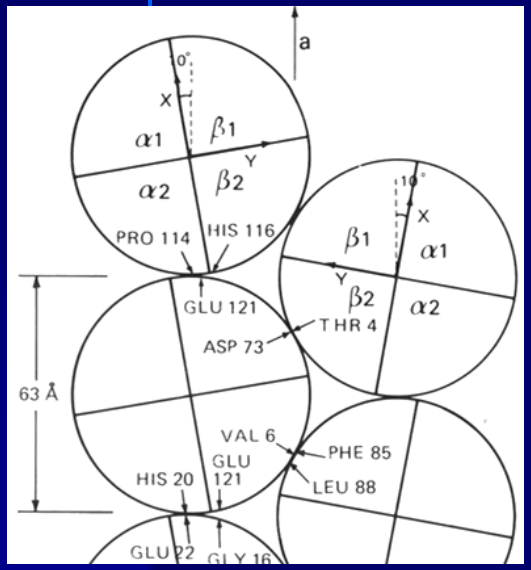
Prevention of complications

The next 100 years….



Physiology

β^{6} glu→val



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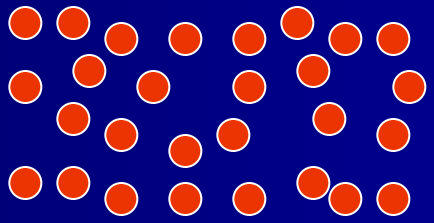

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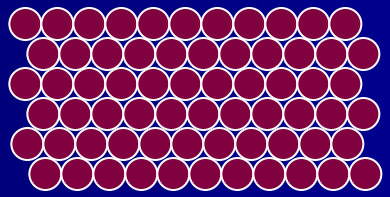
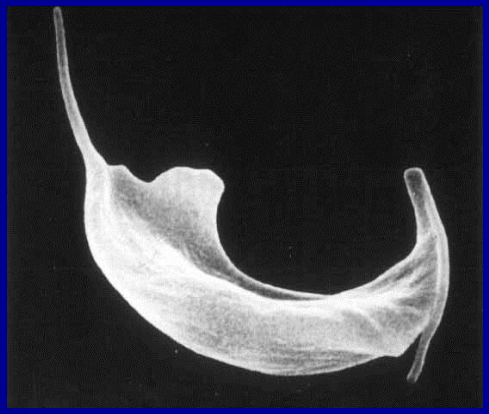
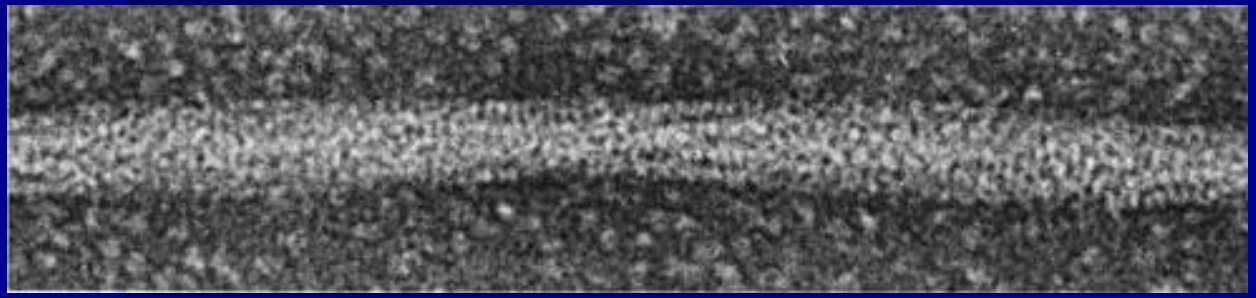
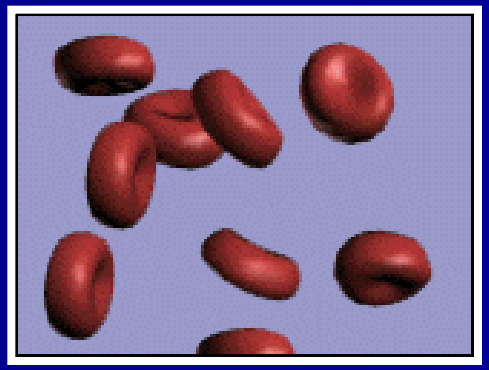
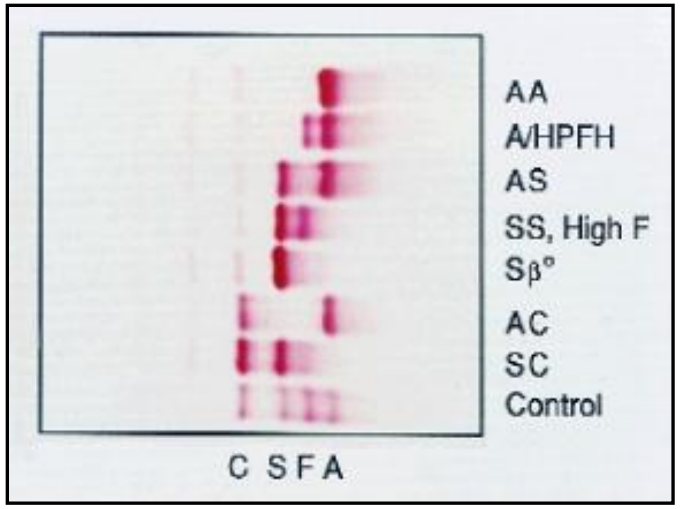




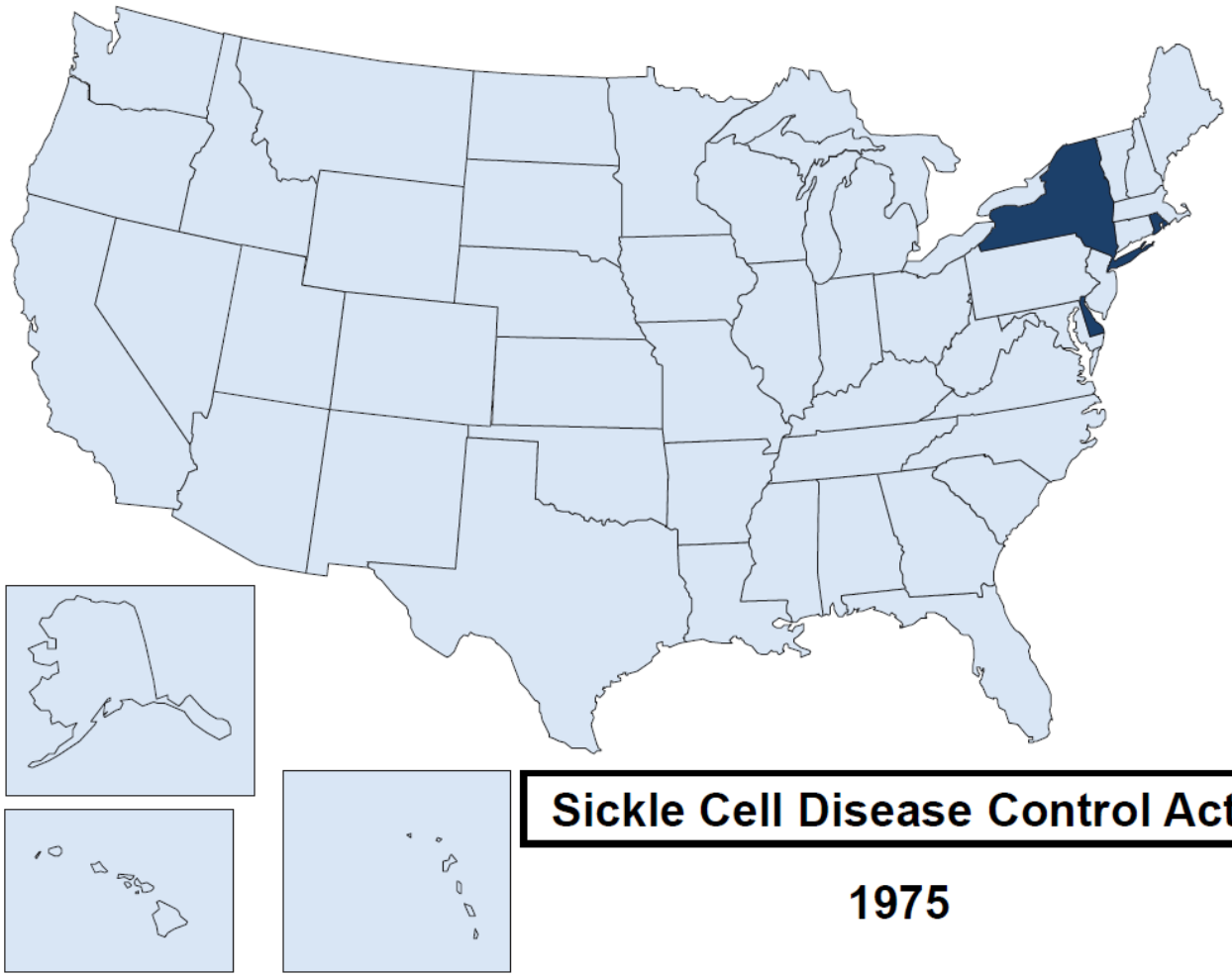




Newborn Screening



- Performed at 24 hrs of life via heel stick
- Technique
  - Hemoglobin electrophoresis
  - Isoelectric focusing
- Follow-up
  - Family, local physician, and state counselor are notified of any abnormal hemoglobin
  - Infant is referred to Sickle Cell Center



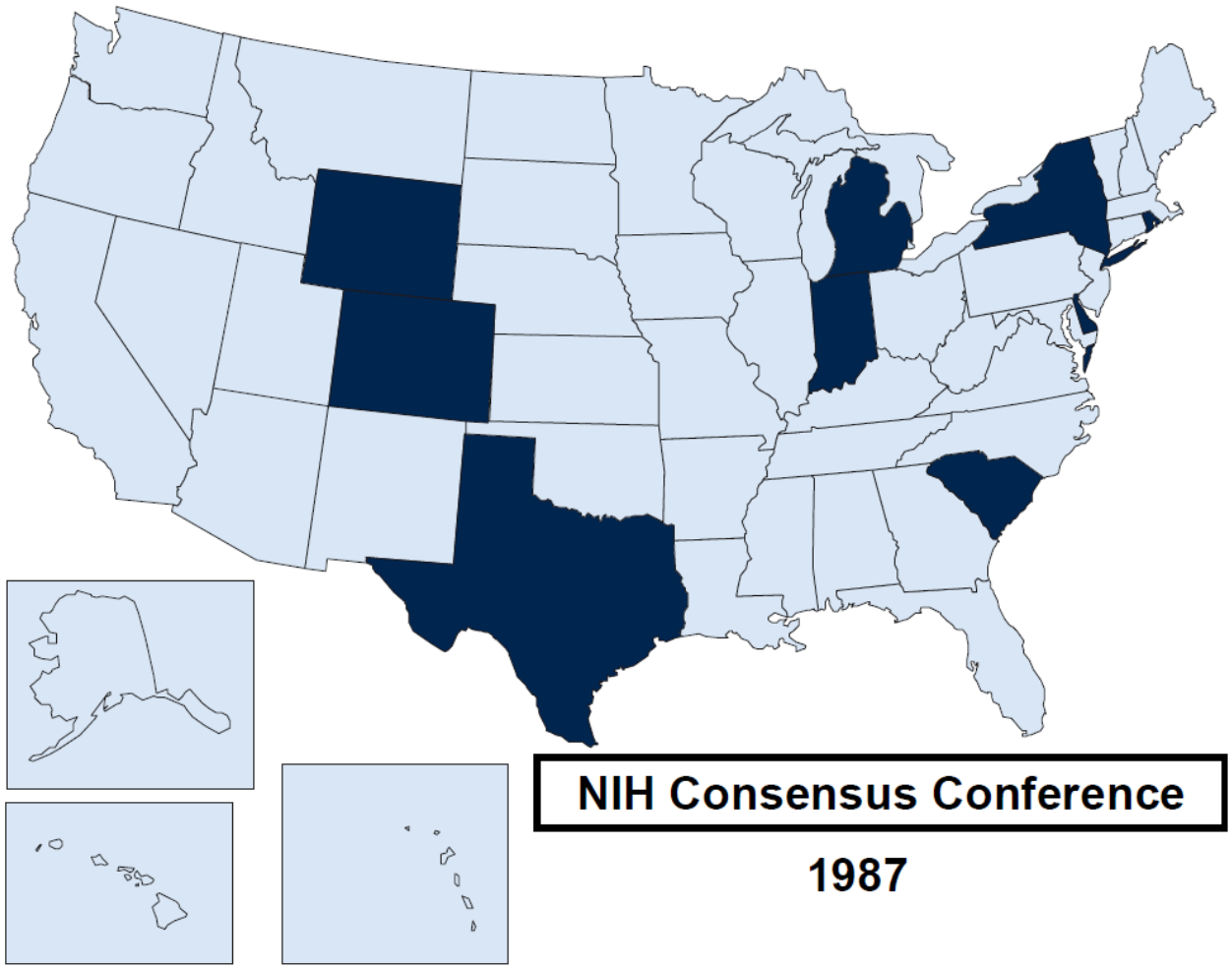
Sickle Cell Disease Control Act

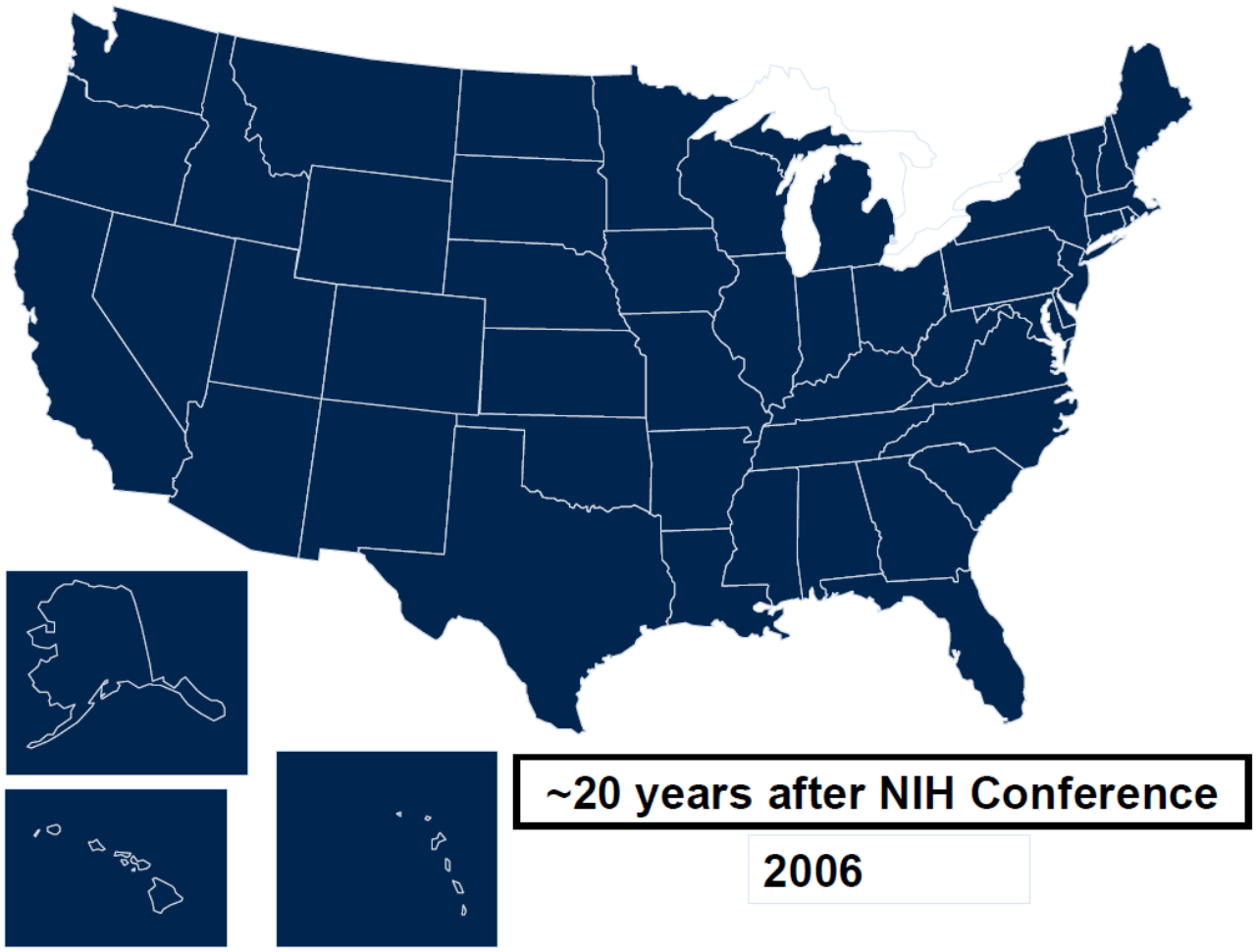
1975

Newborn Screening for Sickle Cell Disease and Other Hemoglobinopathies

National Institutes of Health
Consensus Development Conference Statement
April 6-8, 1987

"....the panel concludes that every child should be screened for hemoglobinopathies to prevent the potentially fatal complications of sickle cell disease during infancy."


NIH Consensus Conference
1987

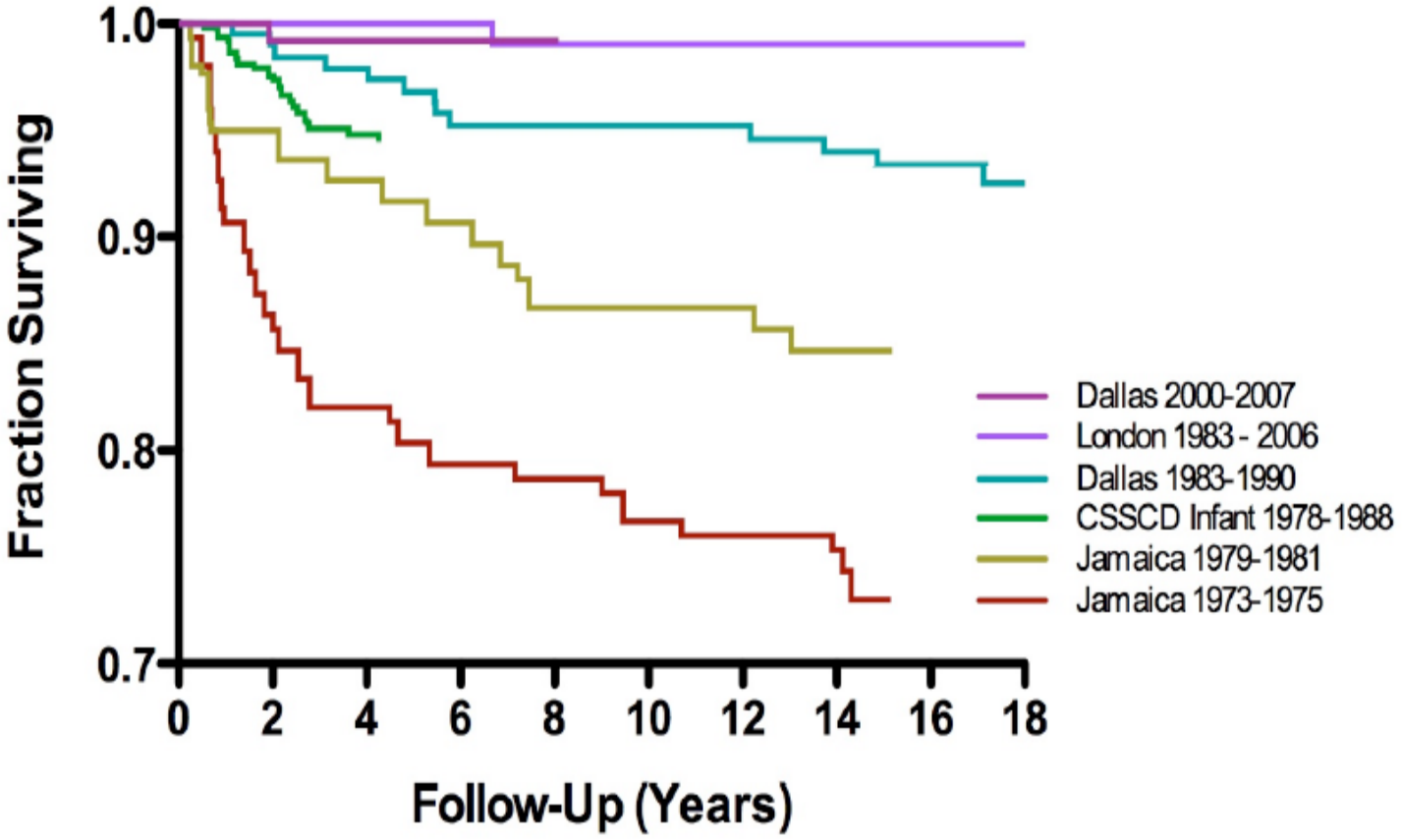


Newborn screening of all infants in North Carolina since 1994

Goals of Early Diagnosis

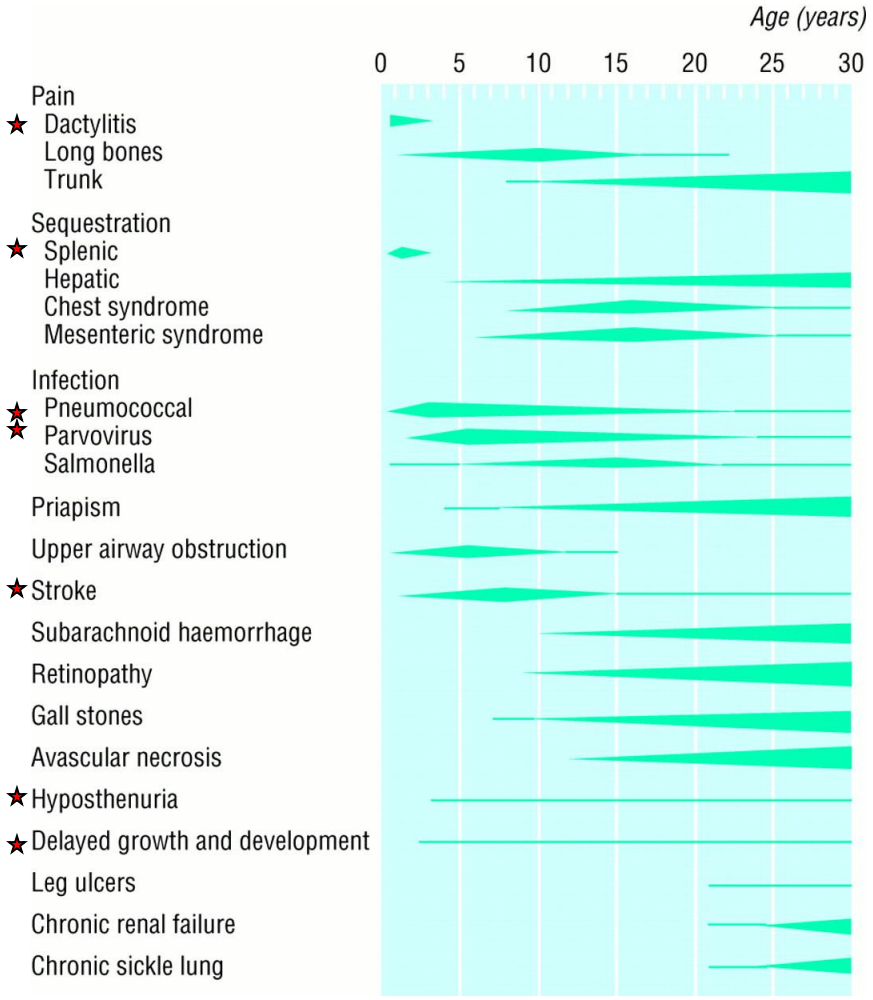
- Diagnose babies before they get sick
- Educate the parents
- Provide genetic counseling
- Prevent complications
- Save lives and improve lives

Improved Survival



Quinn et al. Blood 2010; 115(17): 3447-52.

Age Distribution of Complications



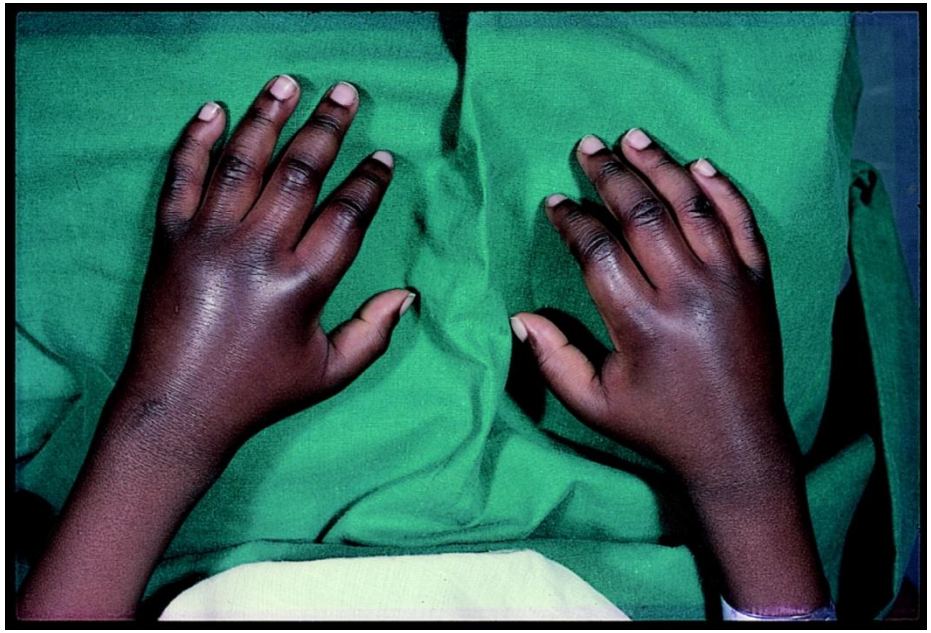
Davies et al. BMJ 1997. 315:656-660

Clinical Presentation

- 6 month old with persistent crying and decreased feeding; dactylitis
- 15 month old with SCD, type SS, with fever, diarrhea and non-productive cough; pneumococcal sepsis
- 3 year old with SCD, type SS, presenting with fever; splenic sequestration
- 5 year old with SCD, type SS, with left knee pain; stroke

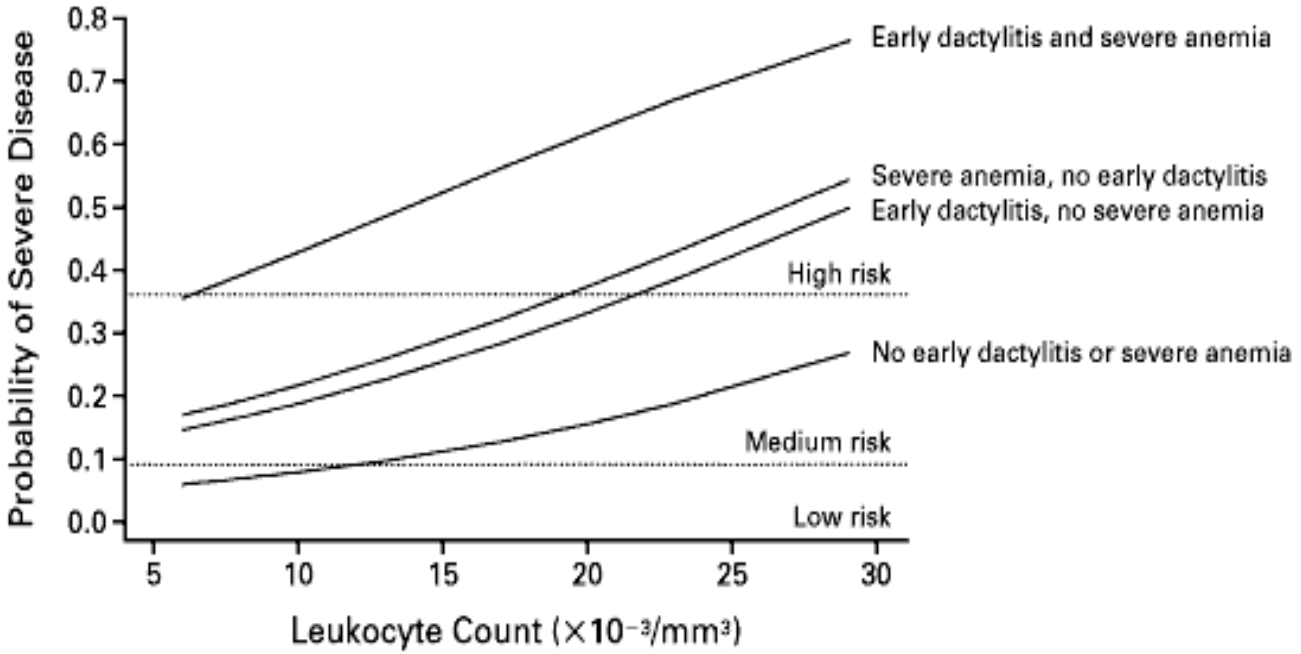
Dactylitis

- Peak occurrence at 6-12 mo of age
- Affects ~45% of children by age 2 y
- Rarely seen after age 3 y
- Treat with hydration and pain medication
- May be a predictor of severe disease



Davies, S. C et al. BMJ 1997;315:656-660

Predictors of Disease Severity



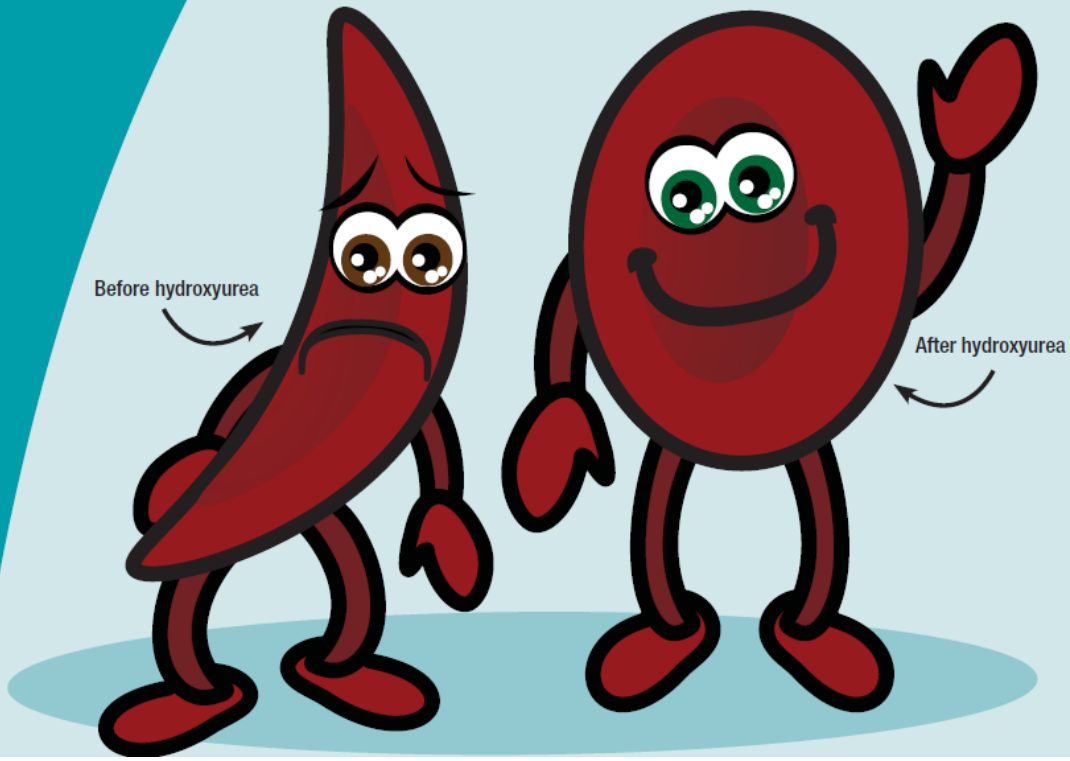
- Dactylitis < 12 mo
- Hgb < 7.0 g/dL
- WBC > 13.7 x 10^9/L

Miller et al. NEJM 2000. 342: 83-89.

An Ounce of Prevention is Worth a Pound of Cure

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Hydroxyurea Treatment for Sickle Cell Disease

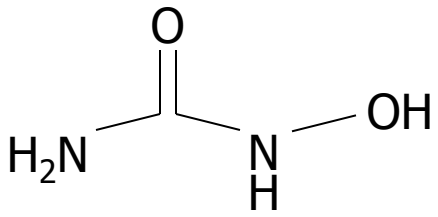


Hydroxyurea Induces Fetal Hb

Rapid Publication

Hydroxyurea Enhances Fetal Hemoglobin Production in Sickle Cell Anemia

Orah S. Platt, Stuart H. Orkin, George Dover, G. Peter Beardsley, Barbara Miller, and David G. Nathan
Division of Hematology and Oncology, Children's Hospital, Division of Pediatric Oncology, Dana Farber Cancer Institute, Department of Pediatrics of the Harvard Medical School, Boston, Massachusetts 02115, and Department of Pediatrics, Johns Hopkins University and Hospital, Baltimore, Maryland 21205



hydroxyurea

JCI 1984. 74: 652-656.

Pleioptropic effects of Hydroxyurea

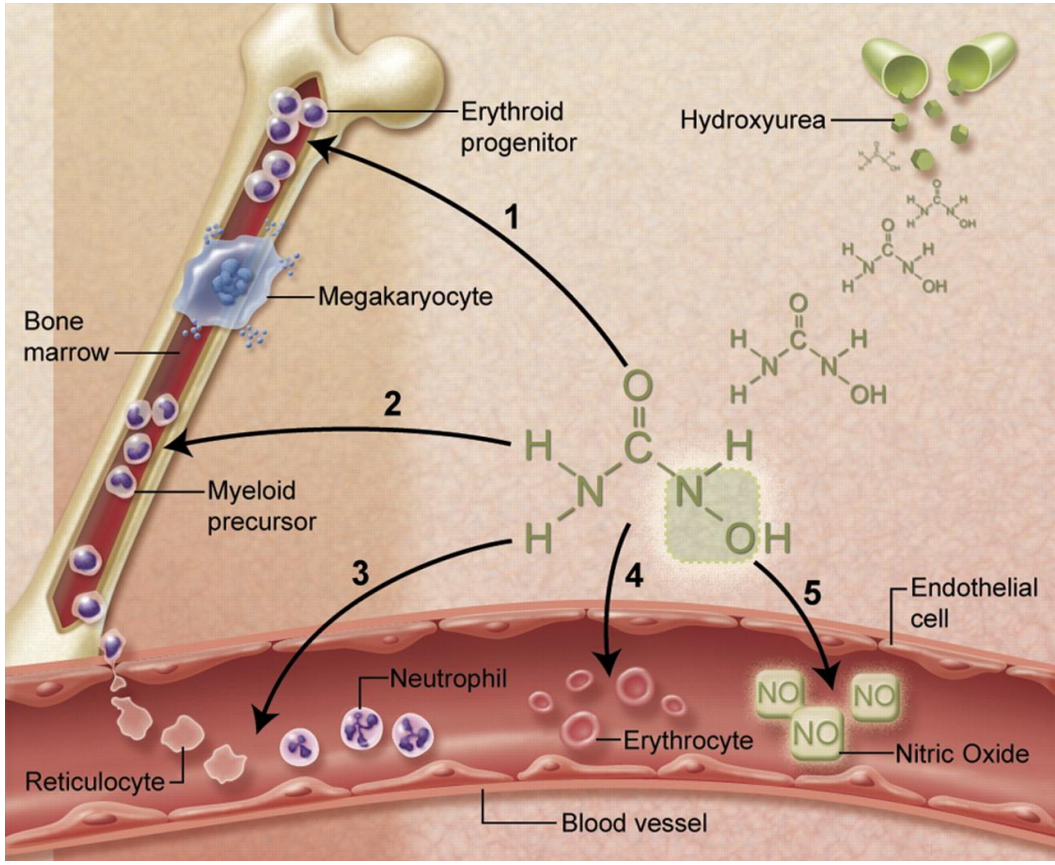
1) Fetal hemoglobin induction

2) Lower neutrophil and reticulocyte counts from ribonucleotide reductase inhibition and marrow cytotoxicity

3) Decreased adhesiveness and improved rheology of circulating neutrophils and reticulocytes

4) Reduced hemolysis through improved erythrocyte hydration, macrocytosis, and reduced intracellular sickling

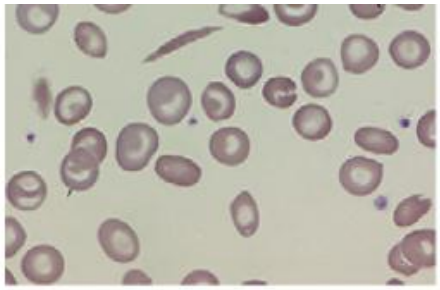
5) Nitric oxide (NO) release with potential local vasodilatation and improved vascular response



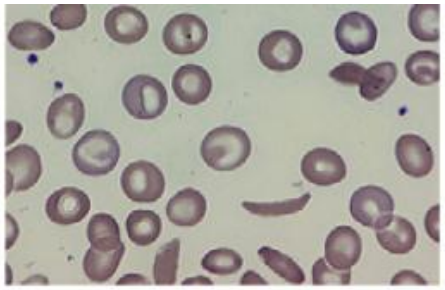
Ware. Blood 2010; 115: 5300-5311

Laboratory Effects

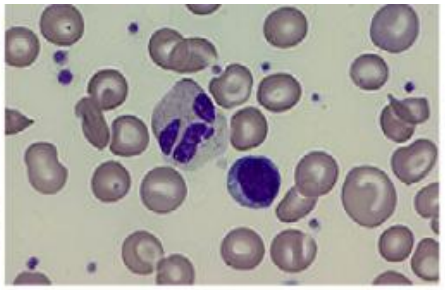
	Adults	Children
MTD (mg/kg/d)	21.3	25.6
Δ Hb (g/dL)	+1.2	+1.2
Δ MCV (fL)	+23	+14
Δ HbF (%)	+11.2	+9.6
Δ Reticulocytes (10^9/L)	−158	−146
Δ WBC (10^9/L)	−5.0	−4.2
Δ ANC (10^9/L)	−2.8	−2.2
Δ Bilirubin (mg/dL)	−2.0	−1.0



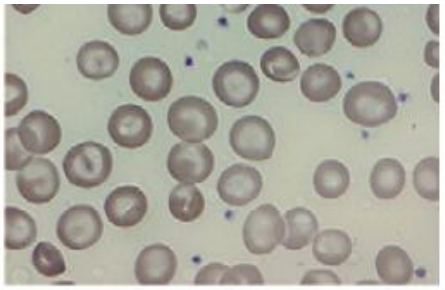
Pre-hydroxyurea
Hb = 7.7 gm/dL
MCV = 84 fL
ANC = 8113
ARC = 247K
HU = 600mg
20 mg/kg/d



8 weeks
Hb = 7.9 gm/dL
MCV = 96 fL
ANC = 3700
ARC = 203K
HU = 780 mg
25 mg/kg/d

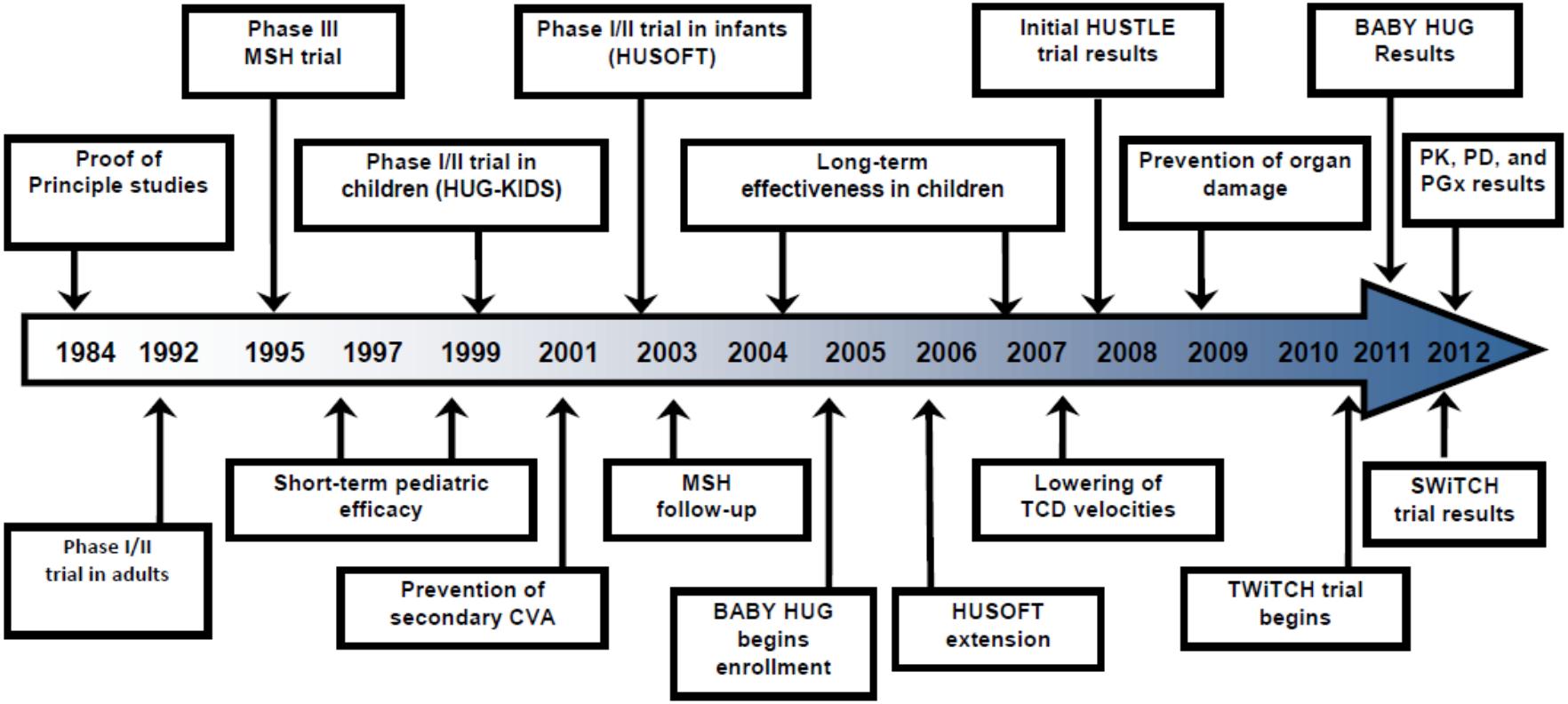


20 weeks
Hb = 9.6 gm/dL
MCV = 105 fL
ANC = 3200
ARC = 150K
HU = 950 mg
30 mg/kg/d



22 months
Hb = 10.0 gm/dL
MCV = 113 fL
ANC = 1200
ARC = 124K
HU = 1040 mg
27 mg/kg/d

Hydroxyurea: 30 Years of Research



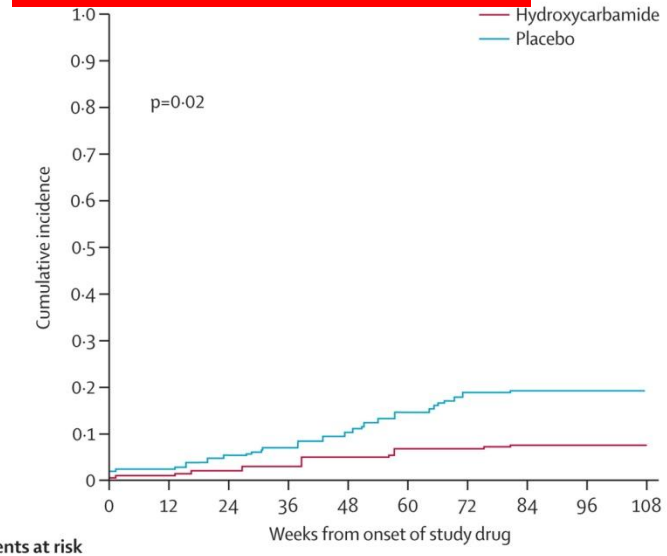
BABY HUG

- BABY HUG (NCT00006400) was a Phase III multicenter, randomized, double-blinded clinical trial of hydroxyurea in infants with sickle cell anemia (SCA).

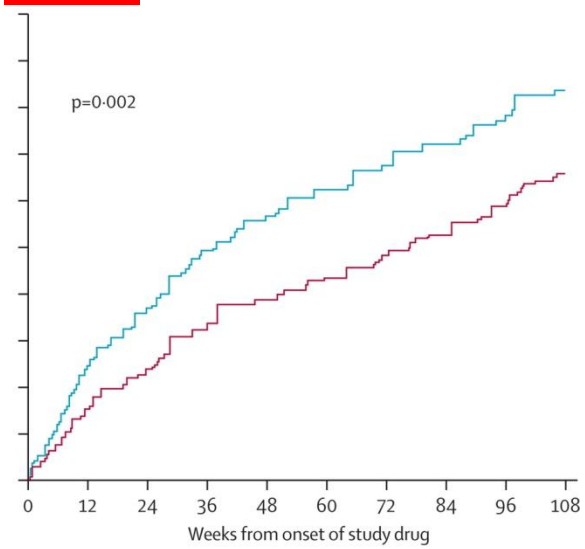
- Secondary endpoints included subjects' rates of vaso-occlusive pain (VOC), dactylitis, and acute chest syndrome (ACS).

Wang et al. Lancet 2011; 377: 1663-1672.

Acute chest syndrome



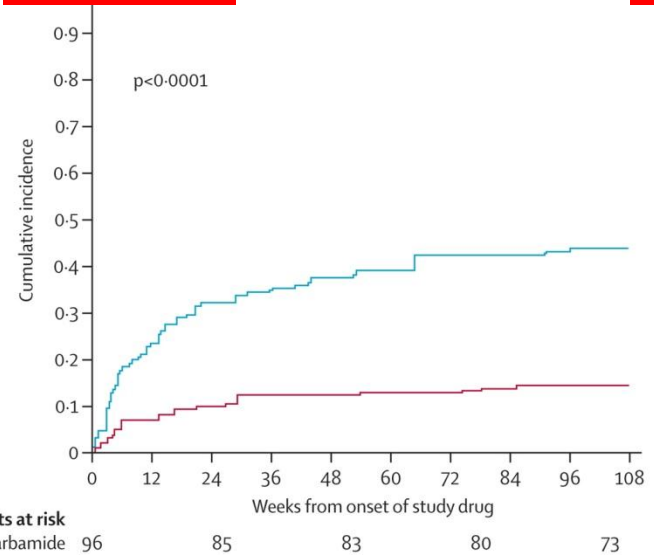
Pain



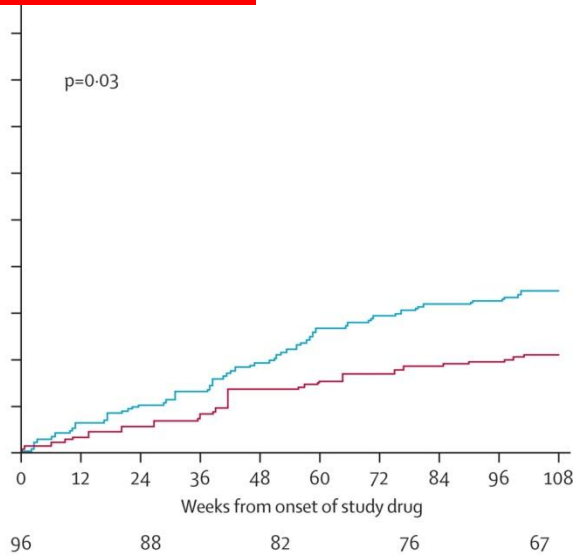
Patients at risk

Hydroxycarbamide	96	90	88	85	78	96	70	60	46	31
Placebo	97	90	79	71	66	97	59	33	26	16

Dactylitis



Transfusion



Patients at risk

Hydroxycarbamide	96	85	83	80	73	96	88	82	76	67
Placebo	97	62	54	50	46	97	84	71	61	54

Dactylitis was also decreased in patients who were asymptomatic at study entry.

Ongoing Assessment in the Real World

- BABY HUG Follow-up Study I
  - Complete
  - Up to 6 years of follow-up

- BABY HUG Follow-up Study II
  - Ongoing
  - Additional 5 years of follow-up
  - Will follow children into adolescence

Hydroxyurea is Underutilized

- The NIH Consensus Conference on Hydroxyurea identified significant challenges to the implementation of hydroxyurea therapy.

- There are barriers at the provider-level, the patient-level including parental acceptance and medication adherence, and systems-level including access to care and insurance.

Brawley et al. Ann Intern Med 2008; 148: 932-8.

Provider-Reported Barriers

- patient adherence with taking medication (86%);
- patient adherence with blood tests (85%);
- lack of contraception in females (85%);
- patient's anticipation of side effects (75%);
- age of patient (68%);
- concern for male infertility (46%);
- lack of formal guidelines in children (30%);
- concern with carcinogenic potential (27%);
- cost (18%);
- lack of time/resources to explain risks/benefits (16%);
- lack of FDA approval in children (12%);
- and doubt of effectiveness of hydroxyurea (11%).

Brandow and Panepinto. Am J Hematol 2011; 86(9): 804-6.
Brandow et al. Am J Hematol 2010; 85(8): 611-3.

Provider-Reported Barriers

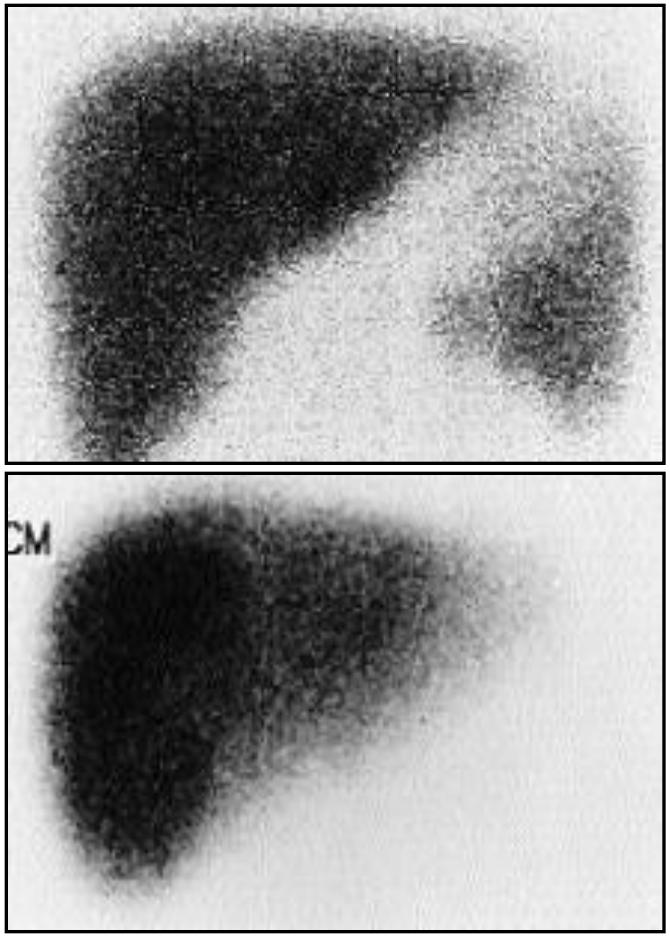
- 26% of providers indicated that the rate of families declining hydroxyurea was greater than 20%.

- Providers reported that families decline hydroxyurea due to the following reasons:
  - fear of cancer (51%);
  - fear of other side effects (62%);
  - do not want to take medication (48%);
  - do not want required laboratory monitoring (28%);
  - and do not think it will work (17%).

Brandow and Panepinto. Am J Hematol 2011; 86(9): 804-6.
Brandow et al. Am J Hematol 2010; 85(8): 611-3.

Pneumococcal Sepsis

- Functional asplenia
- Increased risk of sepsis, particularly with *Streptococcus pneumoniae*
- **Prevention**
  - Immunizations
  - Penicillin prophylaxis
  - Early evaluation for fever



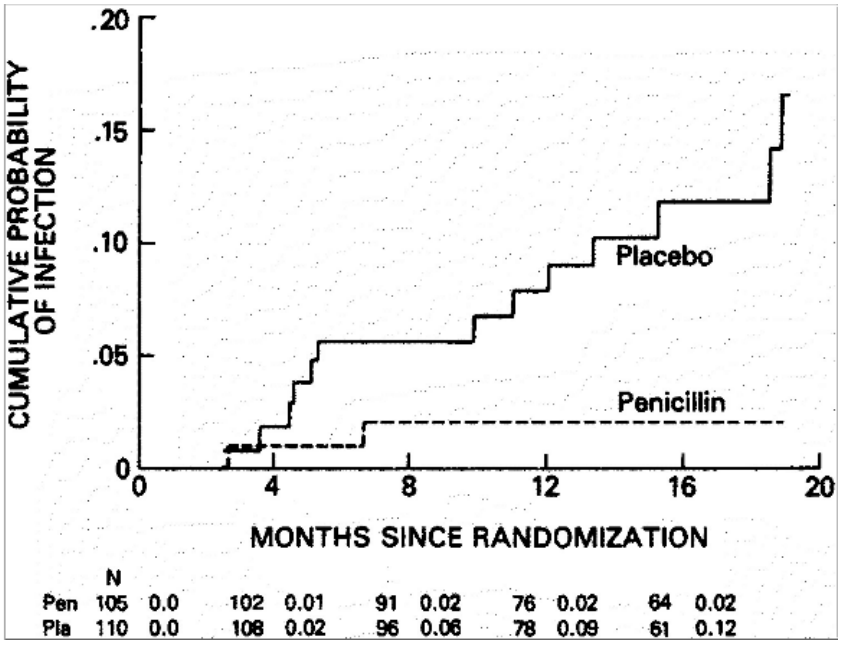
Impact of Penicillin Prophylaxis on Invasive Pneumococcal Disease in Children Less than 3 years Old

Table 1. Characteristics at Entry, According to Treatment Group.

Characteristic	Treatment Group	
	Penicillin (N = 105)	Placebo (N = 110)
	% of patients	
Age (mo)*		
3–5	15.4	10.8
6–11	23.1	21.6
12–17	14.4	20.7
18–23	22.1	17.1
≥24†	25.0	28.8
Boys	48.5	51.4
Palpable spleen	30.8	30.9
Pneumococcal vaccine	67.0	71.6
Previous infection		
Pneumonia	19.2	12.6
Bacteremia	5.8	5.4
Osteomyelitis	2.9	0
Meningitis	—	0.9
	mean values	
Laboratory findings		
Hematocrit (%)	26.1	27.3
Hemoglobin (g/dl)	8.8	9.1
White-cell count ($\times 10^{-9}$/liter)	14.6	14.1
Granulocytes (%)	31.7	35.0

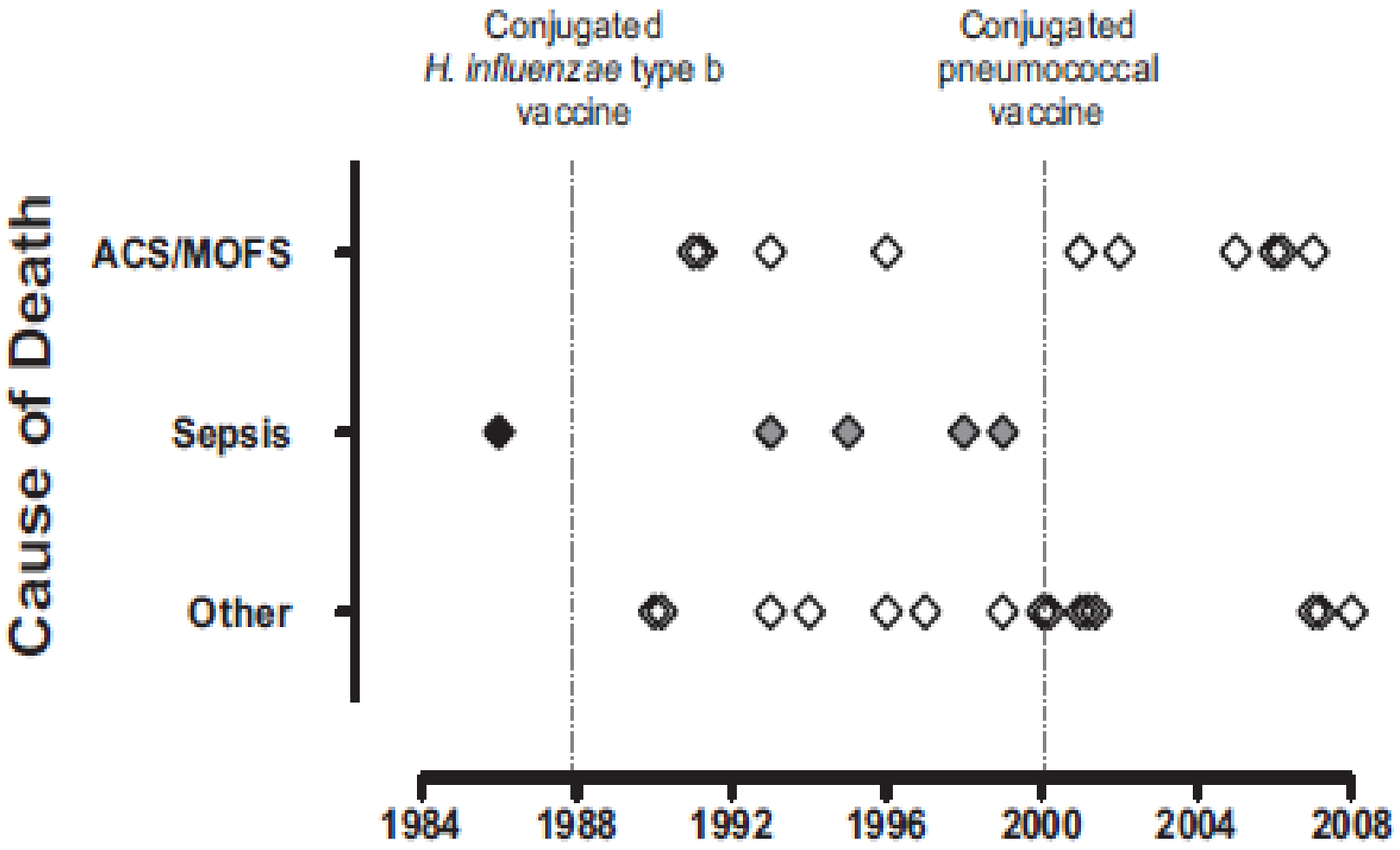
*The mean value for age in the penicillin group was 17.8 months; that in the placebo grou was 18.5.

†One child was older than 36 months.

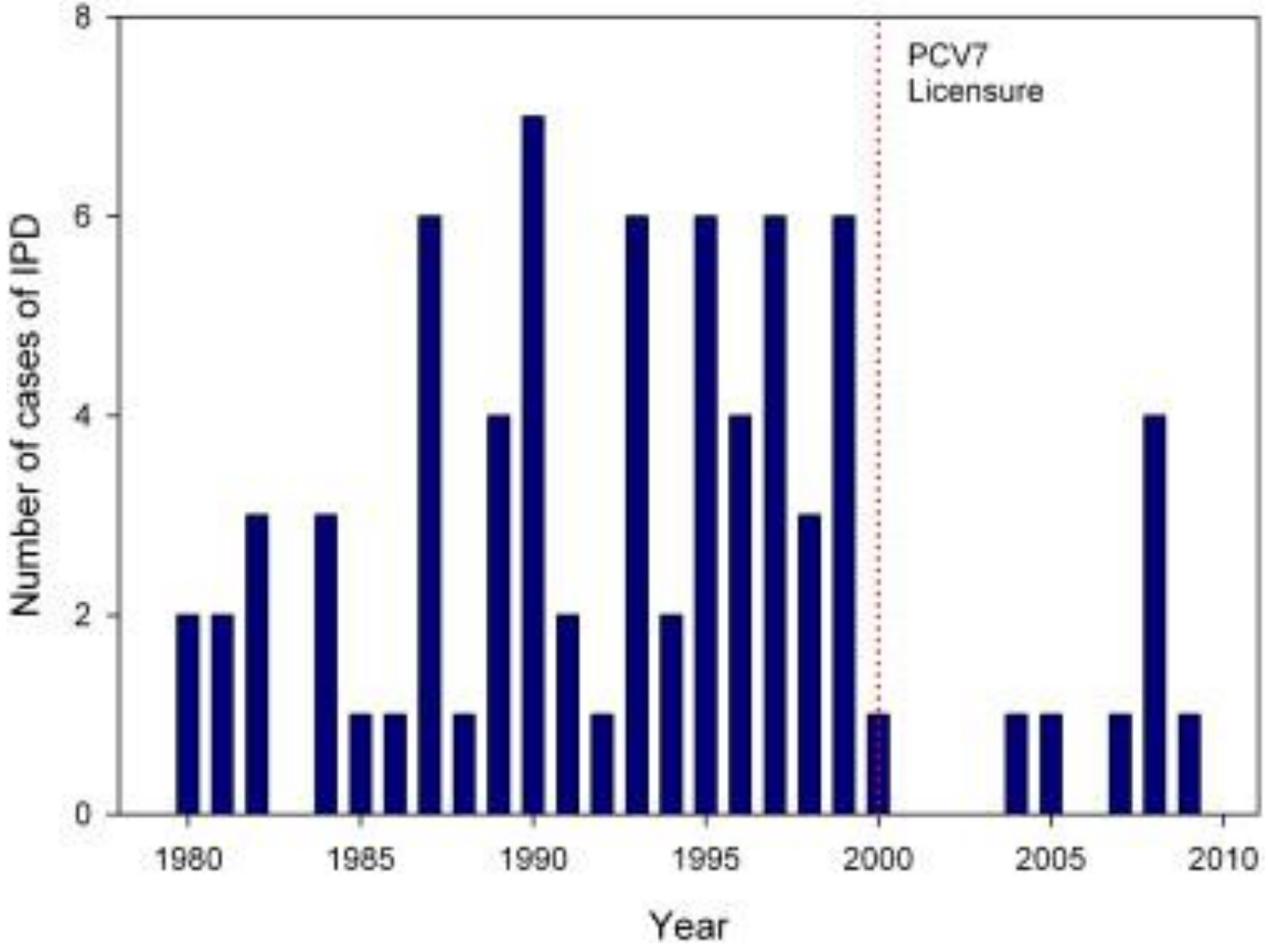


Gaston et al. N Eng J Med 1986; 314:1593-9.
Falletta et al. J Pediatr 1995; 27:685-90.

Changes in Causes of Death



Quinn et al. Blood 2010; 115(17): 3447-52.



McCavit et al. J Pediatr 2011; 158(3): 507-7.

Management of Fever

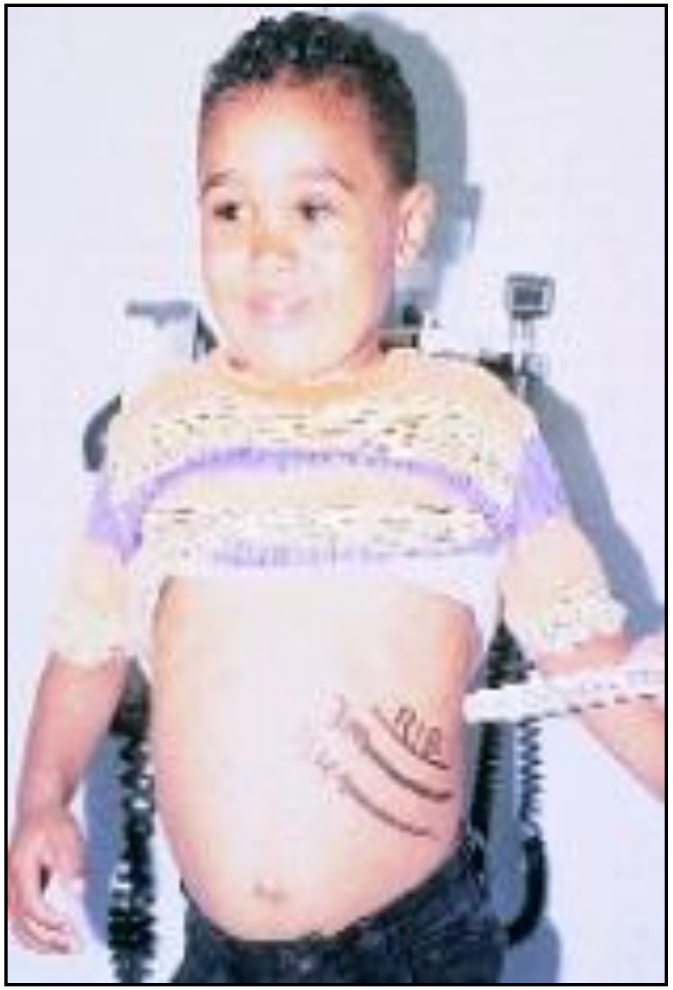
Prompt evaluation for any fever > 38.5°C (101°F)

- CBC, Blood Culture, ± CXR
- Other clinically indicated evaluations
- **Immediate** administration of IV/IM Ceftriaxone or alternative
- Close observation
- Hospitalization of children with high risk feature

Indications for Admission

- Age < 1 year
- Surgically splenectomized
- History of pneumococcal sepsis
- Toxic appearance
- Acute chest syndrome
- Other infection requiring parenteral antibiotics
- Unsure follow-up

Splenic Sequestration

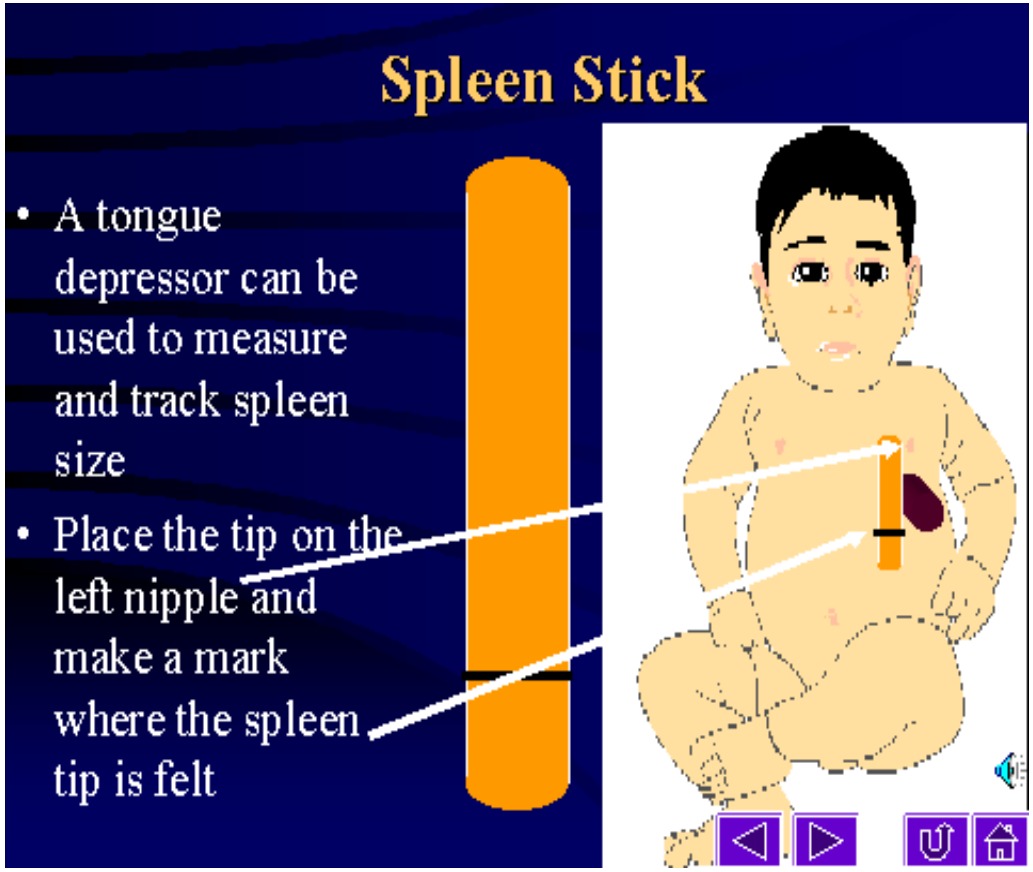


- Most common in young children (< 2 years of age)
- Anemia, thrombocytopenia and splenomegaly
- May cause hypovolemic shock and death if occurs acutely

Management of Splenic Sequestration

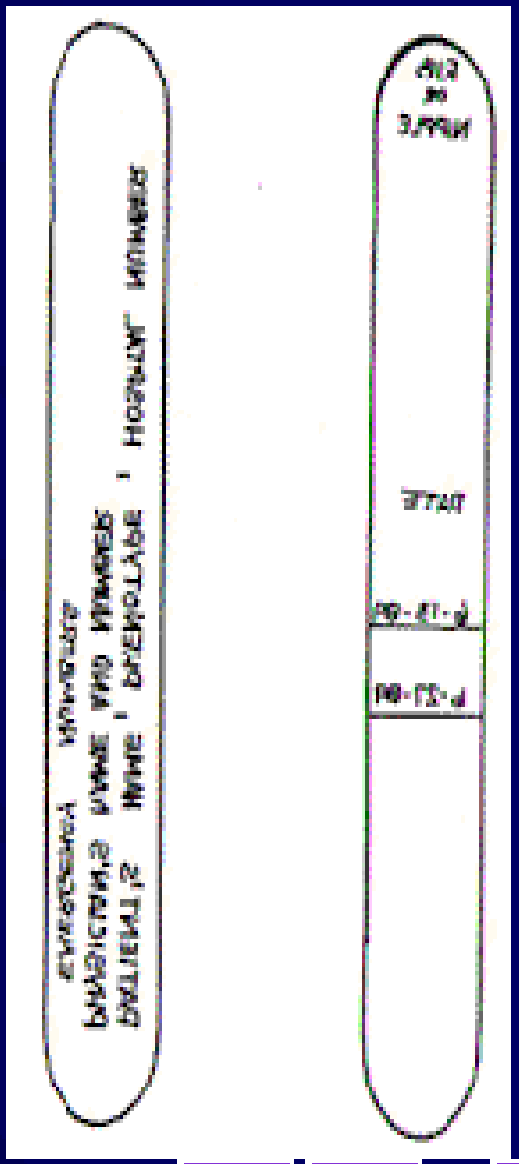
- Acute
  - Fluid resuscitation
  - Red cell transfusion
- Long-term
  - Careful observation
  - Splenectomy

Observation



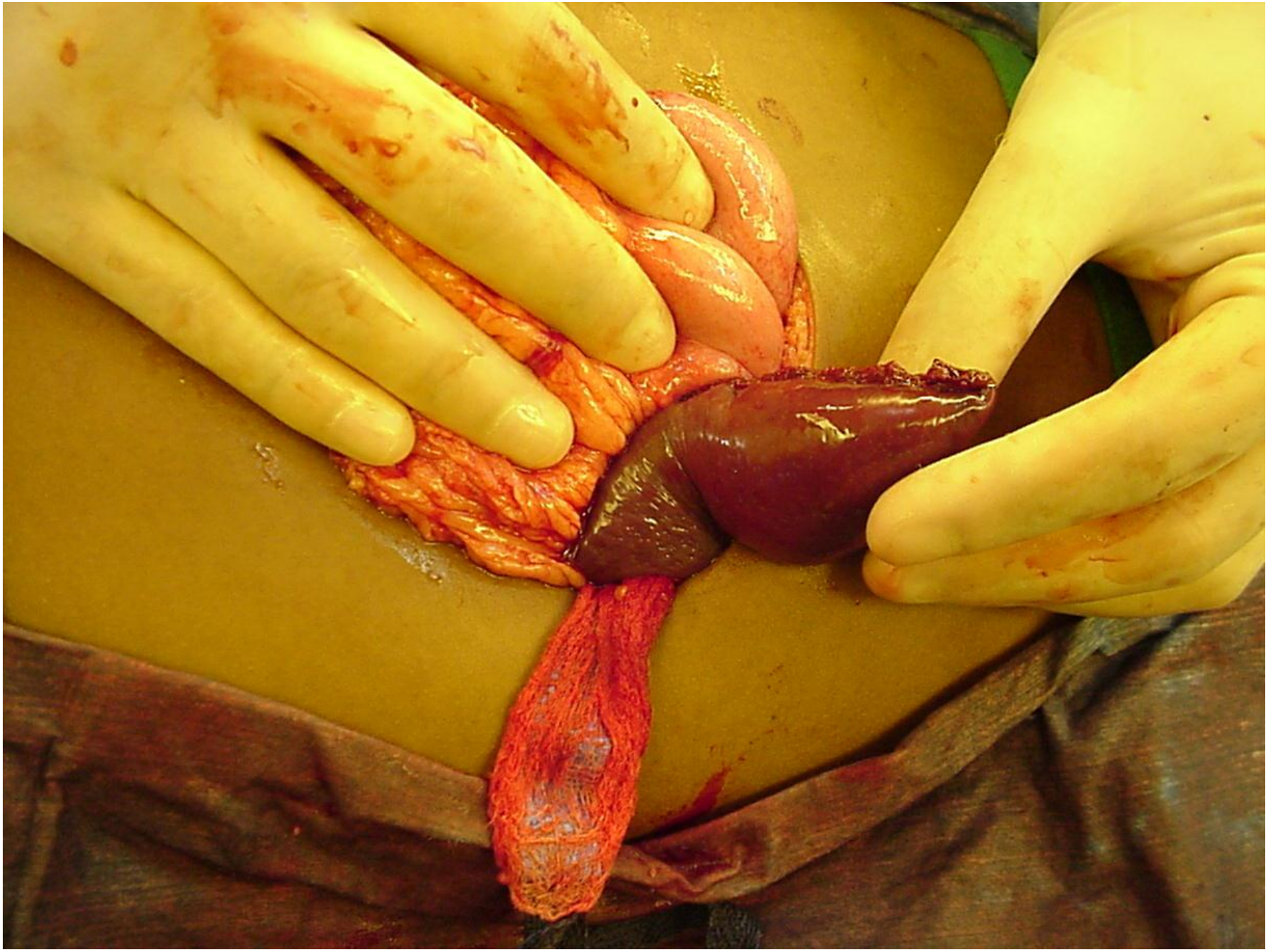
Spleen Stick

- On one side of the stick write the child's name, sickle cell type, and average hemoglobin level
- One the back put dates above the line where the spleen tip was



Splenectomy

- Indications
  - Life-threatening sequestration
  - Recurrent sequestration
  - Hypersplenism
- Timing
  - Age > 18-24 mo
  - After immunizations



Intraoperative photograph of partial splenectomy used with permission of Dr. Henry Rice, Pediatric Surgery, Duke Children's Hospital.

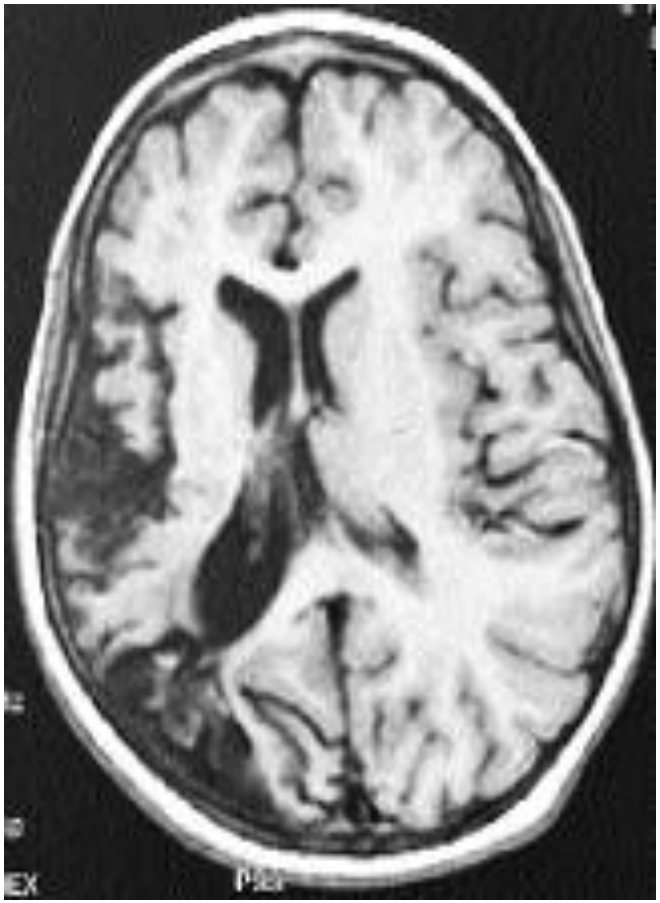
Splenectomy Registry

- Multi-center registry of children with congenital hemolytic anemia
- Follow post-splenectomy outcomes
- Basis for comparative effectiveness research

REDCap
Research Electronic Data Capture

Stroke

- Natural history
  - 0.6-0.8 events per 100 patient-years
  - Affected 7.8% by age 14 years in the Jamaican cohort and 11% by age 20 years in the CSSCD
- Types:
  - Large vessel
  - Small vessel (silent)
  - Hemorrhagic



Incidence of 1st Stroke

300x higher than for all children in US

Age (yr.)	SS	SC	Sβ+	Sβ°	Totals
< 2	0.13* (1)**	0.00	0.00	0.00	0.08 (1)
2 - 5	1.02 (20)	0.27 (2)	0.00	0.00	0.75 (22)
6 - 9	0.79 (15)	0.00	0.00	0.00	0.55 (15)
10 - 19	0.41 (15)	0.09 (1)	0.00	0.00	0.30 (16)
20 - 30	0.52 (14)	0.16 (1)	0.46 (1)	0.43 (1)	0.45 (17)
30 - 39	0.59 (8)	0.00	0.00	0.00	0.39 (8)
40 - 49	0.74 (3)	1.01 (2)	0.00	0.00	0.76 (5)
50 -	1.28 (2)	0.76 (1)	0.00	0.00	0.91 (3
OVERALL	0.61 (78)	0.17 (7)	0.11 (1)	0.10 (1)	0.46 (87)
Age-adjusted	0.61	0.15	0.09	0.08	

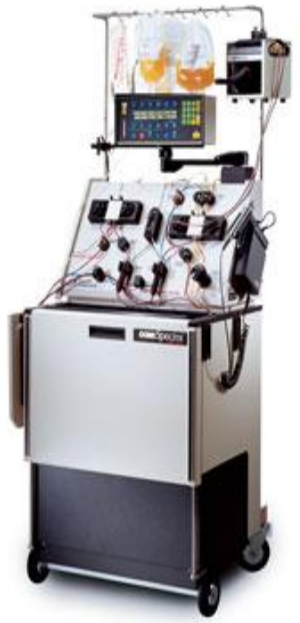
* Number Per 100 Patient-Year followup; **Number of cerebrovascular accidents

Source: Ohene-Frempong et al. Blood. 1998;91:288-294

Treatment of Stroke

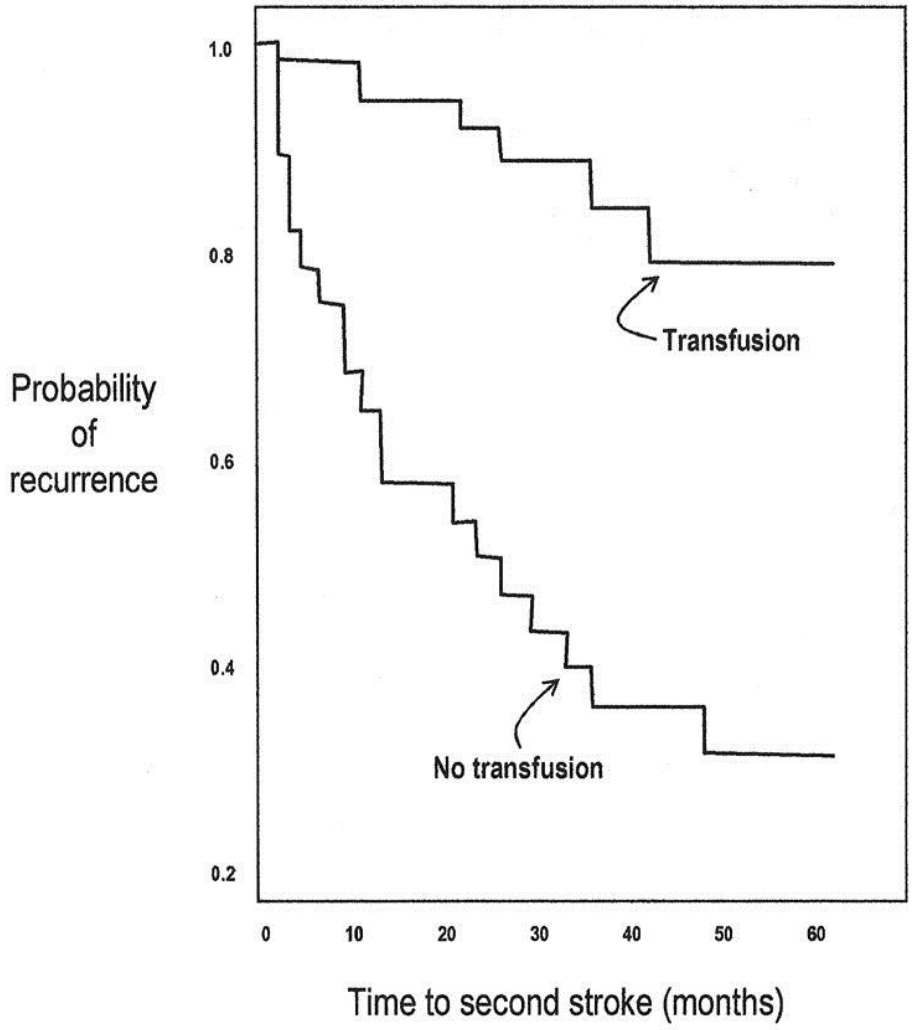
- Critical care management

- Erythrocytapheresis to reduce hemoglobin S <30%



Secondary Stroke Prevention

- Transfusion therapy

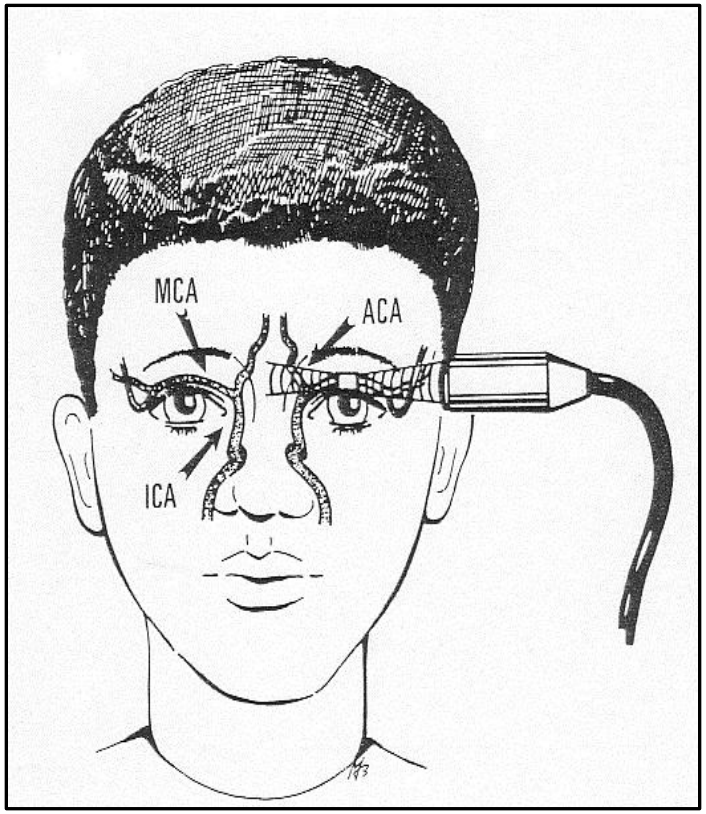


Complications

- Iron overload
- Allo/autoantibodies

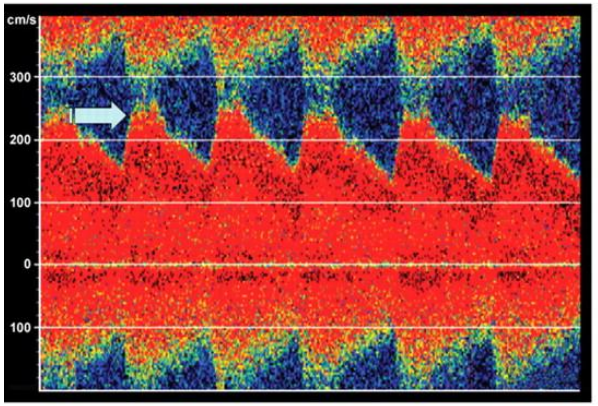
Predicting and Preventing Stroke

Screen with Transcranial Doppler Ultrasound

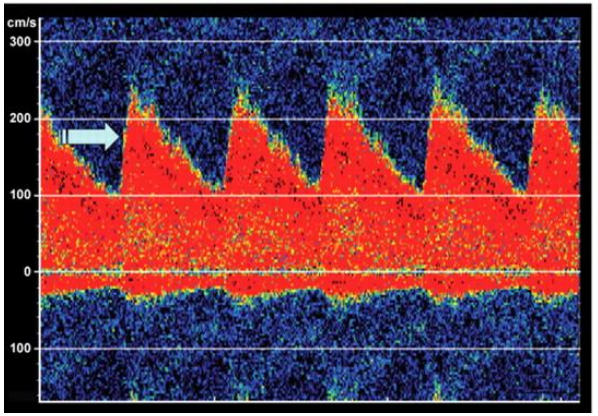


Treat high risk children with transfusion

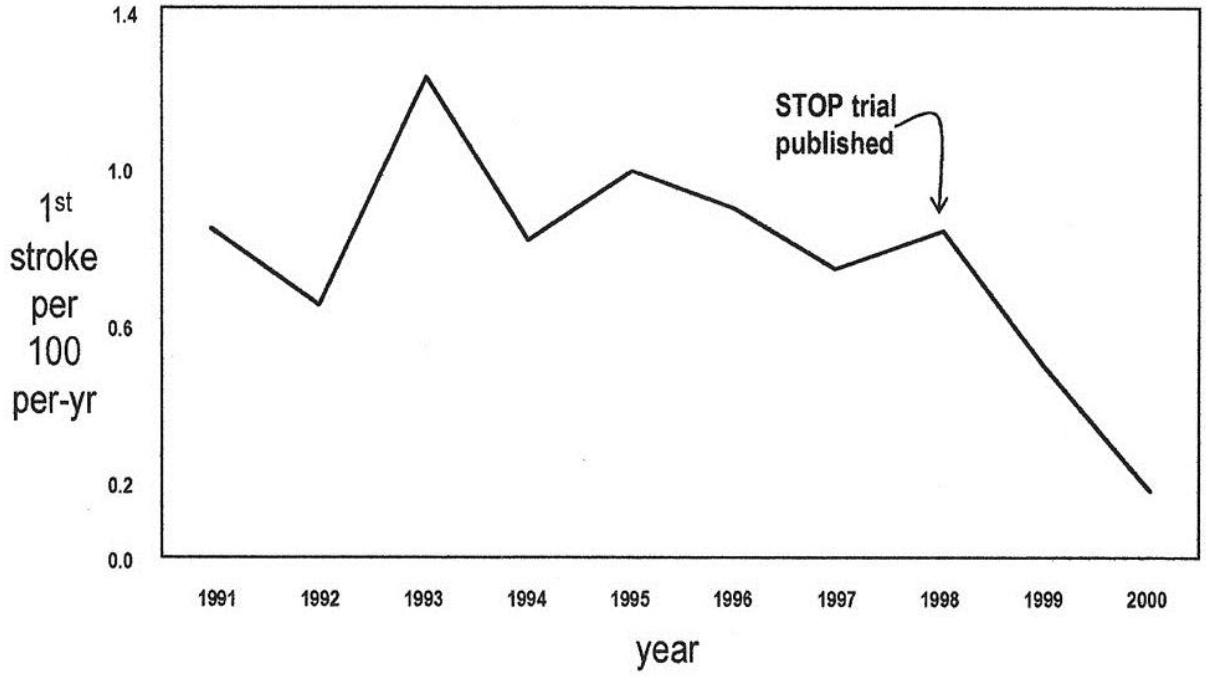
Before transfusion



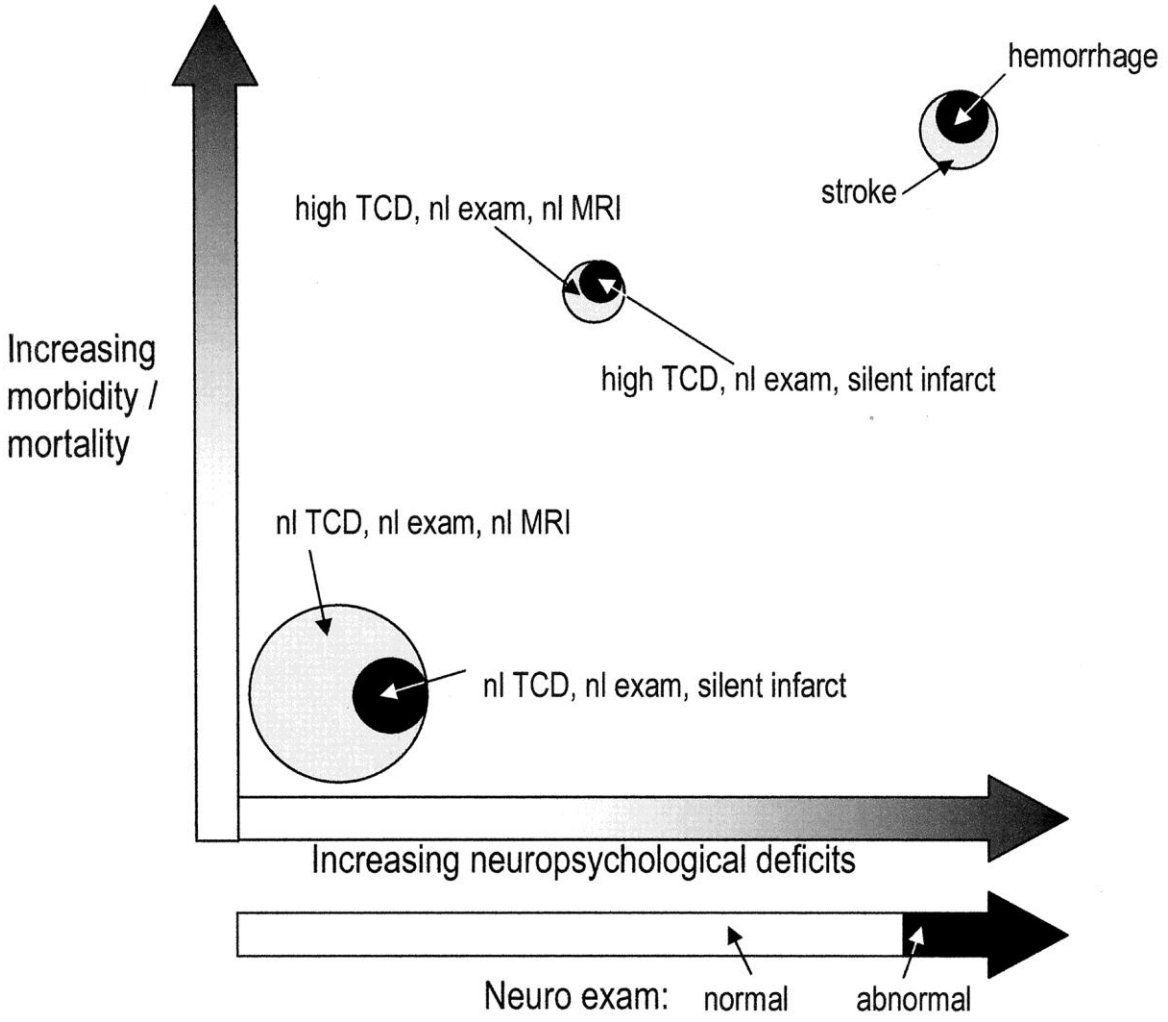
After transfusion



Impact on Stroke Incidence



Spectrum of CNS Disease




SWiTCH
Stroke With Transfusions Changing to Hydroxyurea


SIT TRIAL
Silent Infarct Transfusion Trial

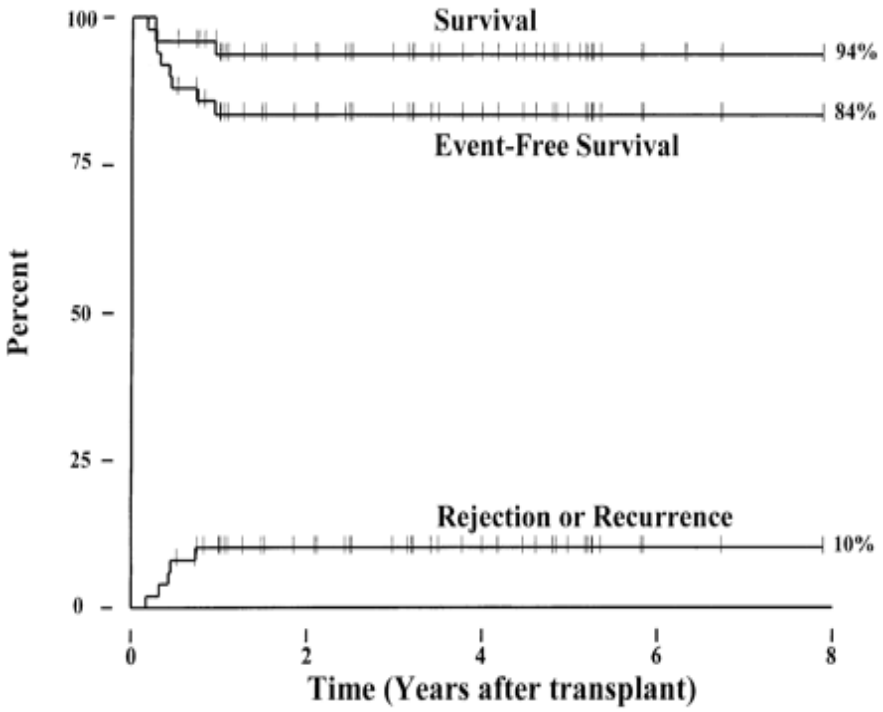

TWiTCH
TCD With Transfusions Changing to Hydroxyurea


SCATE
Sparing Conversion to Abnormal TCD Elevation

The Next 100 Years

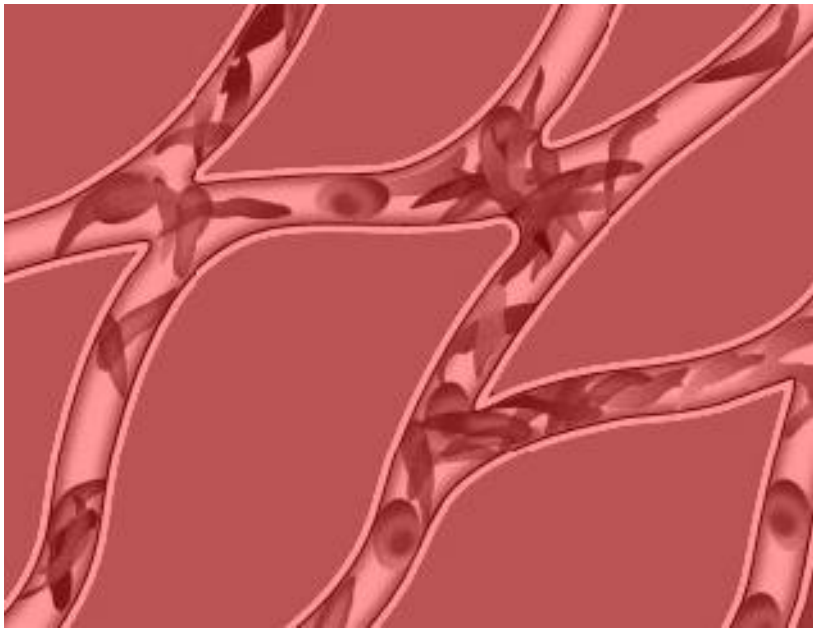
Stem Cell Transplantation

- Issues
  - Eligibility
  - Type of conditioning
  - Source of cells
  - Long-term follow-up



Targeted Therapies

- Open up the vessels
  - Nitric oxide
  - Anticoagulation
- Prevent damage to the blood vessels
- Decrease inflammation

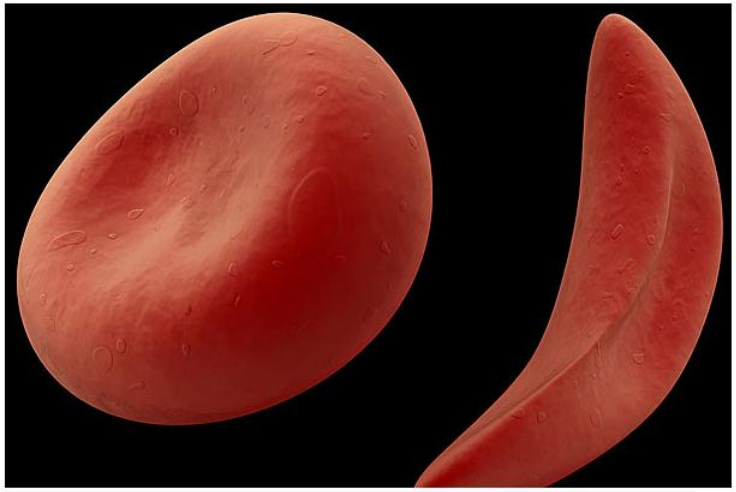


Clinicaltrials.gov

Gene Therapy

Dialing down sickle cell disease

Study in mice says dialing up fetal hemoglobin may bring new therapies



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REPORT

Correction of Sickle Cell Disease in Adult Mice by Interference with Fetal Hemoglobin Silencing

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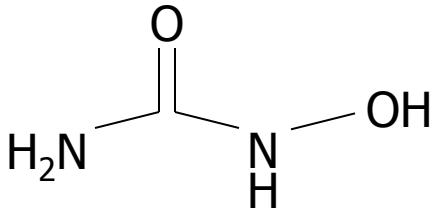
ABSTRACT

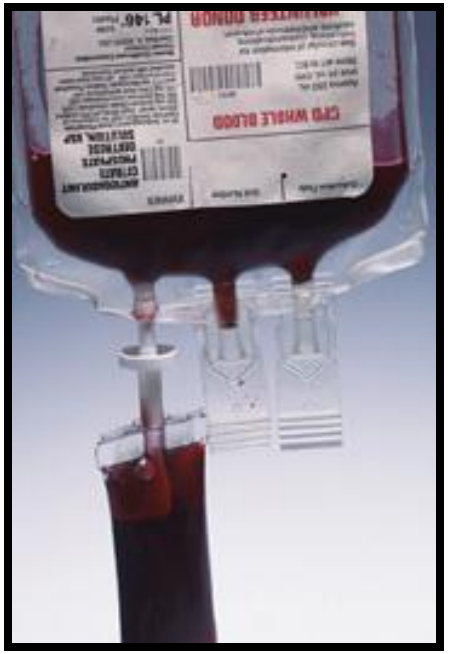
Persistence of human fetal hemoglobin (HbF, $\alpha_2\gamma_2$) in adults lessens the severity of sickle cell disease (SCD) and the β-thalassemias. Here, we show that the repressor BCL11A is required in vivo for silencing of γ-globin expression in adult animals, yet dispensable for red cell production. BCL11A serves as a barrier to HbF reactivation by known HbF inducing agents. In a proof-of-principle test of BCL11A as a potential therapeutic target, we demonstrate that inactivation of BCL11A in SCD transgenic mice corrects the hematologic and pathologic defects associated with SCD through high-level pancellular HbF induction. Thus, interference with HbF silencing by manipulation of a single target protein is sufficient to reverse SCD.

Summary

- Early identification
  - Universal newborn screening
  - Family education
- Focus on prevention and early trt
  - Prophylactic penicillin
  - Immunization
  - Management of fever and pain
  - Transcranial Doppler Ultrasound
- Therapeutic interventions
  - Transfusion
  - Hydroxyurea
  - Stem cell transplantation
  - ????



hydroxyurea



Duke Children's