

Treatment of Sickle Cell Disease: Simple Transfusion and Red Blood Cell Exchange

Sally A. Campbell-Lee, MD
Director
Transfusion Medicine
University of Illinois at Chicago



Lecture Objectives

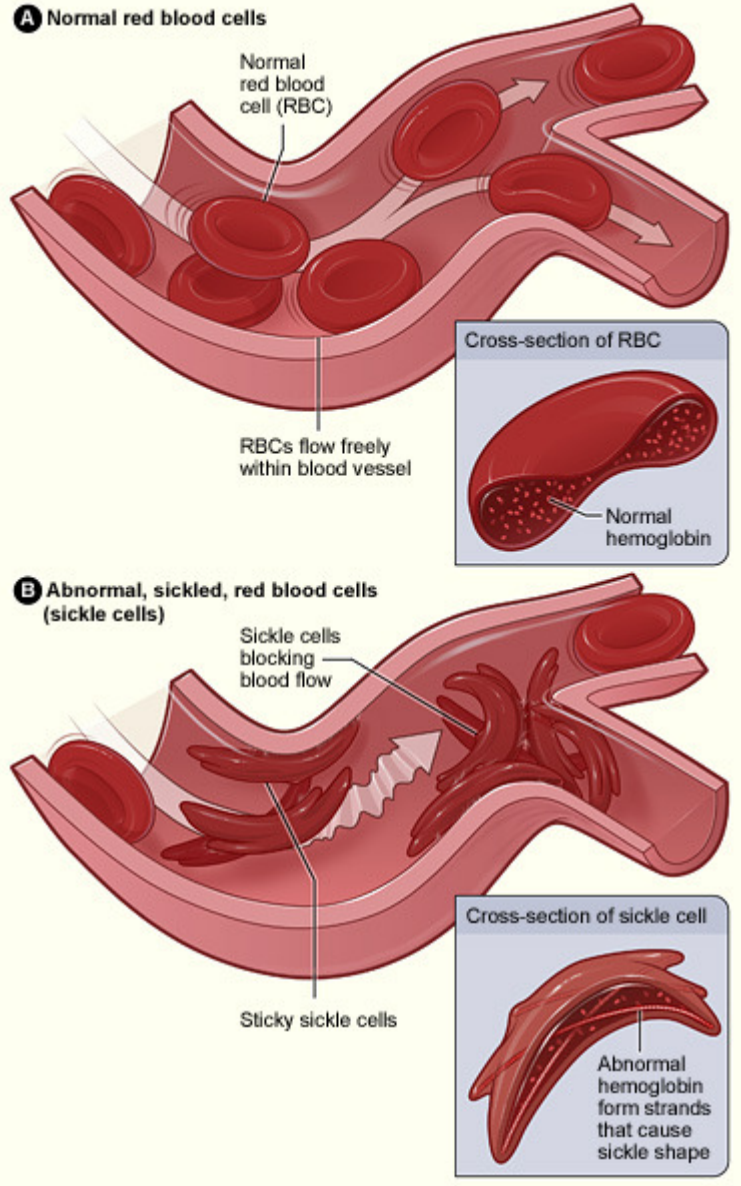
- To review current guidelines for transfusion of red blood cells in sickle cell disease
- To discuss when simple transfusion or red cell exchange may be used

Sickle Cell Disease

- Spectrum:
- Sickle Cell Anemia (Hb SS)
- Hb S Beta zero thalassemia
- Hb S Beta plus thalassemia
- Hb SC
- S HPFH, S-delta, etc
- Characterized by:
- Chronic hemolytic anemia
- Vaso-occlusion
- Painful crisis
- End organ damage
- Caused by:
- Single amino acid substitution Val→Glu at codon 6 in Beta Hb chain

1 in every 500 African-American births in US

Wahl S, Quirolo K, Curr Opin Pediatrics 2009, 21:15-21



Transfusion is Key Component of Therapy in Sickle Cell Disease

THE GOOD

- ✓ Improve oxygen carrying capacity
- ✓ Decrease blood viscosity
- ✓ Suppress production of sickle RBC by increasing tissue oxygenation

THE BAD

- ✓ Transfusion related iron overload

THE UGLY

- ✓ Bystander hemolysis
- ✓ Red cell alloimmunization/ autoantibodies
- ✓ Hyperviscosity

Indications for Transfusion in Sickle Cell Disease (SCD)

- Accepted: stroke, acute chest syndrome, aplastic anemia, acute splenic sequestration
- Controversial: pulmonary hypertension, leg ulcers, infection

Not Indications for Transfusion in Sickle Cell Disease

- Priapism
- Normal pregnancy
- Painful crisis



Simple

Exchange



Simple Transfusion

- Use when increased oxygen carrying capacity needed without need to reduce %HbS
- Volume is issue:
 - increased plasma volume due to chronic anemia + cardiac dysfunction=
volume overload
- Hyperviscosity

Hyperviscosity

%HbS > 60% = marked increased viscosity

%HbS < 40% = minimal increase in viscosity

Hypertension, convulsions, cerebral hemorrhage after rapid transfusion

Serjeant G, The Lancet May 10, 2003



- Patient from Jamaica with HbSS
- From 18 months (1955) to 1997: two painful crises, one ACS, intermittent chronic leg ulceration
- 25 yo: pharmacist, worked full time
- Normal Hb : (5.0-7.0 g/dL), never transfused.
- Last clinic visit in Jamaica: Hb 3.9 g/dL
- Moved to US in 1997
- 1999: Hb 3.8 g/dL
- Admitted and transfused:
- 2 units RBC: 4.9 g/dL
- 4 units RBC (total 6 units in 24 hours)
- Systolic and diastolic increased 30 mmHg, headaches
- Cerebral hemorrhage in 72 hours, died

Iron Overload

- 90% SCD patients have received transfusion by adulthood
- Each unit RBC contains 250 mg iron
- End organ damage: liver, cardiac
- Treatment: chelation
 - Deferoxamine: 8-12 hour, 5-7d/week iv administration
 - Deferasirox: once daily, oral; impact on renal function
- Prevention
 - RBC exchange: decreases iron burden

Walter P, Harmatz P, Vichinsky E. Acta haematol 2009;122:174-183

Red Blood Cell Exchange

- Exchange
- Acutely reduce proportion of HbS RBC
 - Remove sickle RBC and replace with normal RBC
 - Decrease %HbS to <30% without increasing volume
 - More exposure= more alloimmunization (autoantibodies)

Red Blood Cell Exchange

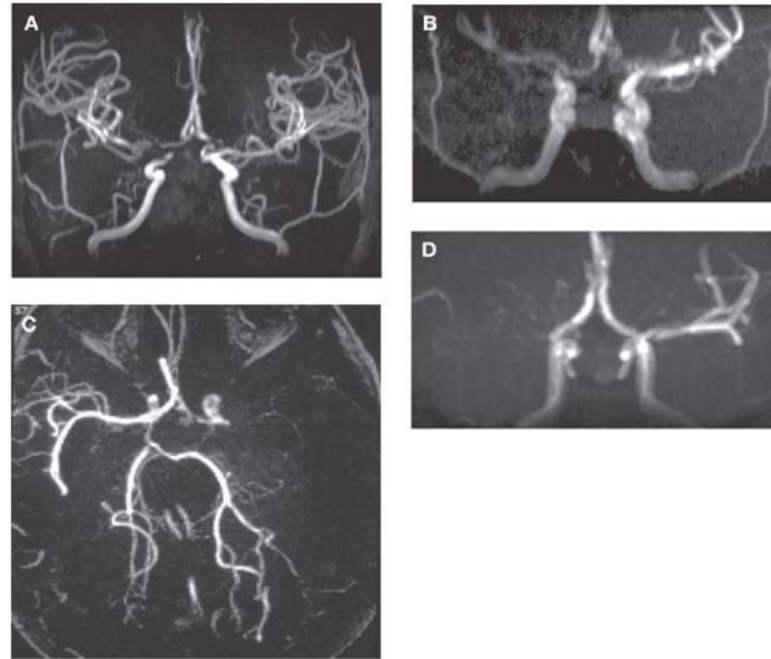
Acute

- Acute stroke
- Acute sequestration
- Acute chest syndrome
- Multiple organ failure
- Pre-operative

Chronic

- Prevention recurrent stroke
- Prevention first stroke
- Chronic renal failure

Figure 5 Magnetic resonance angiography (MRA)



Kirkham FJ (2007) Therapy Insight: stroke risk and its management in patients with sickle cell disease
Nat Clin Pract Neurol **3**: 264–278 doi:10.1038/ncpneuro0495

Acute Stroke

- ASFA category I
- Medical Emergency: start within 6 hours admission
- Goal: suppress HbS production
- Children: ischemic
- Adults: hemorrhagic
- Frequency: 6%

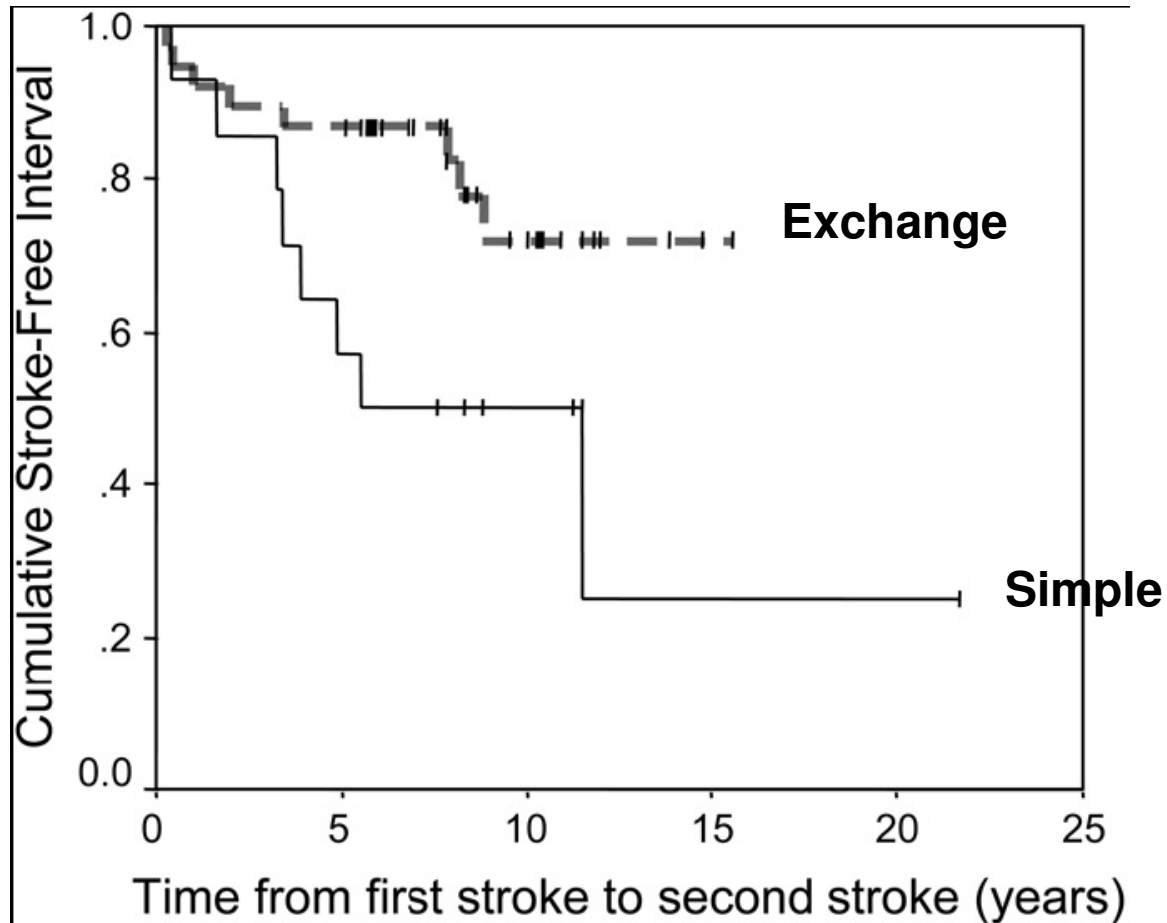
EXCHANGE BLOOD TRANSFUSION COMPARED WITH SIMPLE TRANSFUSION FOR FIRST OVERT STROKE IS ASSOCIATED WITH A LOWER RISK OF SUBSEQUENT STROKE: A RETROSPECTIVE COHORT STUDY OF 137 CHILDREN WITH SICKLE CELL ANEMIA

MONICA L. HULBERT, MD, et al (*J Pediatr* 2006;149:710-2)

A retrospective cohort study of children with sickle cell anemia (SCA) and strokes was used to test the hypothesis that exchange transfusion at the time of stroke presentation more effectively prevents second strokes than does simple transfusion.

Children receiving simple transfusion had a 5-fold greater relative risk (95% confidence interval 1.3 to 18.6) of second stroke than those receiving exchange transfusion.

J Pediatr 2006;149:710-2



Initial simple transfusion for first overt stroke in children with SCA who presented within 24 hours of symptom onset is associated with increased risk of recurrent stroke compared with exchange transfusion. Initial exchange transfusion, n 38; initial simple transfusion, n 14; **p=.02**

Prevention of Stroke Recurrence

- Without prevention, stroke recurrence rate = 46 to 90%
- Chronic transfusion: recurrence <15%
- Goal: HbS < 30%

Pegelow et al J Pediatr 1995;126:896-9

Russell M et al Blood 1984;63:162-9

Once You Start, You Can't Stop

- Stopping prophylactic transfusion led to recurrent stroke (Woods et al, The Journal of Pediatrics 2002;140:348-354)
- Modified: let HbS% drift to 50% once stable
- 35 children with stroke, switched from transfusion to HU/phlebotomy
 - 10/35 (29%) had recurrent stroke after switching
 - Lower ferritin (591 ng/mL vs 3410 ng/mL, p=0.02)
 - Am J Hematol 2011, 86:357-361

Acute Chest Syndrome

- New infiltrate on CXR with respiratory symptoms (SOB, tachypnea, cough, hypoxemia), chest pain, fever
- Etiology often not definitive
 - Infection
 - Fat embolism
 - Intrapulmonary sickling
- The leading acute cause of death
- RBC transfusion early on is recognized as important

ACS: Simple vs Exchange

- RBC exchange within 48 hours improves ACS rapidly
- Observational studies: patients continued to worsen in spite of simple transfusion

- Simple transfusion improves ACS if done within 24 hours
- Early ACS responds to simple transfusion

Less serious respiratory compromise: simple transfusion

Progressive decline in PaO₂ (<60 mmHg adults, <70 mmHg in children) or rapid deterioration: exchange transfusion

Josephson, et al. Transfusion Medicine Reviews 2007;21(2):118-133

ACS Treatment

- Antibiotics
- Oxygen
- Hydration
- Pain Control
- Red Cell Transfusion
 - Exchange: NIH Study Group—multiple lobe involvement, rapid progression, severe hypoxemia

Early Dx: Preemptive Transfusion?

- NACSS: extensive lobar involvement, platelets < 200, history of cardiac disease
- WBC (19 vs 13) and Hb (7.7 vs 9.3) Pediatr Blood Cancer 2005;45(5):716-724
- Elevated sPLA2—earlier transfusion = less ACS
- Pre-emptive transfusion in ACS needs further study

Chronic Transfusion

- Recurrent ACS---transfusion reduces episodes
- STOP trial—also showed reduction of ACS in children transfused for stroke prevention
- Multicenter Study of Hydroxyurea: in adults, reduced ACS by 50% and txn by 30%
- Many centers use HU instead of transfusion

ACS and RBC Exchange

- Transfusion: HbS negative RBC—exchange reduces amount of HbS
- Abnormal upregulation of adhesion molecules (VCAM-1)---may be decreased by transfusion
- Exchange transfusion: predominates
 - Adding small numbers of normal RBC to sickle RBC leads to large increase in viscosity which reduces oxygen delivery
 - May be better if fat emboli

Acute Multi-organ Failure

- Failure of at least two: lung, liver, kidney
- Starts as crisis then progresses to severe bone pain, fever, CP, dyspnea
 - Rapid drop in Hb, platelets
 - DIC, rhabdomyolysis, elevated liver enzymes, bili
 - Mental status changes: confusion → coma
 - Systemic fat embolization

Treatment of Acute Multi-organ Failure

- Aggressive supportive Rx: O₂, if fluids, pain control, dialysis
- Red Cell Exchange:
 - HbS% < 20
 - Hct: 28%

Rosse WF, Telen MJ, Ware RE. Transfusion support for patients with sickle cell disease. 1998, AABB Press

RBC Alloimmunization

- Large concern for chronic/exchange (more RBC exposure)
- Phenotype matching reduces alloimmunization
- Limited antigen matching (Rh, Kell) for patients on chronic RBC exchange
 - No increase in alloimmunization rate (24%)

Venkateswaran L et al, Pediatr Blood Cancer 2011

Vascular Access

- Peripheral veins
 - Two sites, one with large gauge needle
 - Children < 20 kg, older patients (repeated access)
- Central access
 - Infection
 - Clot

Long Term Access

Pediatr Blood Cancer 2005;44:669-672

Study	Patients	# with SCD	Rate of Infection	Rate of thrombotic events
Raj A, et al	Peds	15	0.00	0.16
Jeng et al	Adult and Peds	19	5.50	0.99
Abdul-Rauf et al	Peds	25	0.86	0.29
McReady et al	Adult	5	4.00	N/A
Phillips et al	Adult	10	0.46	0.46

Summary

- Red Cell Transfusion is an important part of therapy in sickle cell disease
- Common indications for transfusion are acute stroke, stroke prevention, acute chest syndrome
- Simple or exchange transfusion may be selected depending upon clinical circumstances
- Exchange transfusion can be used to decrease %HbS without increasing volume, such as in acute chest syndrome, acute stroke
- Additional studies are needed to evaluate simple versus exchange transfusion in sickle cell disease