Transfusion in Sickle Cell Disease:

Why I love Blood Bankers

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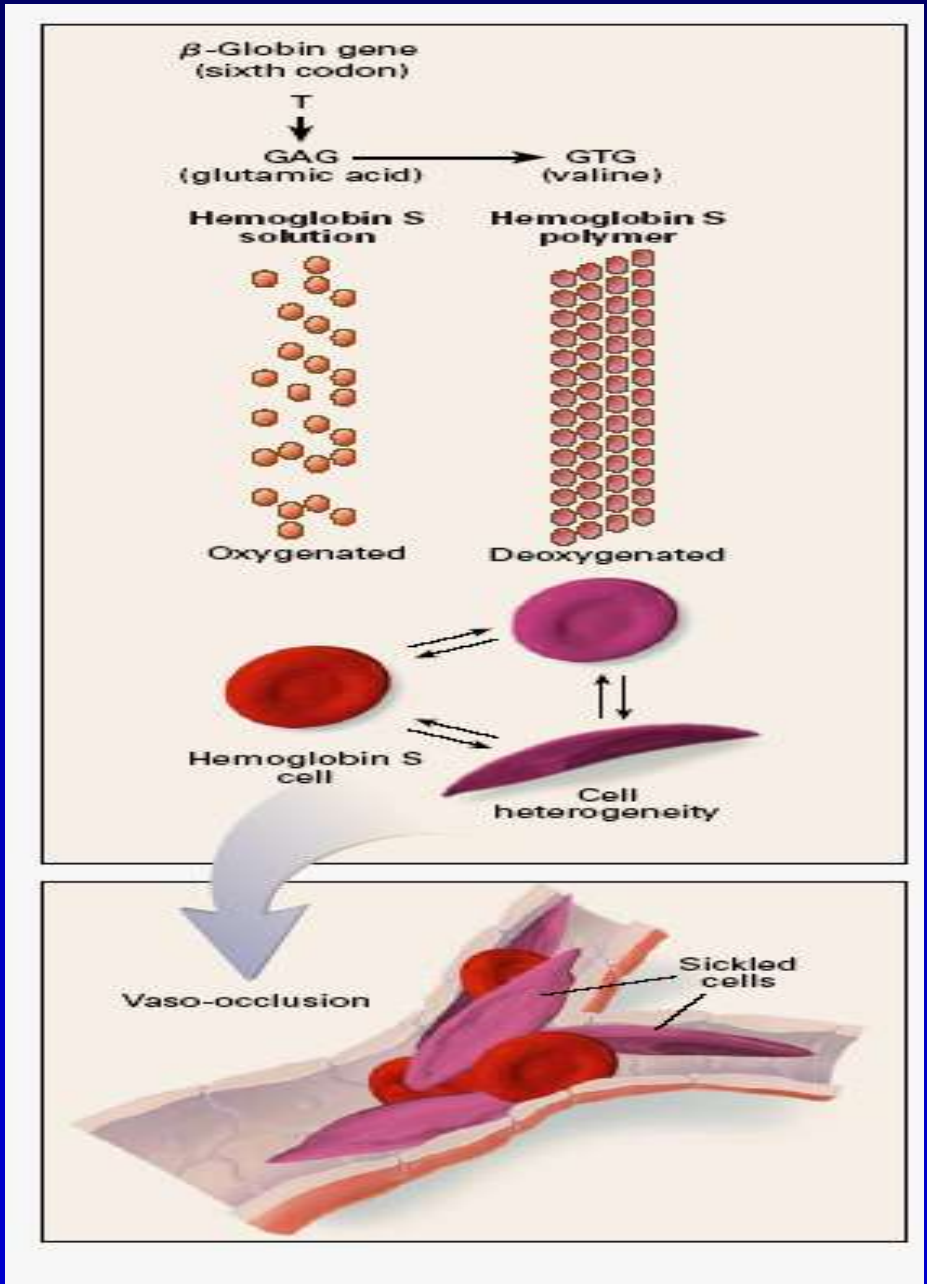
Disclosures

Dr. James Eckman,
Personal/Professional Financial Relationships with Industry

External Industry Relationships *	Company Name(s)	Role
Equity, stock, or options in biomedical industry companies or publishers**	None	
Board of Directors or officer	None	
Royalties from Emory or from external entity	None	
Industry funds to Emory for my research	None	
Other	None	

THE PROBLEM



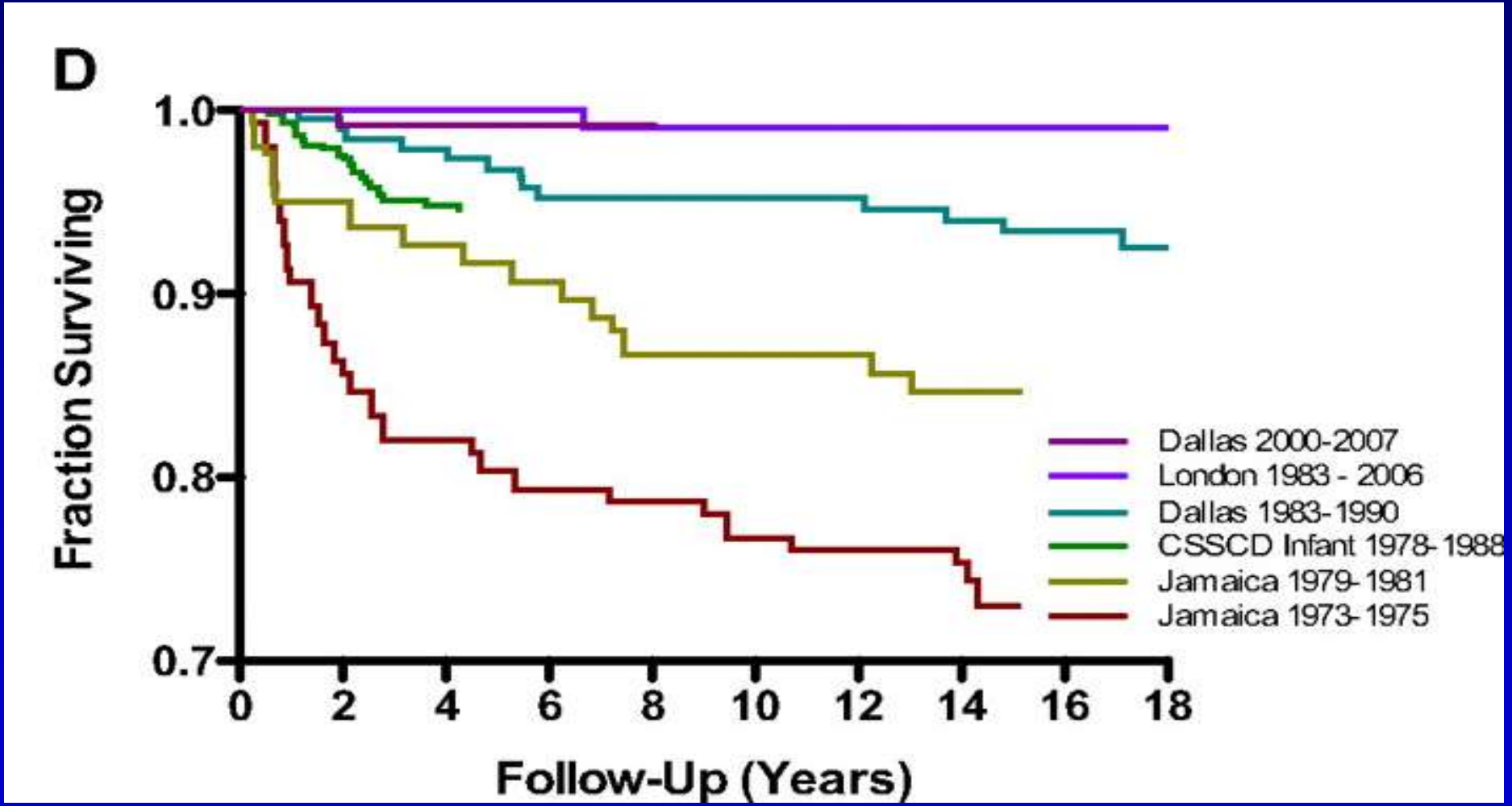
Steinberg MH
Management of Sickle Cell Disease
New J Med 1999;340:1021

CLINICAL CONSEQUENCES

- Hemolytic anemia
- Increased severity of infection
- Tissue infarction with organ failure
- Episodes of pain

SICKLE SURVIVAL

Quinn et al Blood 2010;103:4023

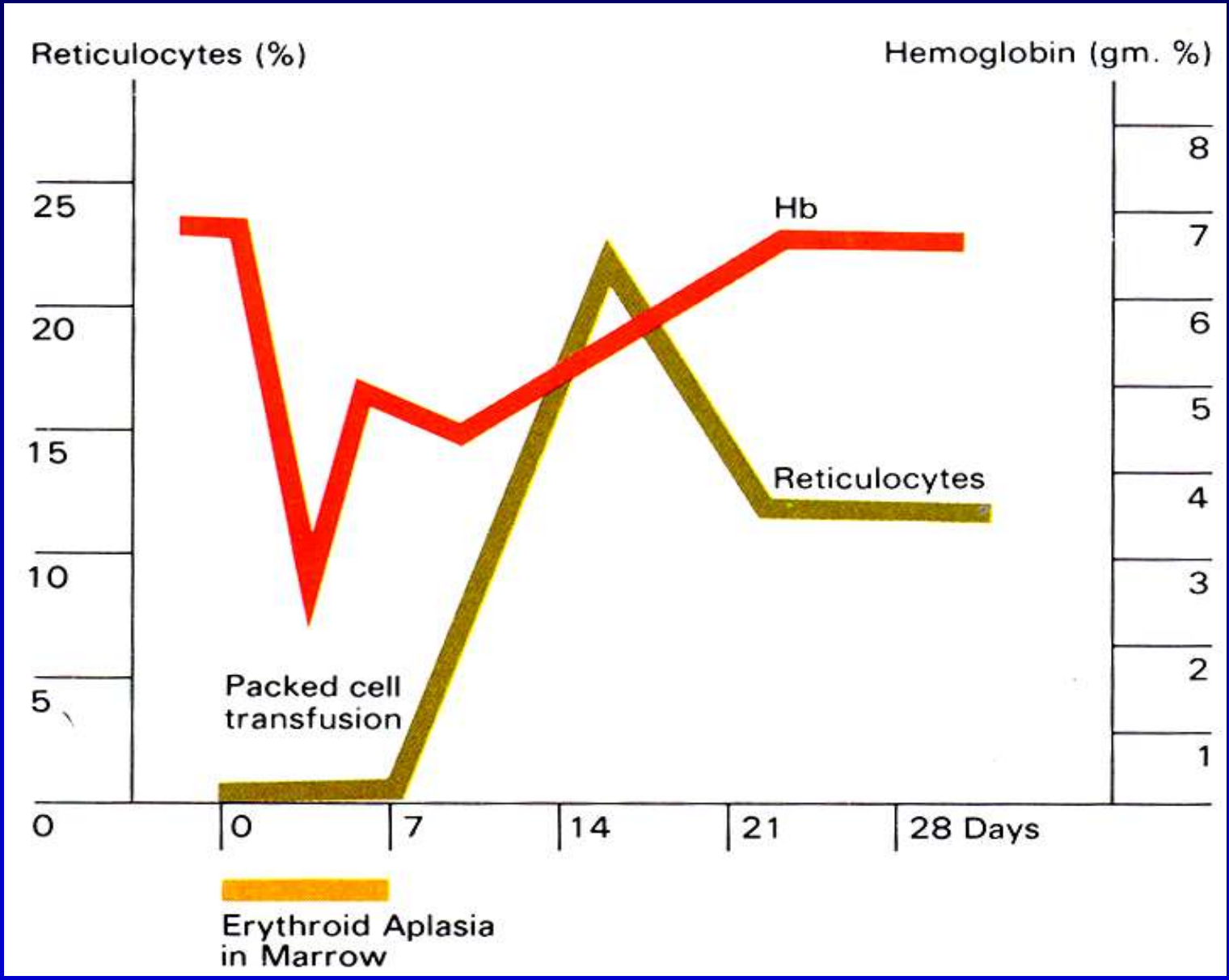


Reasons For Transfusion

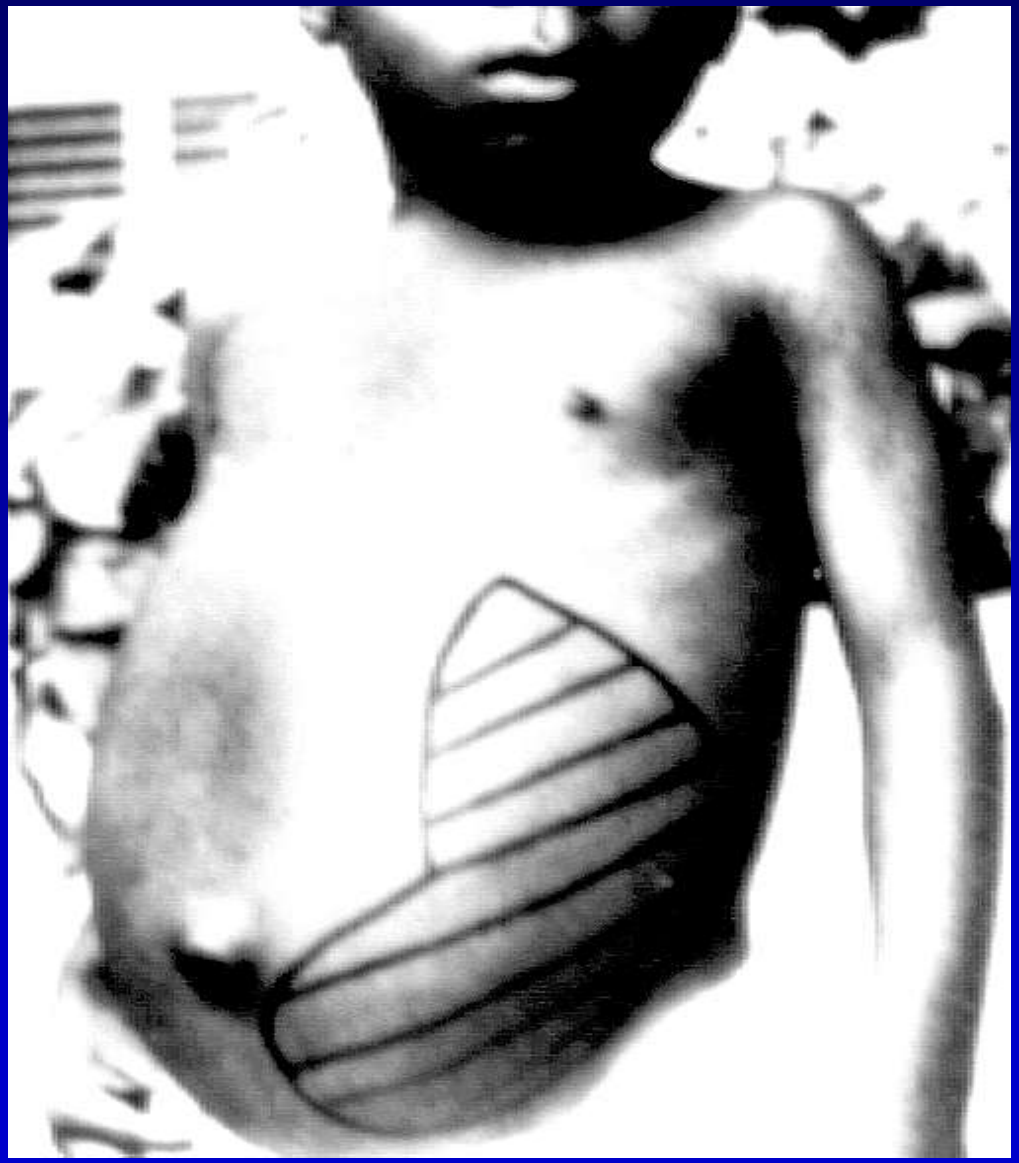
Sickle Cell Anemia

- **Physiologic correction of symptomatic anemia**
- **Reduce the whole blood viscosity**
- **Suppress production of sickle cells**
- **Reduce hemolysis**
- **Prevention of complications**

ANEMIA in SICKLE CELL



SPLENIC SEQUESTRATION



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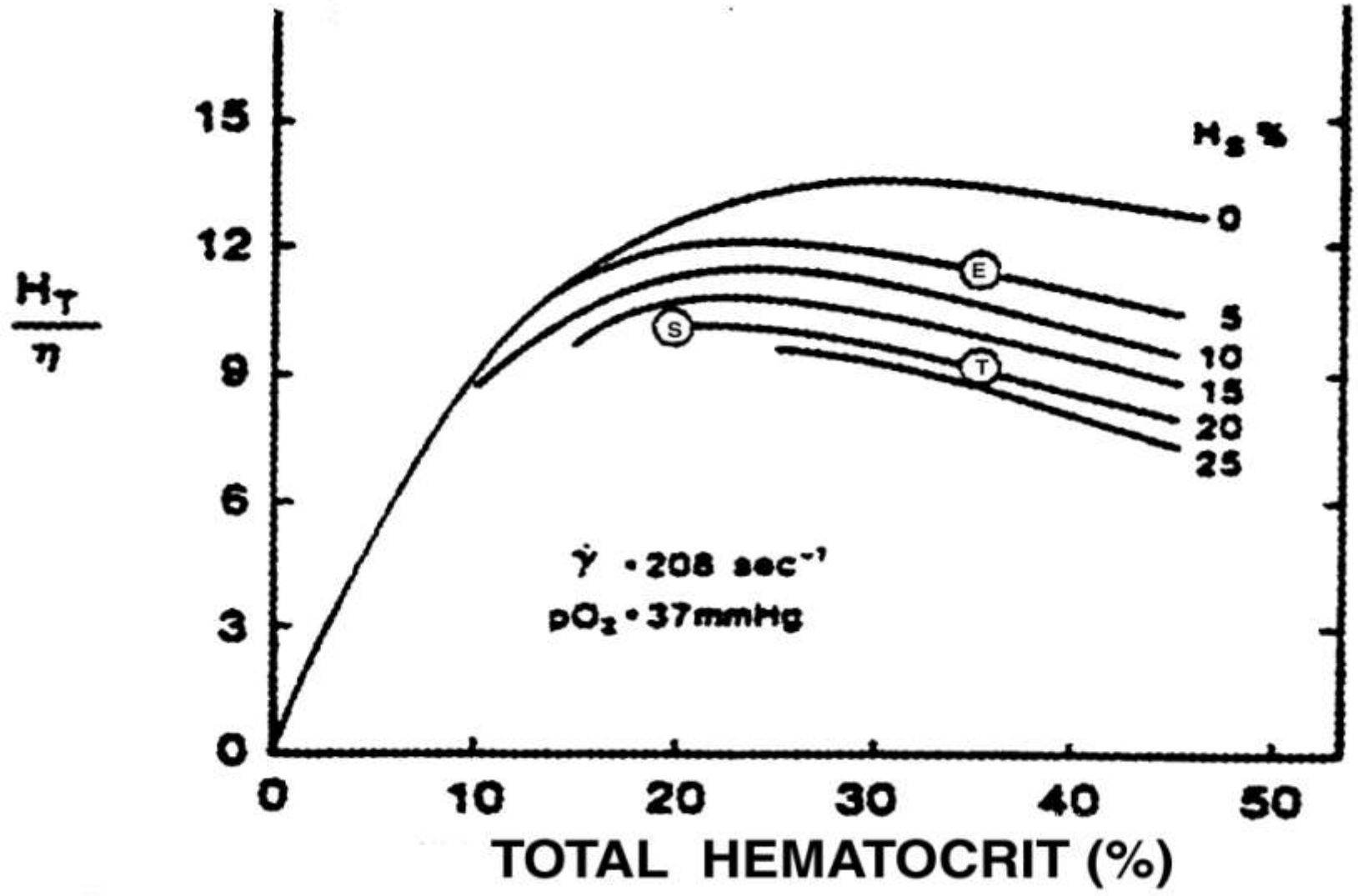
VISCOSITY of SICKLE BLOOD



Schmalzer et al. Transfusion 27:228, 1987.

Reasons For Transfusion

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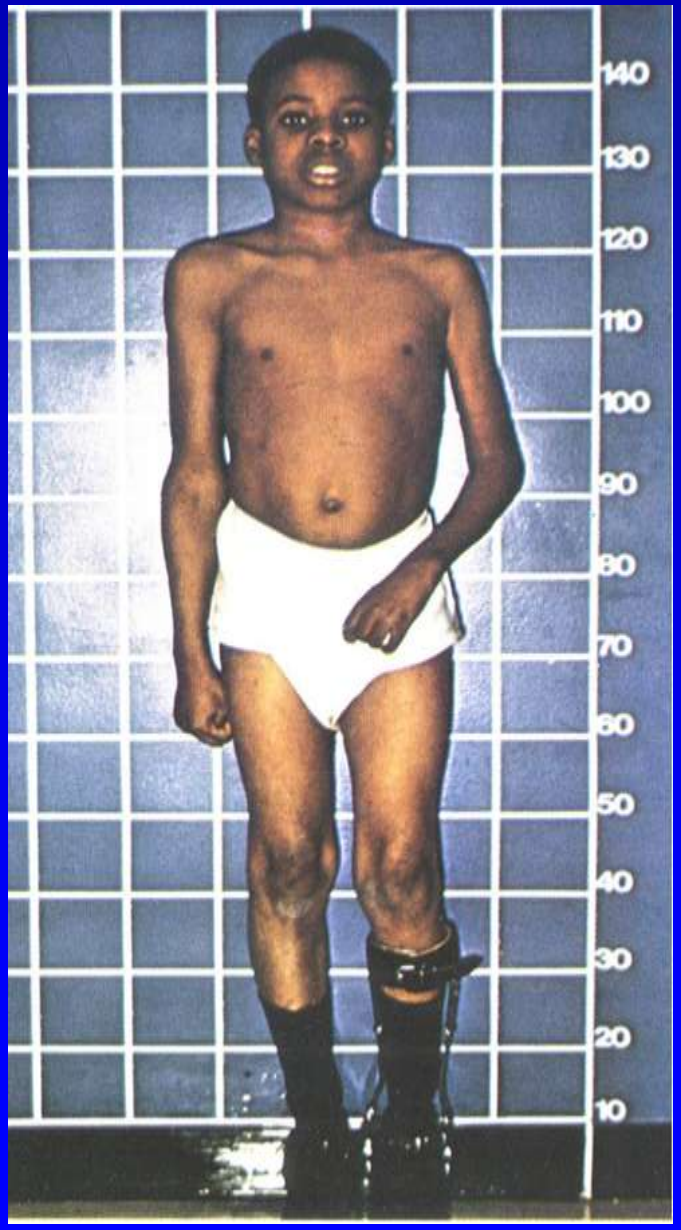
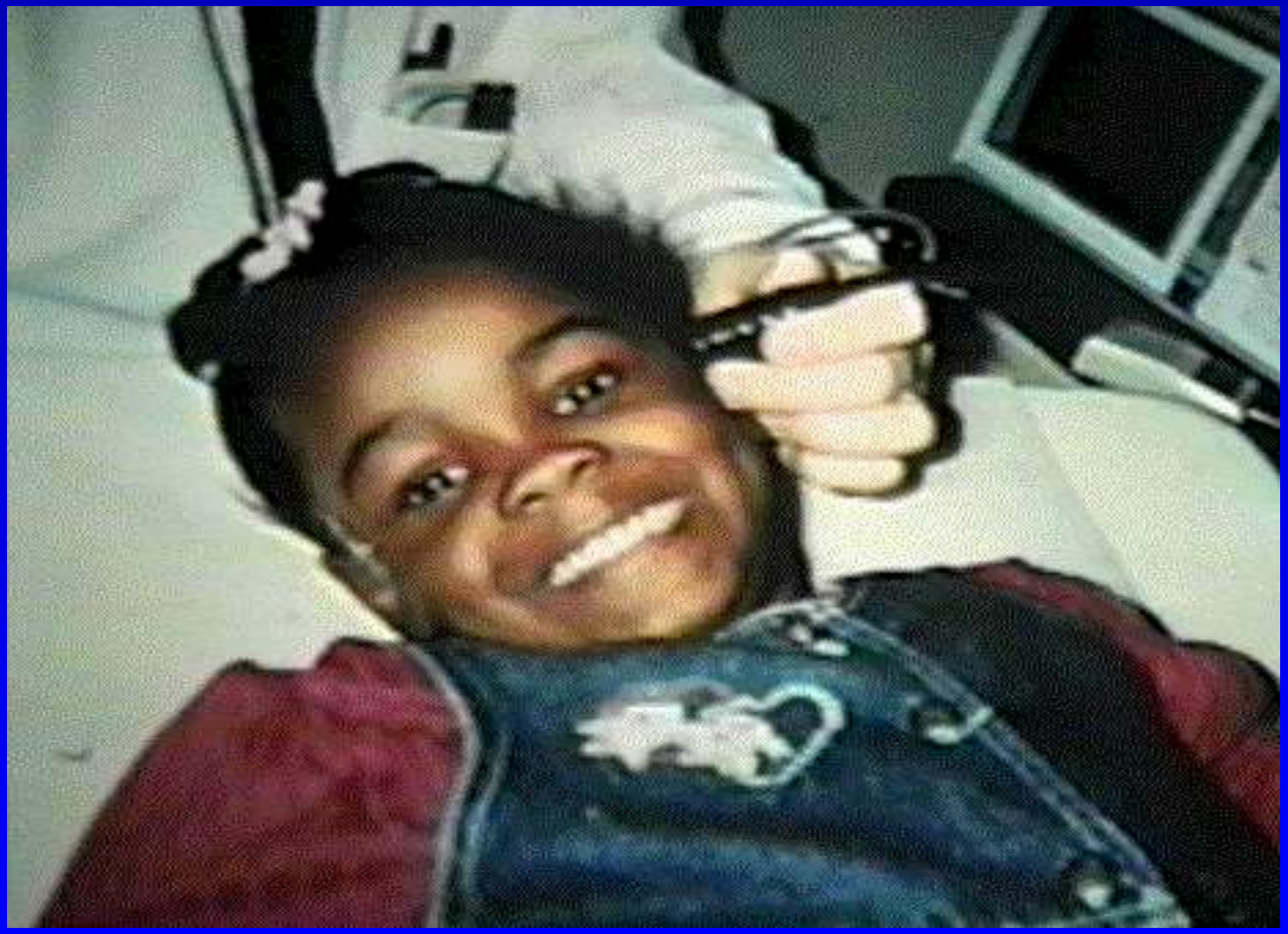
STROKE RECURRENCE REDUCED



STOP: STROKE PREVENTION



STROKE PREVENTION

Adams et al. New Engl J Med 339:5, 1998

- In 67 patients not transfused, 11 strokes
- In 63 patients transfused, 1 stroke
  - At least 10 patients benefited from transfusion
  - “A 92% difference in the risk of stroke”
  - Up to 53 transfused but no benefit

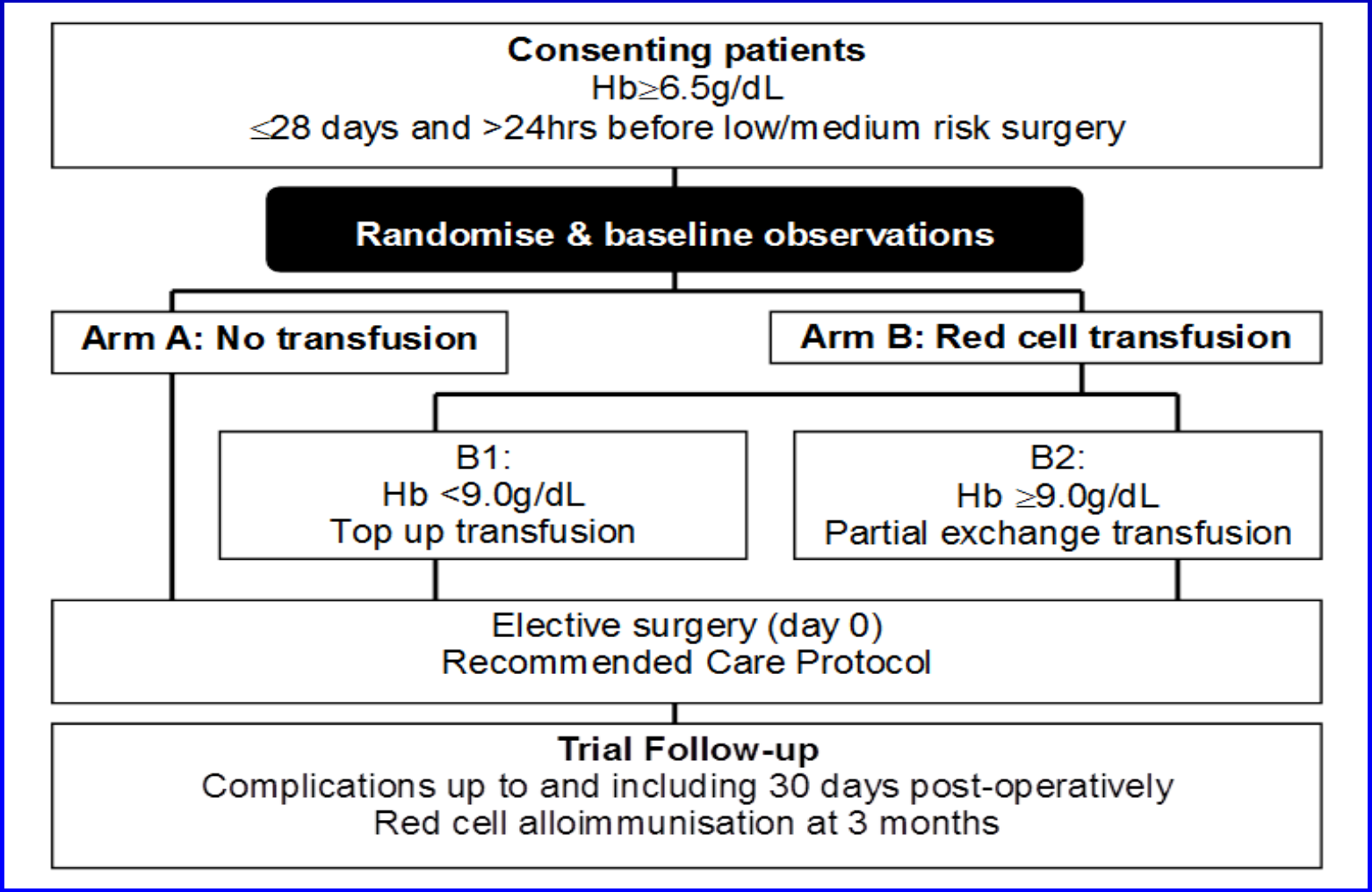
What is the role of pre-operative blood transfusion in patients with SCD?

J Howard et al. TAPS Study Group 2011 ASH Abstract #9

- Surgery in SCD is associated with high rate of complications, especially acute chest syndrome (ACS)
- Only 2 randomised controlled trials
  - Vichinsky et al. (N = 118): simple & exchange equivalent
  - Al-Jaouni et al. (N = 369): no advantage to pre-op transfusion
- UK & US surveys: mixed practice
- Transfusion-related complications
  - Known: alloimmunization, iron overload, infection
  - Possible: immunosuppression, vCJD
- Equipoise on role of pre-operative transfusion

What is the role of pre-operative blood transfusion in patients with SCD?

J Howard et al. TAPS Study Group 2011 ASH Abstract #9



J Howard et al. TAPS Study Group 2011 ASH Abstract #9

Primary Outcome and Serious Adverse Events

Patients	Arm A No Pre-operative Blood Transfusion	Arm B Pre-operative Blood Transfusion	Comparison of Study Arms
Patients Recruited	N = 33	N = 34	Total N = 67
Patients with significant complications	13 (39.3%)	5 (14.7%)	18 (26.9%) **OR 3.8 (CI 1.2-12.2)** P = 0.027
Patients with SAEs	10 (30.3%)	1 (2.9%)	11 (16.4%) **27.4% difference** **(CI 10.6-44.0)** P = 0.003
Patients with ACS	9 (27.3%)	1 (2.9%)	10 (14.9%)

Adapted from Howard et al. Abst #9

J Howard et al. TAPS Study Group 2011 ASH Abstract #9

Primary Outcome and Serious Adverse Events

Endpoints	Arm A No Pre-operative Blood Transfusion	Arm B Pre-operative Blood Transfusion	Difference of Proportions
Primary Endpoint – Complications – Alloimmunization	13 13 0	5 5 1	**24.7%** (CI 4.2-45.2%)
Pre-op transfusions	1	31*	
Intra- or post-op transfusions	12	3	**27.5%** (CI 8.6-46.5%)
Total transfusions	13	34	
Total PRBC units	38	71	

* 26 top-up, 1 exchange

Adapted from Howard et al. Abst #9

Sickle Cell Disease

ACUTE SIMPLE TRANSFUSION

- Symptomatic anemia
- Severe anemia and hypoxia
- Sequestration crisis
- Aplastic crisis
- Preoperative preparation
- Acute blood loss

Modified from Wayne, Kevy, Nathan. Blood 81:1109, 1993.

Sickle Cell Disease

Indications For Immediate Exchange Transfusion

- Acute Stroke
- Selected acute chest syndrome
- Acute multi-organ failure
- Priapism in selected children
- Selected preoperative preparation

Modified from Wayne, Kevy, Nathan. Blood 81:1109, 1993.

Sickle Cell Disease

CHRONIC SIMPLE TRANSFUSION

- Cerebrovascular disease
- Chronic cardiac decompensation
- Chronic pulmonary insufficiency
- Renal failure
- Selected complicated pregnancy
- Debilitating frequent pain episodes

Modified from Wayne, Kevy, Nathan. Blood 81:1109, 1993.

COMPLICATIONS OF TRANSFUSION

- Cardiovascular Complications
- Transmission of Infection
  - Hepatitis
  - Human Immunodeficiency Virus
  - Other Agents - CMV, EB
  - Bacterial Infections
- Iron Overload
- Alloimmunization
  - Delayed Transfusion Reactions
  - Autoimmune Hemolytic Anemia

IRON LOADING FROM TRANSFUSION

- There is 200 mg iron in 1 unit PRBC (from 420 mL of donor blood)
  - 0.47 mg iron/mL of whole blood
  - 1.16 mg iron/mL of "pure" red cells
- In thalassemia major (splenectomized), if mean Hb 12 g/dL
  - ~300 mL PRBC/kg/y (0.4 mg iron/kg/d from transfusion)
  - Add 1-4 mg/d from gut absorption
  - Total 0.4-0.5 mg/kg/d
  - But wider variability in transfusion 0.36-0.64 mg/kg/d

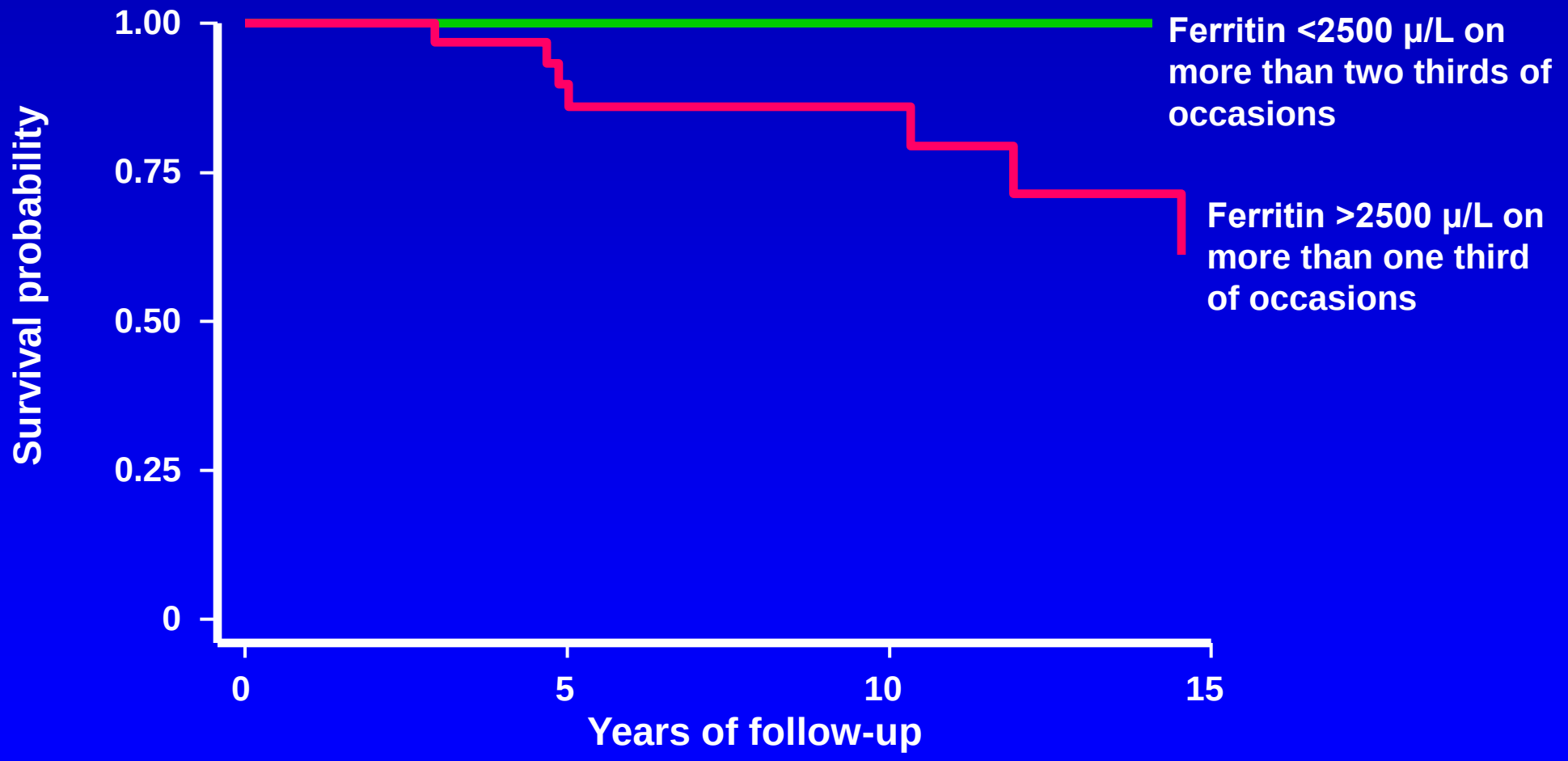
PRBC = packed red blood cells; Hb = hemoglobin.

Porter. *Br J Haematol*. 2001;115:239.

IRON OVERLOAD

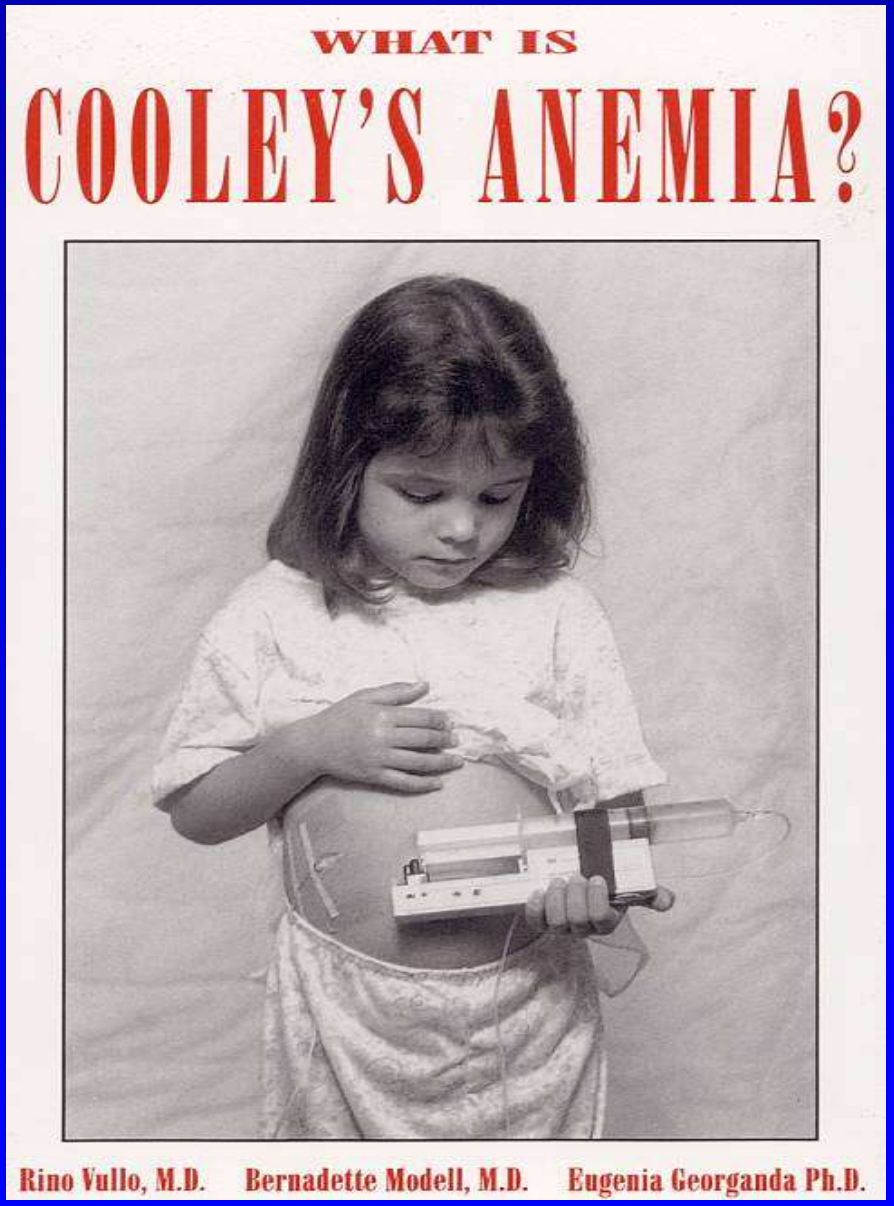
- Cardiac Disease
- Cirrhosis
- Endocrine Failure

MAINTENANCE OF LOWER FERRITIN LEVEL PREDICTS SURVIVAL AT UCLH



UCLH = University College London Hospital.

Porter. Unpublished data.


WHAT IS
COOLEY'S ANEMIA?
Rino Vullo, M.D.
Bernadette Modell, M.D.
Eugenia Georganda Ph.D.

IRON OVERLOAD

PREVENTION BY ERYTHROCYTOPHORESIS

Transfusion Protocol	Annual Net RBC Load ml RBC/kg/yr, Mean ± 1 SD	Packed RBC Usage ml RBC/kg/yr, Mean ± 1SD
Erythrocytophoresis (Target Hb S ,50%)	17.8 ± 12.9	214.6 ± 45.0
Conventional Simple (Target Hb S <30%)	133.0 ± 29.3	176.9 ± 39.3
Modified simple (Target Hb S ,50%)	99.4 ± 37.7	132.8 ± 49.5

Kim et al. Blood 83 : 1136, 1994.

IRON OVERLOAD

PREVENTION BY ERYTHROCYTOPHORESIS

Transfusion Protocol	**Annual Net Iron Load** mg iron/kg/yr, Mean ± 1 SD	**Annual Net Iron Load** mg iron/kg/yr, Range
Erythrocytophoresis (Target Hb S ,50%)	19.4 ± 14	6 to 50
Conventional Simple (Target Hb S <30%)	144.0 ± 32	116 to 210
Modified simple (Target Hb S ,50%)	107.0 ± 41	76 to 171

Kim et al. Blood 83 : 1136, 1994.

IRON OVERLOAD

PREVENTION BY ERYTHROCYTOPHORESIS

- **Advantages**
  - **Reduced iron toxicity**
  - **Reduced need for chelation therapy**
- **Disadvantages**
  - **Increased blood utilization**
  - **Donor exposure**
  - **Venous access**
  - **Costs $20,000 to $25,000 extra a year**

COMPLICATIONS OF TRANSFUSION

- Cardiovascular complications
- Transmission of infection
  - Hepatitis
  - Human immunodeficiency virus
  - Other agents - CMV, EB
  - Bacterial infections Iron overload
- Alloimmunization
  - Delayed transfusion reactions
  - Autoimmune hemolytic anemia

Alloimmunization is a Real Problem

TABLE 1. Comparison of pediatric and adult transfusion data

	Pediatric (n = 78)	Adult (n = 62)
Age range in years (mean age)	1-31 (11.1)	19-57 (31.5)
Total number of transfusions (units)	1860	1379
Number of transfusions (units/patient)	1-139	1-141
Mean number of units per patient	23.8	23.3
Alloimmunized patients (%)	23 (29%)	29 (47%)
Percentage of males to females with alloimmunization	28.5 vs. 31.4	38 vs. 54.5
Number of delayed hemolytic and/or serologic transfusion reactions (%)	7 (9%)	5 (8%)
Incidence of hyperhemolysis in transfused patients (%)	4 (5.1%)	1 (1.6%)
Number of patients with autoantibodies	6 (8%)	6 (9.7%)

Aygun et al. Transfusion 2002;42:37-31

SICKLE CELL DISEASE

ALLOANTIBODY RESPONSE

Transfusion Number	RBC Antibodies	WBC Antibodies
None	0 %	29 %
< 50 units	10 %	33 %
51 - 99 u	25 %	48 %
100 - 199 u	46 %	34 %
> 200 u	57 %	71 %

Reisner et al. Tissue Antigens 30:161, 1987

SICKLE CELL ALLOANTIBODY RESPONSE

EFFECTS OF SEX AND PARITY

Sex/Parity Status	Number	RBC Antibodies	WBC Antibodies
Males	22	13.6 %	27.3 %
Females			
Nullip	9	66.7 %	37.5 %
Parous	20	55.0 %	50.0 %

Reisner et al. Tissue Antigens 30:161, 1987

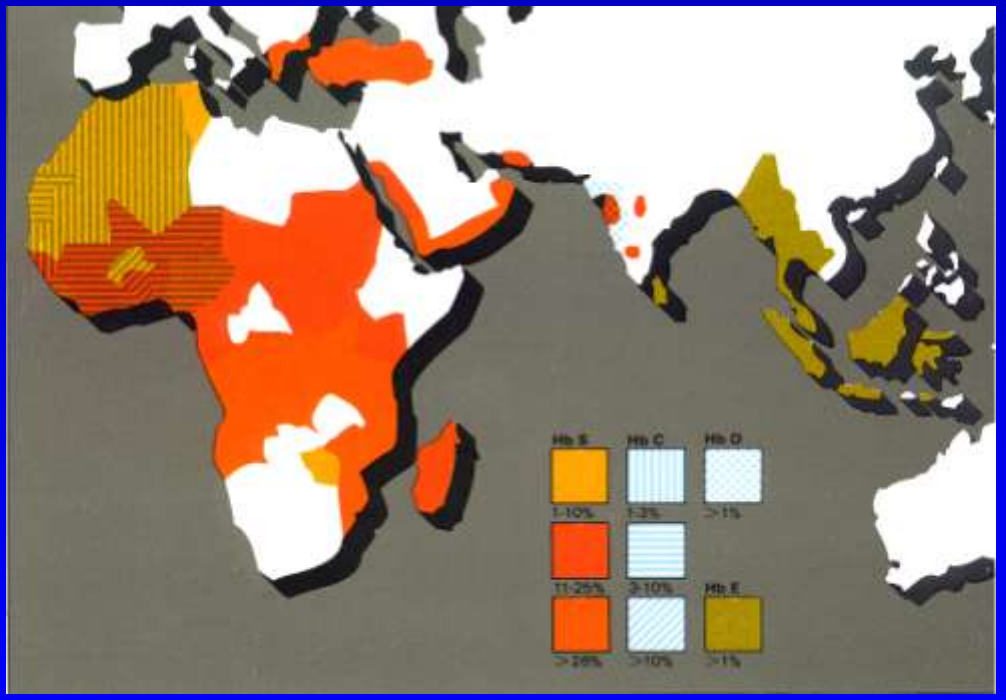
ALLOIMMUNIZATION

107 SICKLE CELL PATIENTS

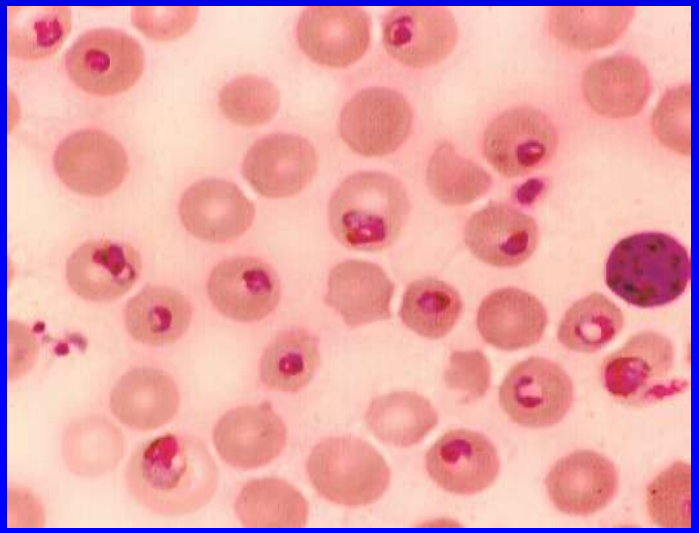
Antibody	Percent of Patients
Anti - K	16.8
Anti - E	14.9
Anti - C	10.3
Anti - Jk^b	6.5
Anti - Fy^a	3.7
Anti - M	2.8
Anti - Le^a	2.8
Anti - S	1.9
Anti - FY^b	1.9

Vichinsky et al. New Engl J Med 322:1617, 1990

GEOGRAPHIC DISEASES



GEOGRAPHIC DISEASES



ALLOIMMUNIZATION IN SICKLE CELL

Antigen	Patients, % N = 158	Donors, % N = 200	P Value
K	2	9	< 0.001
E	24	35	< 0.01
Jk^b	11	82	< 0.001
Fy^a	15	67	< 0.001
M	69	80	< 0.01
Le^a	21	22	NS
S	26	55	< 0.001
Fy^b	11	82	< 0.001

Vichinsky et al. New Engl J Med 322:1617, 1990

Extended Phenotypic Matching

LaSalle-Williams Transfusion 2012;51:1732-1739.

TABLE 4. Alloimmunization in patients treated with extended matching protocol*

Period, reference	Patient group	Matching	Percentage of patients immunized	Rate (antibodies/100 units transfused)
Before 1978 (control), Ambruso et al.[4]	Chronic transfusions n = 85	ABO, D	34%	3.4
1979-1983, Ambruso et al.[4]	Chronic transfusions n = 12	Extended matching All had previously received ABO, D	25%	0.3
1983-1990, Ambruso et al.[22]	Chronic transfusions n = 13	Extended matching only	8%	0.08
1993-2006, Present report	Chronic and intermittent n = 99	Extended matching	All—7%† Eliminate D mosaic—4%†	0.10† 0.06†

* Patients described in each period group were analyzed spearately and not included in the summary for any other group.

† Different from historical control, $p < 0.00005$.

Extended Phenotypic Matching

LaSalle-Williams Transfusion 2012;51:1732-1739.

	Matching ABO, D only	
Reference	Number of patients/transfusions	Percentage alloimmunized/number of alloantibodies per 100 units transfused
Ambruso et al.[4]	85/1,941	34%/3.4
Rosse et al.[6]	1,044/—*	18-31% (27% in study group)/—
Vichinsky et al.[7]	107/—	30%/—
Aygun et al.[9]	140/3,239† (pediatric and adult patients)	37%/2.8†
Castro et al.[10]	351/8,939†	29%-35%/3.8†
Sakhalkar et al.[11]	387/14,263†	31%/1.7†
	Matching extended beyond ABO, D, including C, E, K	
	Number of patients/transfusions	Percentage alloimmunized/rate, alloantibodies per 100 units transfused
Vichinsky et al.[13]	Extended matching for C, E, K 61/1,830	8-11%/0.5
Sakhalkar et al.[11]	Extended matching for C, E, K 113/2,345	5%/0.26

Red Cell Exchange Does Not Increase Immunization

Venkateswaran et al. Pediatr Blood Cancer 2011;57:294-296.

- Reported 93 patients
- Limited red cell antigen matching for ABO, D, C, E, and Kell
- Antibodies developed in 23 (24%)
  - 15 auto-antibodies
  - 18 allo-antibodies
- Red cell exchange for 15 patients using 2,289 units and none developed antibodies

TRANSFUSION IN SICKLE CELL

- Acquire and maintain adequate transfusion records
- Screen for antibodies 2 months after transfusion
- Erythrocyte phenotyping in all transfused
- Limit the use of transfusion
- Molecular phenotyping

TRANSFUSION IN SICKLE CELL

- Transfuse C, D, E, Kelly similar units
- Transfuse exclusively with phenotypically similar blood after the first alloantibody
- Some advocate phenotypically similar blood for all transfusions
- Recruit for blood donation from the African American population

*Eckman and Reid, Charache, Lubin NIH Pub No. 95-2117, 1995.

Thank You

http://www.scinfo.org