Transfusion Support for Sickle Cell Disease

First Principles and Best Practices

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DISCLOSURES

- None

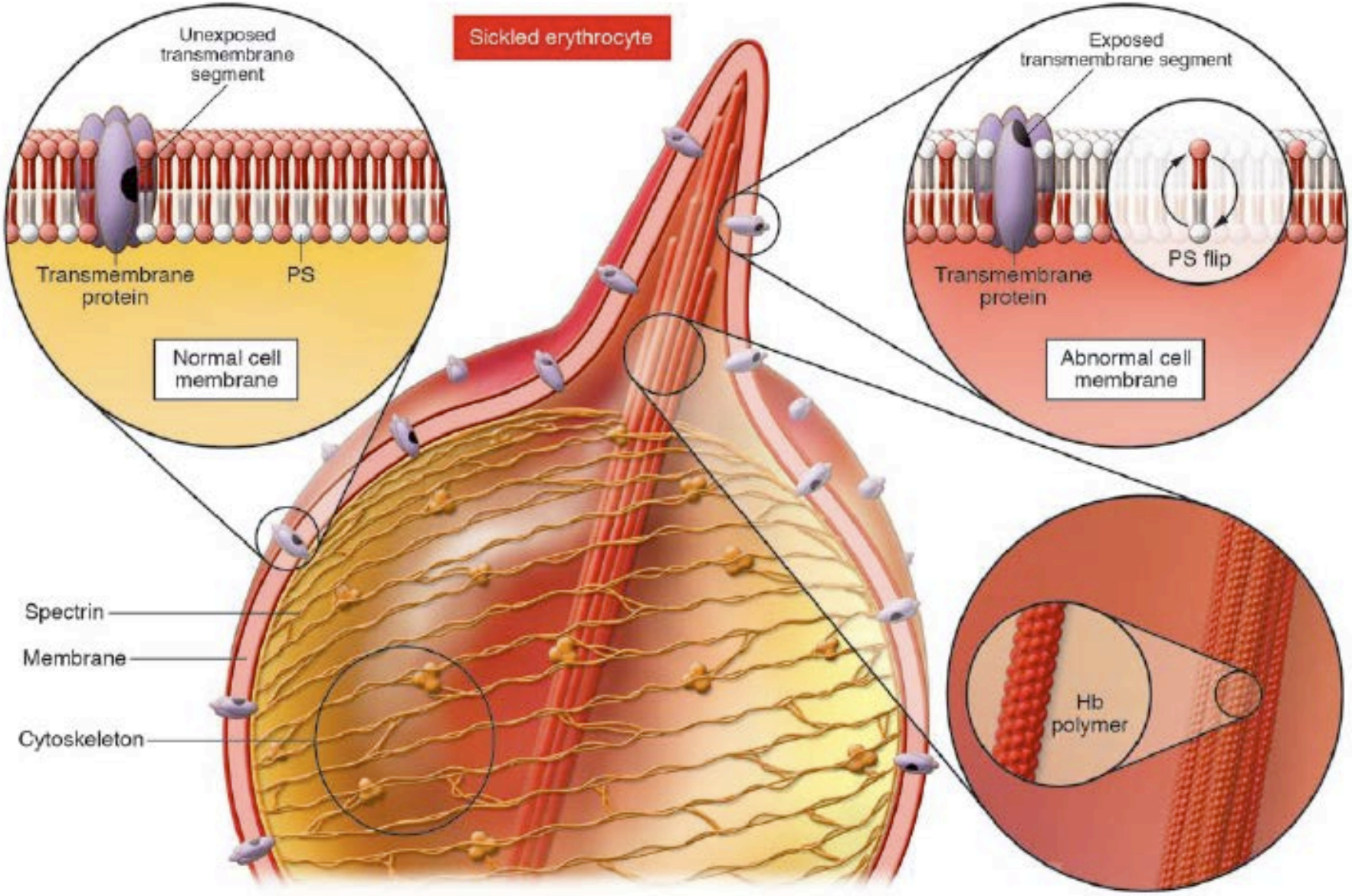
Objectives

1. Outline the principles of RBC transfusion in sickle cell disease

2. Define accepted indications for RBC transfusion in sickle cell disease

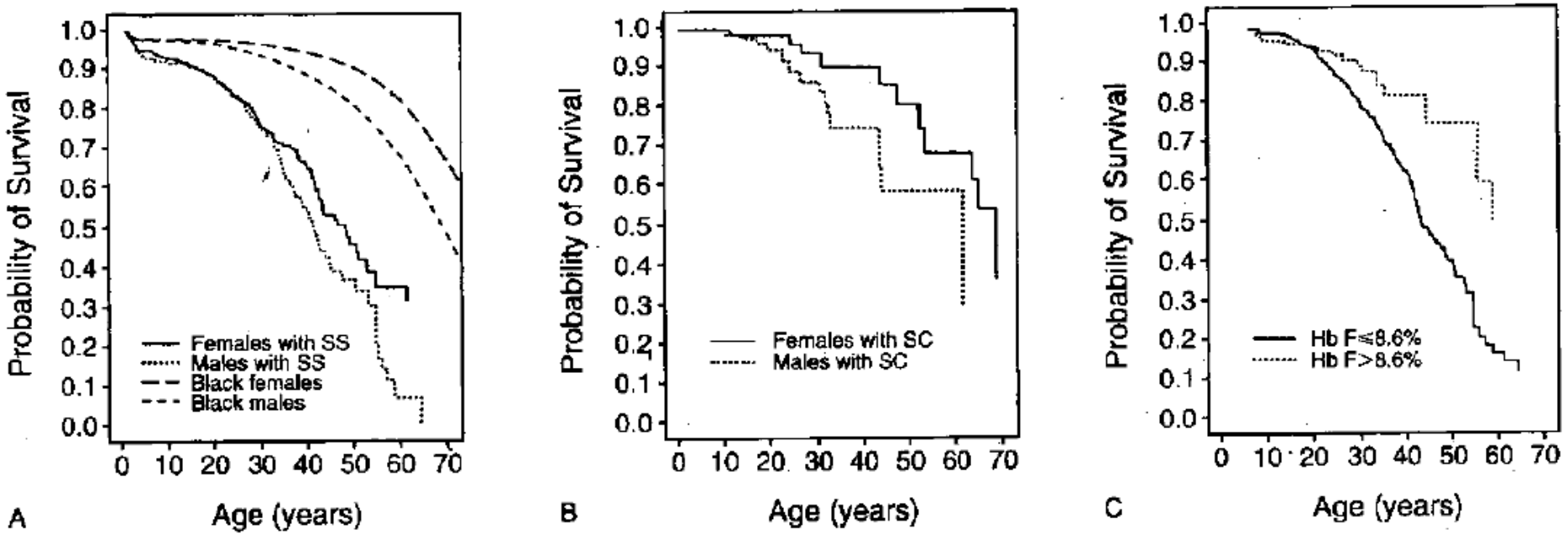
3. Recognize the syndrome of hyperhemolysis and the importance of careful RBC selection in preventing it

What is Sickle Cell Disease?



Frenette P, J Clin Invest 2007;117:850

Genotype	HgbS	Typical clinical severity
$ß^S/ß^A$	HgbS: 20-30%	Asymptomatic
$ß^S/ß^C$	HgbS: 50%	Mild-moderate
$ß^S/ß^+$	HgbS: 70-85%	Moderate
$ß^S/ß^o$, $ß^S/ß^S$	HgbS: 90-95%	Severe



Epidemiology of Sickle Cell Disease

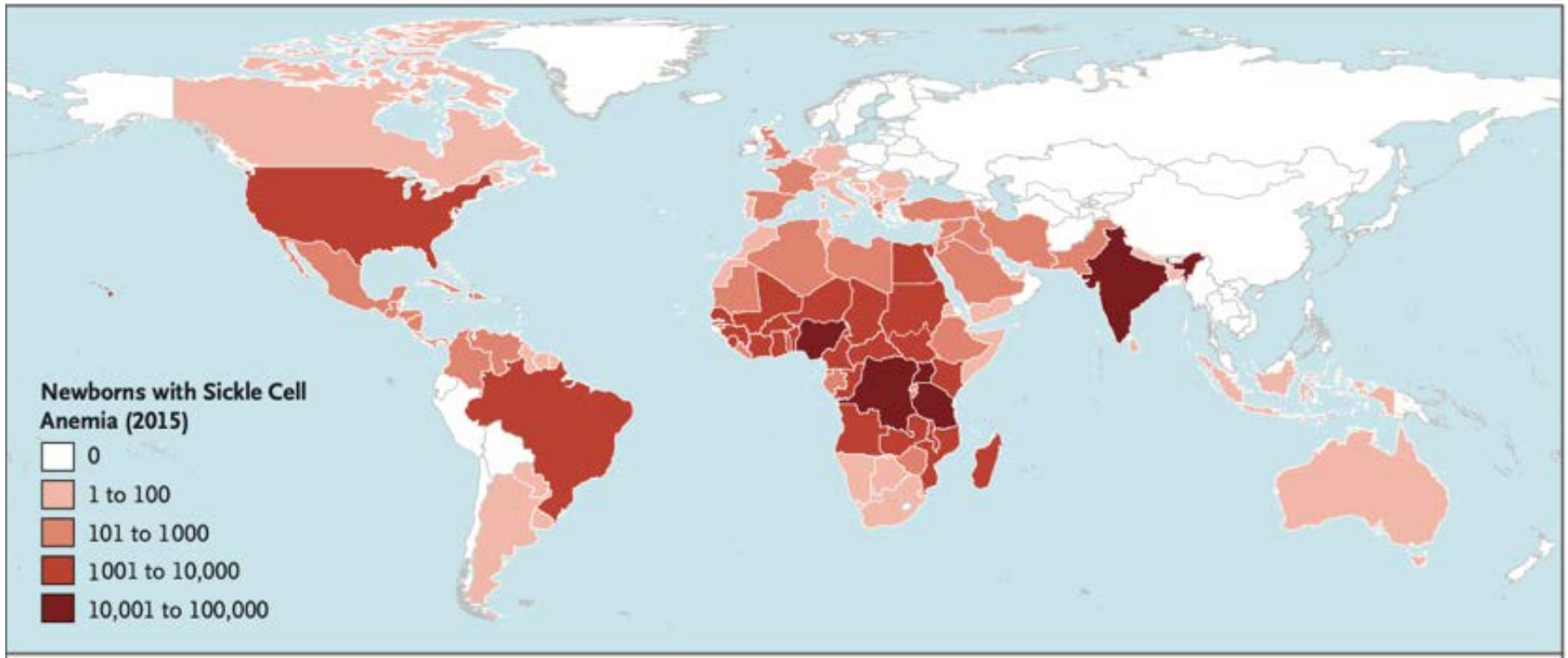
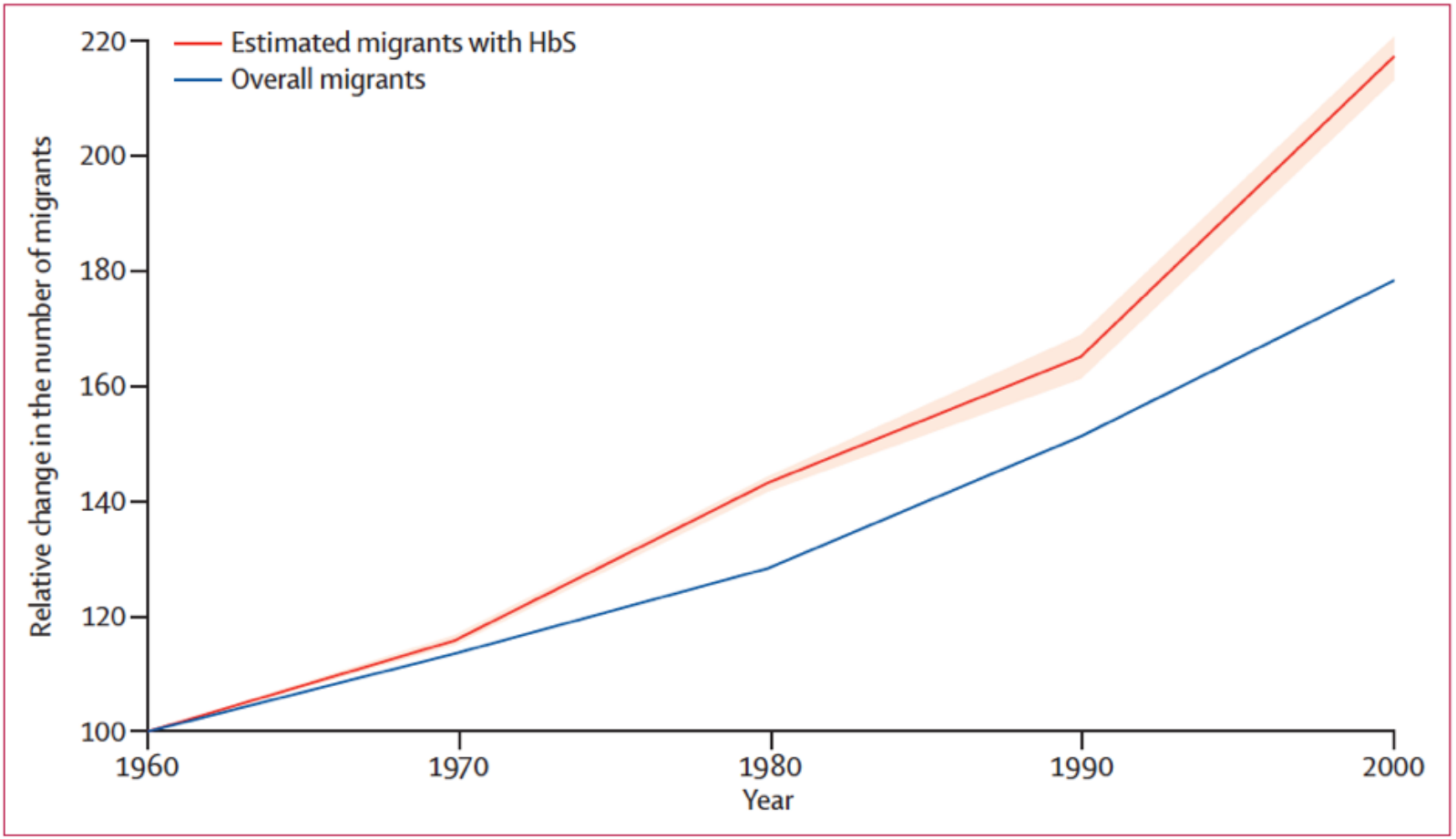


Figure 1. Number of Newborns with Sickle Cell Anemia in Each Country in 2015.
Data are based on estimates from Piel et al.[1] Alaska is shown separately from the rest of the United States.

HgbS mutation carried by ~5% of human race
Approximately 300 000 children born each year with SSD, expected to reach 400 000/year by 2050
Global population ~25 million; in low-income nations, but up to 90% of patients die before age 5

Piel, NEJM. 2017;376;1561

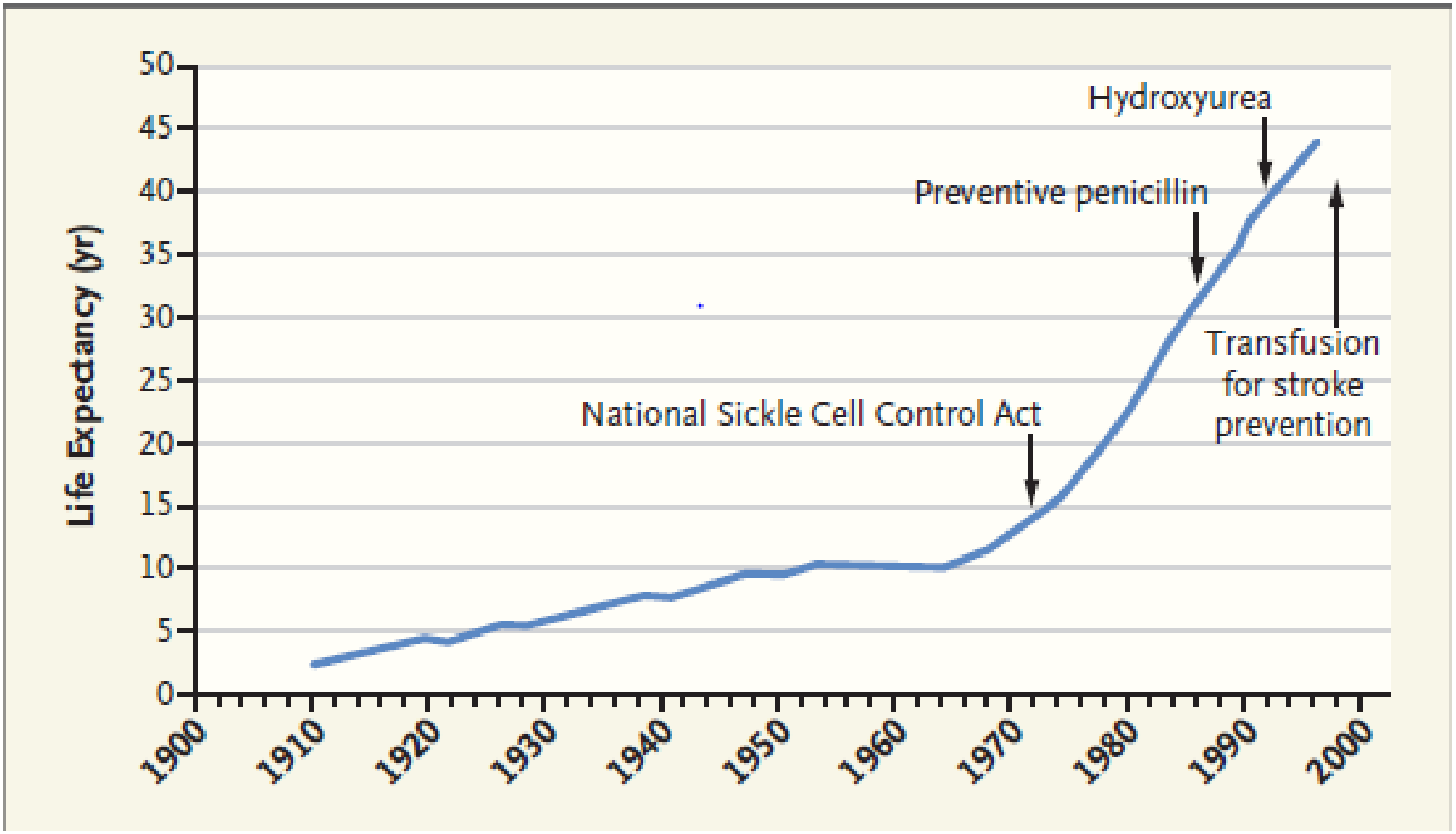
Epidemiology of Sickle Cell Disease



- Between 1960 and 2000, the estimated number of individuals with HgbS migrating to the United States has increased six-fold

Piel, Lancet Glob Health 2014;2:180

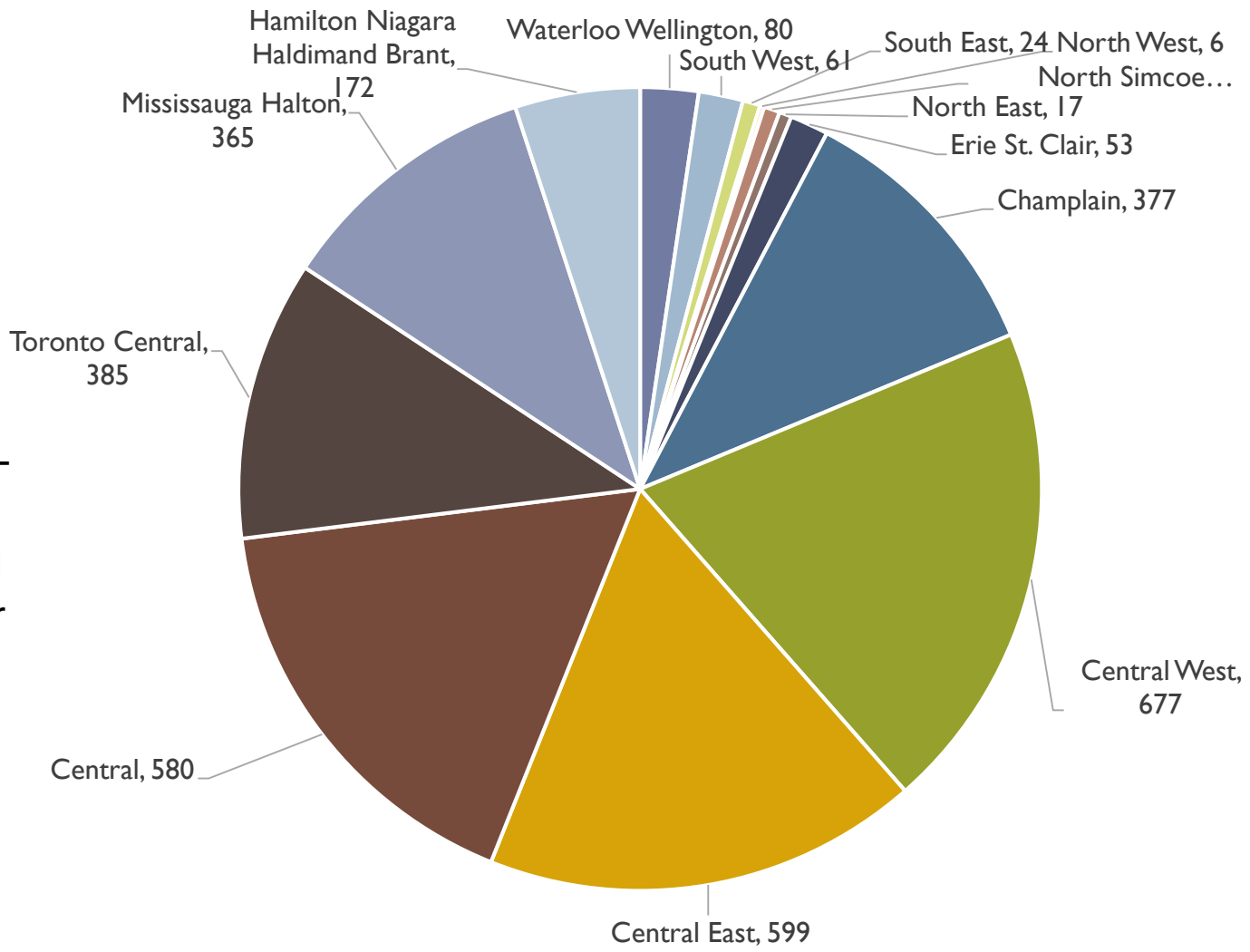
Epidemiology of Sickle Cell Disease



Wailoo, NEJM. 376:805

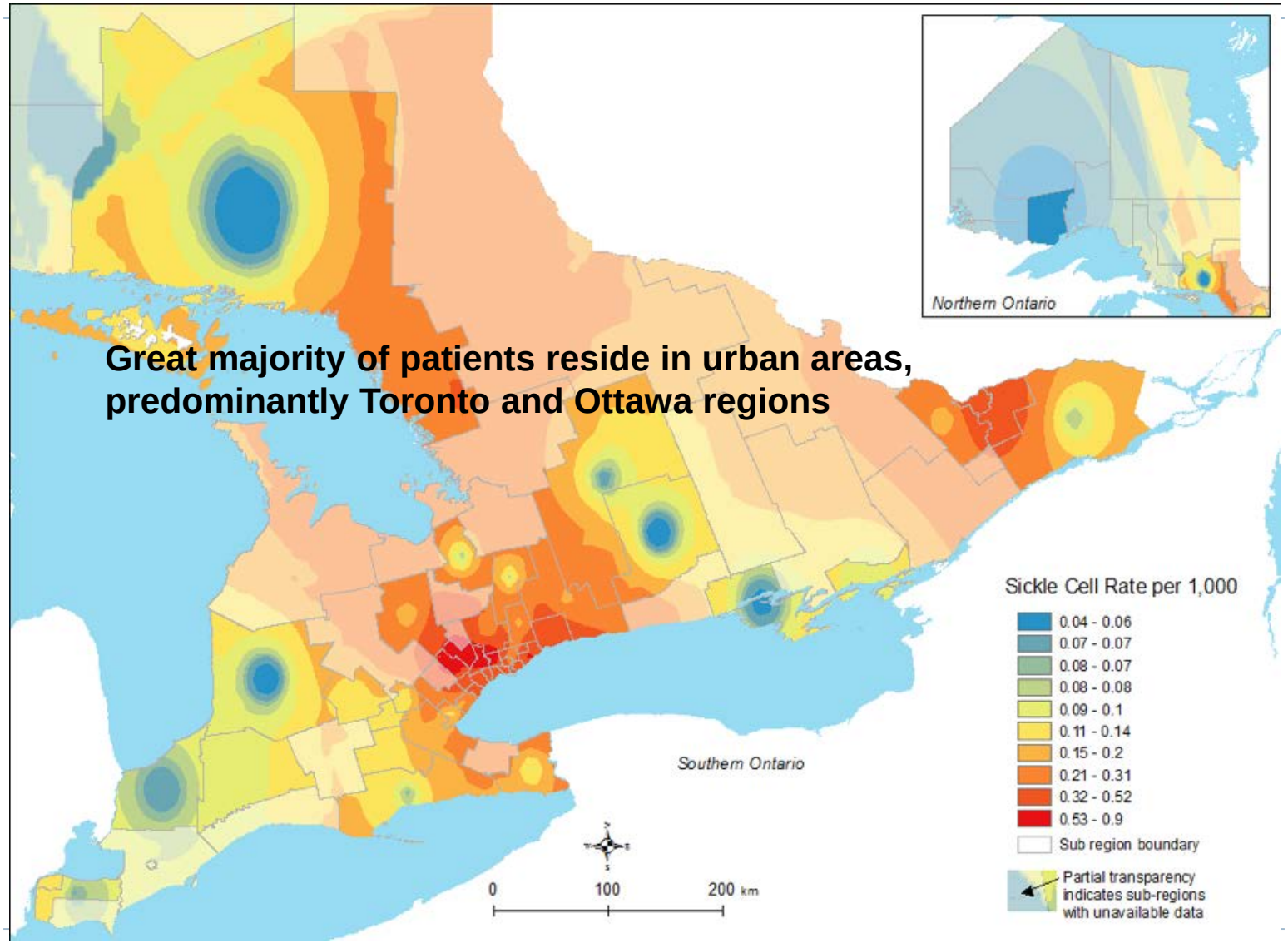
Epidemiology of Sickle Cell Disease: **Ontario**

- ***~3500 patients***
  - Median of 1 hospitalization (IQR 1-5) and 2 ER visits (IQR 1-7) per patient, but data skewed by small number of “superusers”



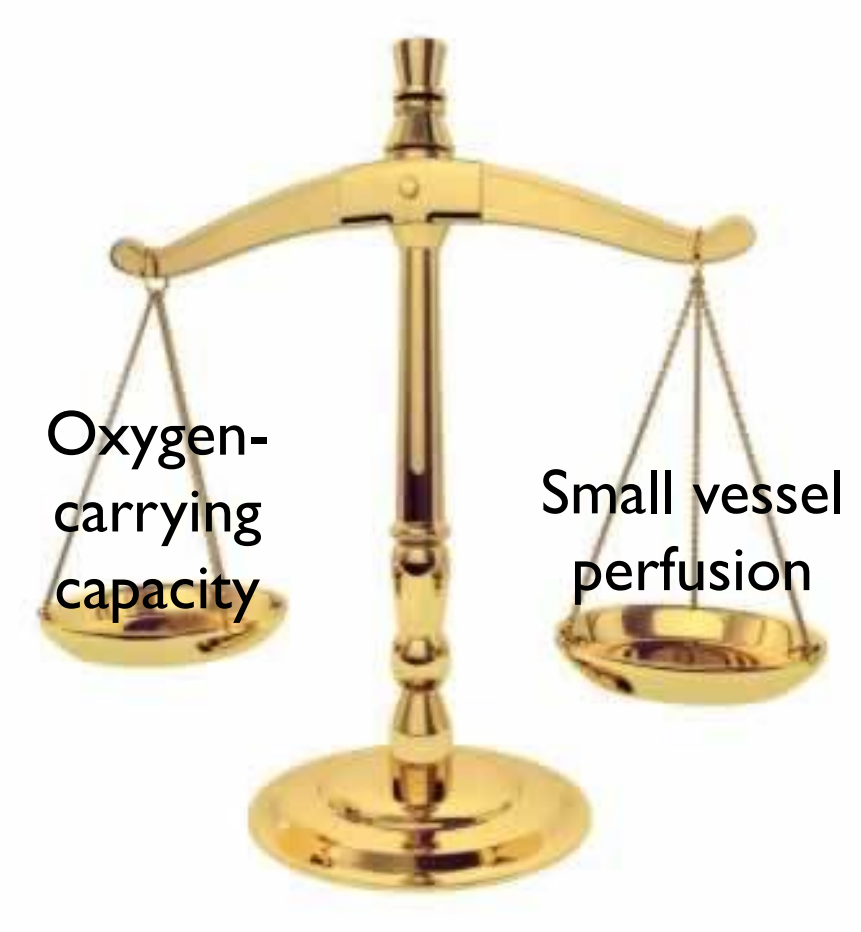
Pendergrast (unpublished)

Epidemiology of Sickle Cell Disease: **Ontario**



Pendergrast (unpublished)

Transfusion and Oxygen Delivery: A Balancing Act



Oxygen Delivery

MACROCIRCULATION

Oxygen Delivery = Cardiac Output x Oxygen Carrying Capacity of Blood

$DO_2 = CO \times CaO_2$

Predominantly determined by Hgb

Higher Hgb = <u>More</u> Oxygen Delivery

MICROCIRCULATION

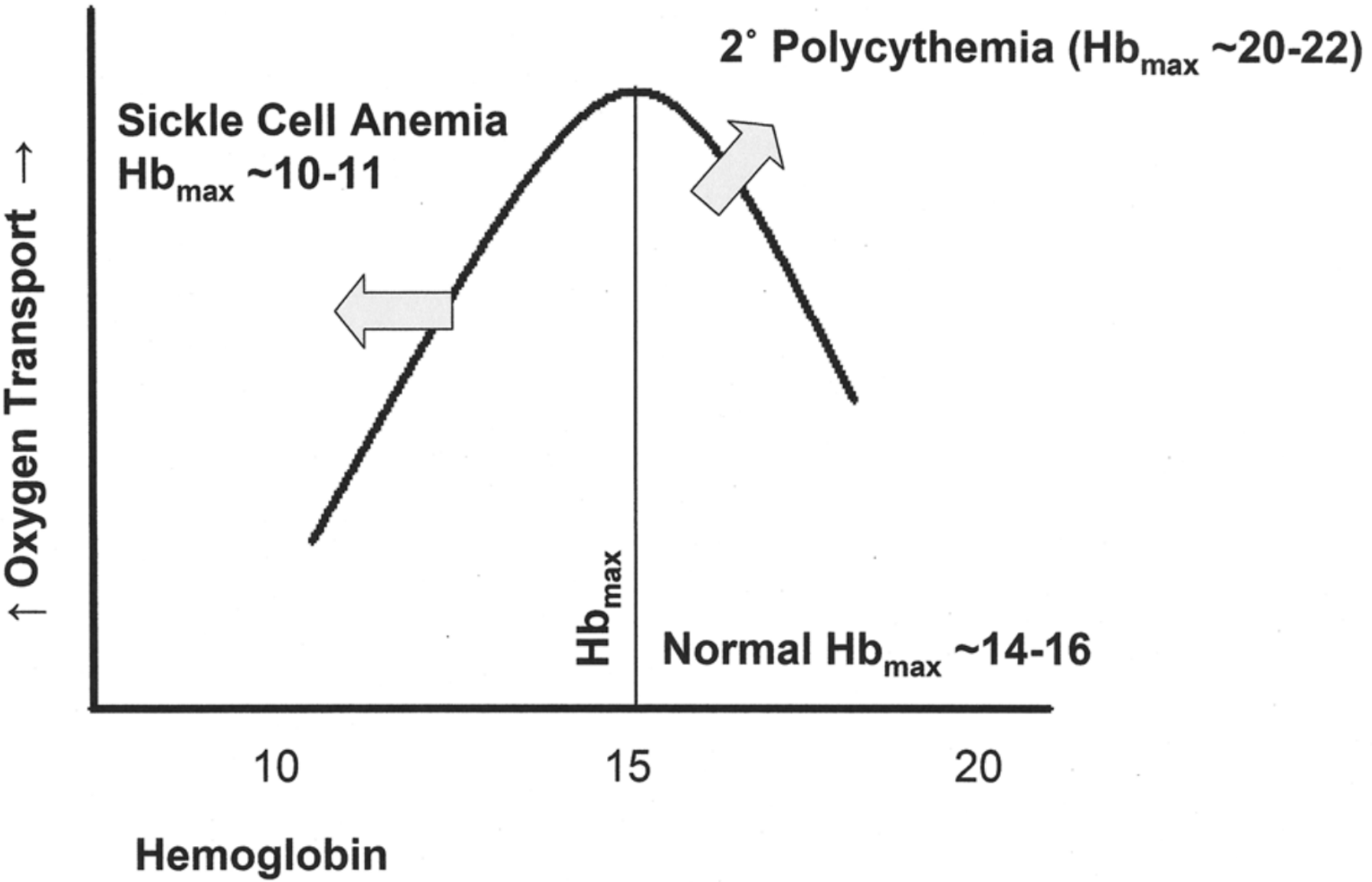
$$\text{Flow} = \frac{\text{pressure} \times \text{radius}^4 \times \pi}{8 \times \text{tube length} \times \text{viscosity}}$$

$$V = \frac{P \times r^4 \times \pi}{8 \times l \times \eta}$$

Predominantly determined by hematocrit

Lower flow = lower oxygen delivery

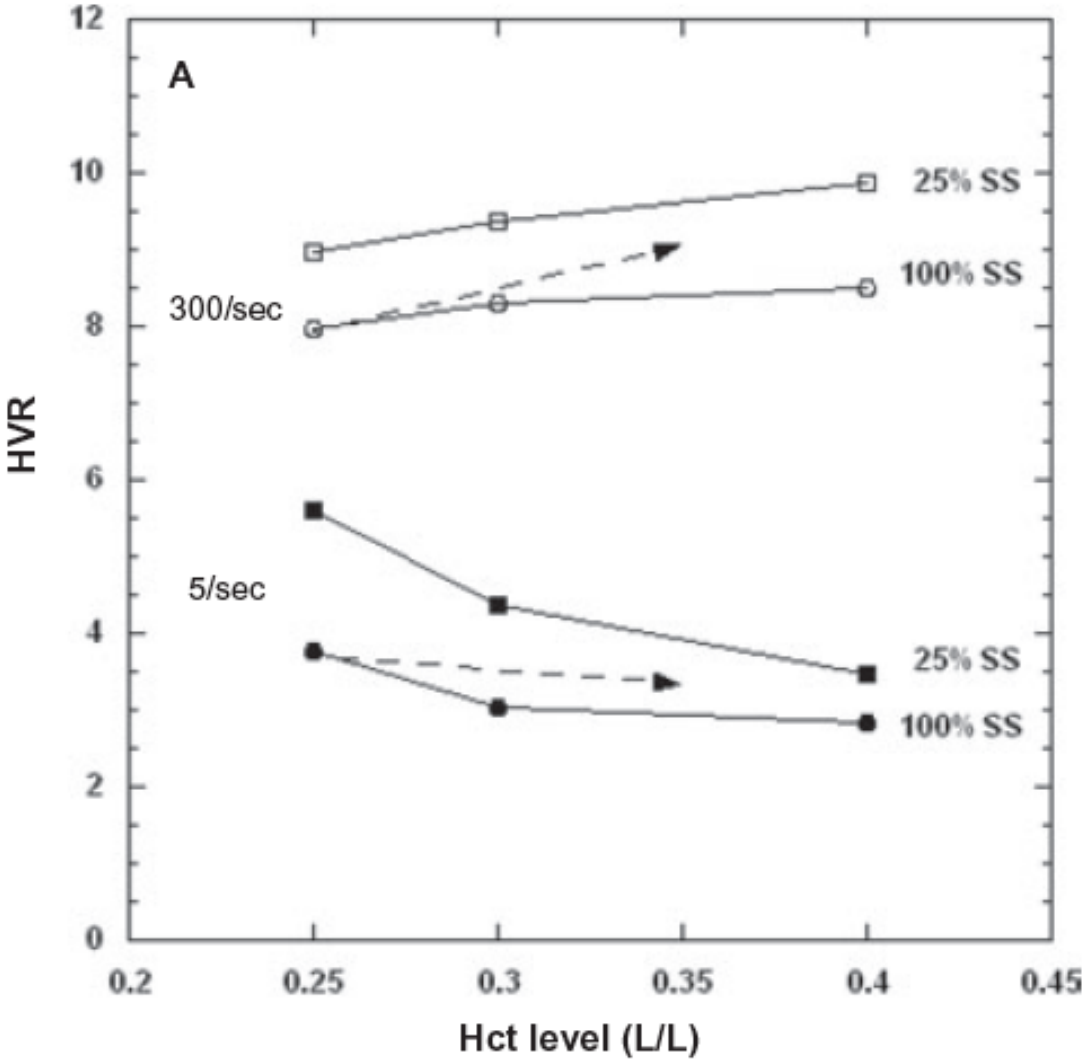
Higher Hgb = <u>Less</u> Oxygen Delivery



Swerdlow, Hematology Am Soc Hematol Educ Program. 2006;48

Hematocrit:Viscosity Ratio vs Hct for **Oxygenated** Sickle Cell RBCs

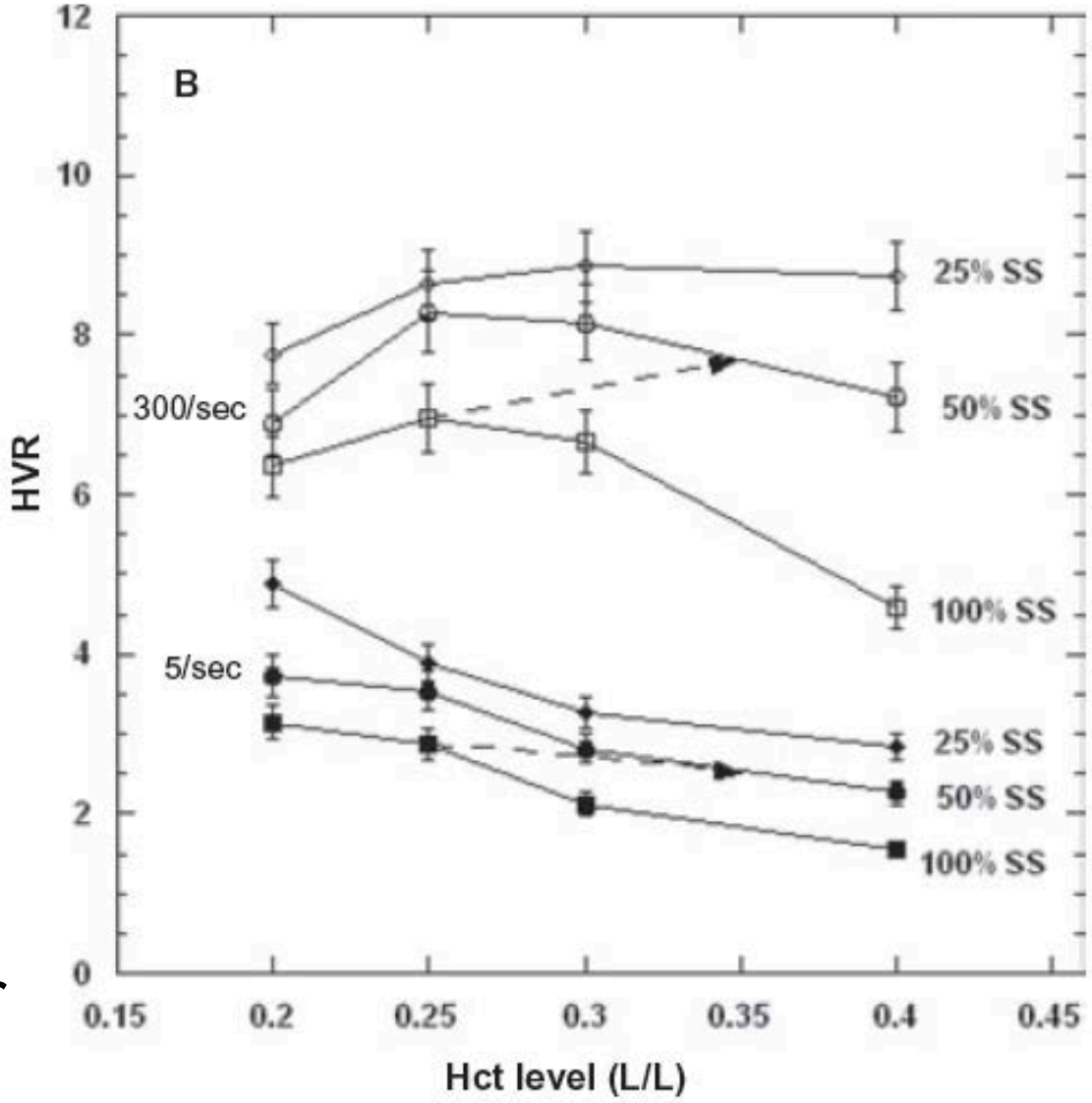
- At high shear blood flow, viscosity increases at a slower rate than Hct over wide-range of Hct values, whether HgbS is 100% or 25%
- At low shear, however, increased RBC:protein interactions exacerbate viscosity, which therefore increases faster than Hct



Alexy T, Transfusion 2006;46:912

Hematocrit:Viscosity Ratio vs Hct for **Deoxygenated** Sickle Cell RBCs

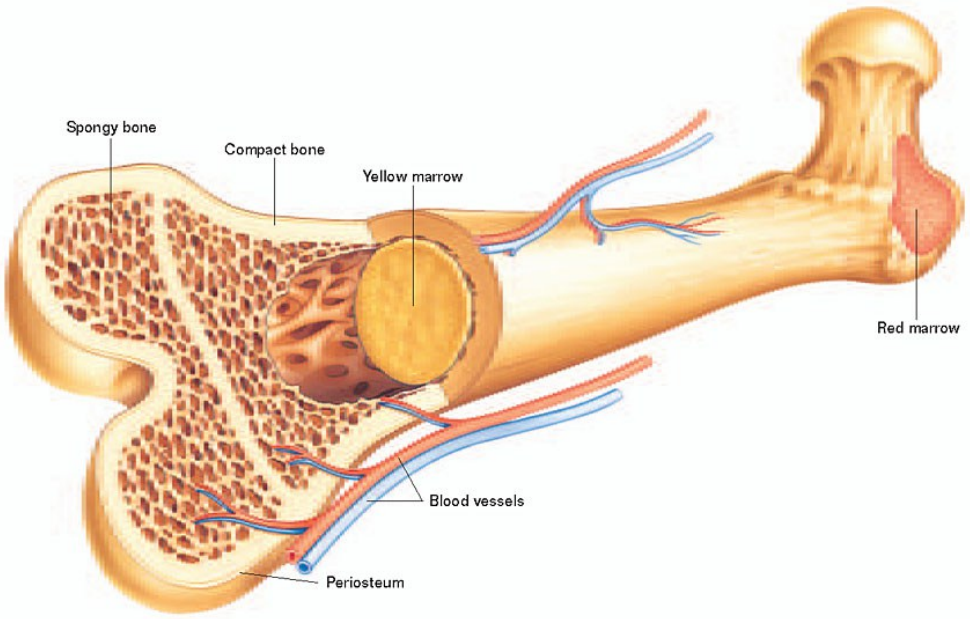
- While oxygenated sickle blood is already more viscous than normal blood, the viscosity increases dramatically when deoxygenated
- Result is an apparent optimal Hct of 25% at high shear, even if HgbS diluted to 25%, no further benefit in increasing Hct past 30%
- Even lower Hct may be better at low shear



Alexy T, Transfusion 2006;46:912

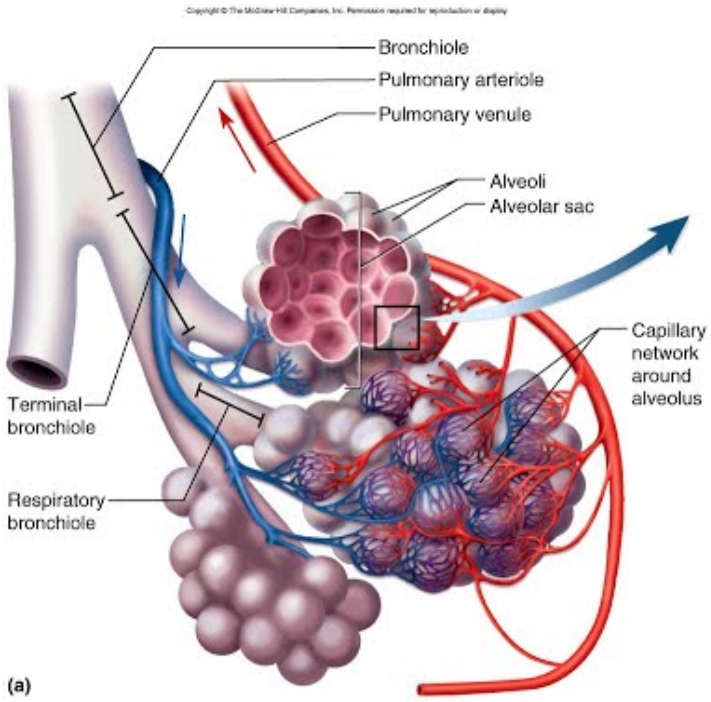
Implications of Viscosity Studies

- In vascular beds with low shear, particularly those with low oxygen tension (eg., post-capillary venules, bone marrow), any increase in oxygen delivery achieved by transfusion is likely offset by increases in viscosity
- This would suggest that top-up transfusions are unlikely to be of benefit as treatment for vaso-occlusive crises manifesting as bony pain



Implications of Viscosity Studies

- In vascular beds with high shear (eg., brain, kidneys, lungs), oxygen delivery may be optimized by increasing the Hct, but with deoxygenated sickle blood there is likely little benefit and possibly harm of transfusing to exceed a Hct of 30%, even if patient's own blood has already been diluted by 75%
- Moreover, any improvements in oxygen delivery achieved by transfusion in high-shear vascular beds may result in worsened oxygen delivery in low shear beds



Implications of Viscosity Studies: Rules of Thumb

1. In most cases, the benefits of transfusing a patient with sickle cell disease will come from decreasing the viscosity of their blood rather than by increasing its oxygen-carrying capacity
   - **Goal of transfusion is to decr HgbS%, not incr total Hgb**
2. Transfusing a patient with sickle cell disease to Hgb > 100-110 g/L may *worsen* their condition, particularly if the patient is already in a hyperviscous state (dehydrated, low-flow, hypoxic)
   - **Target HgbS% may only be safely achievable by removing patient's own blood prior to transfusing = *EXCHANGE TRANSFUSION***

Exchange Transfusions

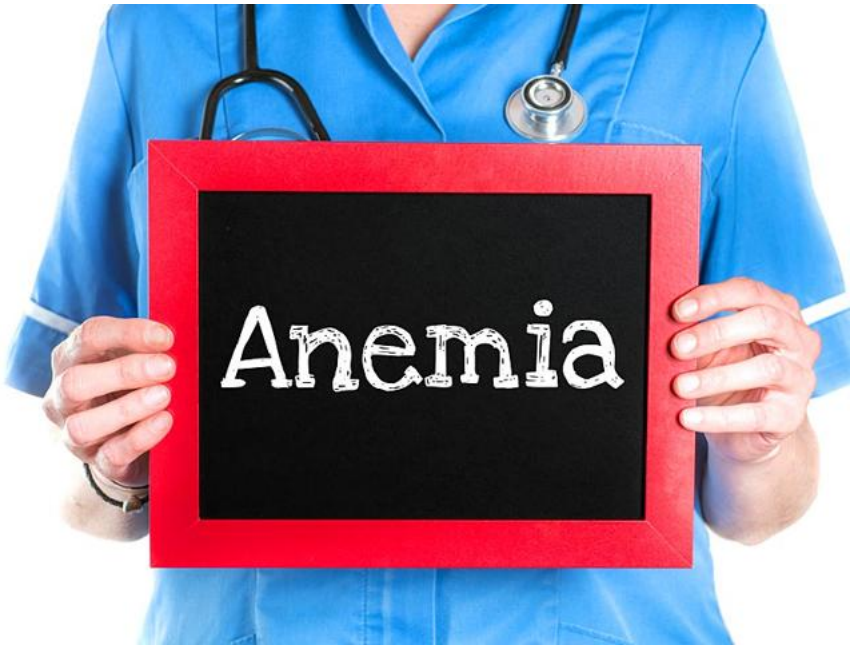
- "All hospitals that are likely to admit sickle cell disease patients should have staff trained in manual exchange procedures and clearly identified manual exchange procedures, as this can be lifesaving in emergency situations (Grade 1C)"
- "Large referral centres managing patients with sickle cell disease should have facilities and trained staff for automated exchange transfusion (Grade 1C)."

BCSH, Br J Haem 2017;176:179

Exchange Transfusions

- Manual exchange: No special equipment required, but slow
  1. Phlebotomize 500 cc
  2. Infuse 500 cc saline
  3. Phlebotomize another 500 cc
  4. Transfuse 2 units RBCs
  5. Repeat as necessary (alternative 1 and 2 units for step 4 if starting Hgb near 100 g/L)
- Automated erythrocytopharesis: Specialized equipment/personnel, but fast
  - Blood volume estimated based on patient height, weight and Hct
  - Approximately 150 cc autologous RBCs removed with each cycle and replaced with either saline or homologous RBCs, depending on patient baseline status and goals of therapy

Transfusing to Increase the Oxygen Carrying Capacity



Transfusing for CaO_2

- Remember: O2 dissociation curve is *right-shifted* in sickle cell: what seem like symptoms of anemia may in fact reflect medication effects (eg., fatigue), hypovolemia (eg., tachycardia, hypotension), or other disease (eg., dyspnea)
- Prophylactic transfusions to prevent complications of anemia in sickle cell disease not advised unless Hgb < 50 g/L!

bjh guideline

Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion

"Transfusion is not recommended in uncomplicated painful crises but should be considered if there is a substantial drop in Hb from baseline (e.g. >20 g/l or to Hb <50 g/l), haemodynamic compromise or concern about impending critical organ complications (Grade 1C)."

BCSH, Br J Haem 2017;176:192

Is there ever a need to increase CaO_2?

- After excluding hemorrhage and hemodilution, there are three major causes of acute anemia exacerbations in sickle cell disease (Hgb decr > 20 g/L from baseline):
  - Aplastic crisis
  - Sequestration crisis
  - Hyperhemolysis

Aplastic crisis

- Most commonly due to erythrovirus (parvovirous B19)
- Erythematous rash and arthropathy x 2-3d, then severe reticulocytopenia (< 50 x 10^9/L)
- Reticulocytopenia lasts 1 week and then recovers as virus cleared by neutralizing antibodies
  - Lifelong immunity following infection (~75% by age 20)
- As patients with sickle cell disease have RBC lifespan of only 16-20d, severe anemia may occur during interim (Hgb decr > 30 g/L)

Smith-Whitley, Blood 2004;103:422

Aplastic crisis

- As fall in hemoglobin occurs over days, plasma volume has time to increase in compensation
- Further transfusions therefore risk volume overload; administer slowly and consider prophylactic diuretics
- For patients with humoural immunodeficiency IVIG 0.5 mg/kg weekly x 4 is reasonable
- Most patients with SCD have self-limiting disease

Anderson D, Trans Med Rev 2007;21(S1):S9

Splenic Sequestration Crisis

- Trapping of sickle erythrocytes in sinusoids results in massive enlargement of spleen (abd pain and distension) and severe anemia over a period of hours, accompanied by reticulocytosis
  - Often accompanied by thrombocytopenia
- If untreated, can cause death from hypovolemic shock/anemia
  - Hepatic sequestration rarer and less severe (liver not as distensible)
- ~25% incidence in pts with sickle cell disease, most common first 2 years of life, very rare after puberty
- Chronic transfusions appear to decrease the risk of recurrence, which otherwise occurs in 50% of patients, although mortality rate decreases over time
  - Goal of transfusion is to buy time for splenectomy

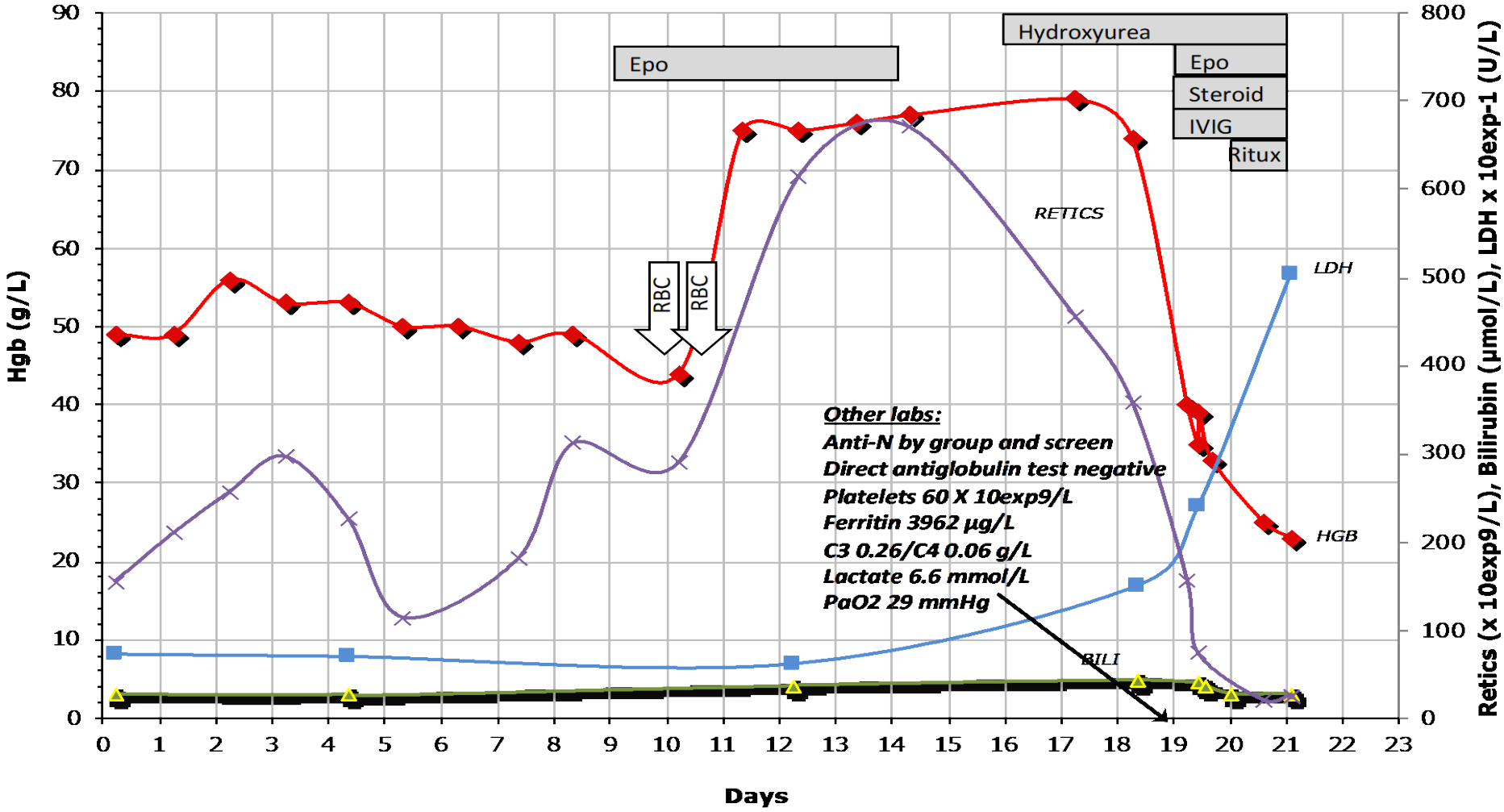
Owusu-Ofori, Cochrane Database 2002; CD003425.

Splenic Sequestration Crisis

- Post-transfusion hemoglobin levels often higher than expected, suggesting *autotransfusion*: sequestered RBCs released back into circulation
- Care must therefore be taken not to accidentally induce polycythemia with attendant risks of hyperviscosity; in children, advisable to administer transfusions in smaller than normal aliquots (eg., 3-5 mL/kg)
- Often a single transfusion is sufficient to reverse a sequestration crisis

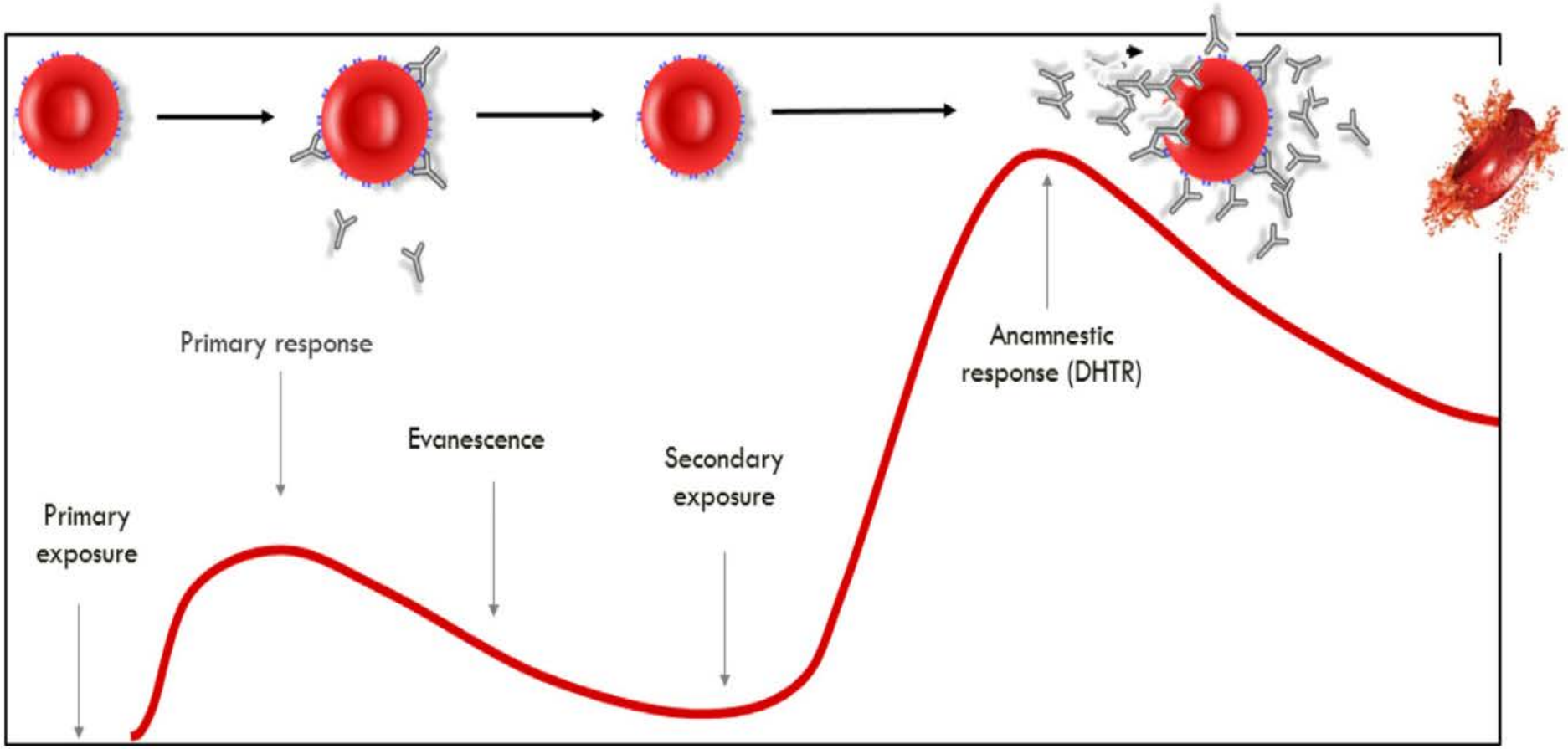
Hyperhemolysis

- Defined as a rapid hemoglobin decline to below pretransfusion level, accompanied by rapid decline of posttransfusion HbA%
- Cases may initially present as fever and pain, with fall in hemoglobin occurring shortly after
- Two types
  - Acute (<7 days post-transfusion): often no evidence of new antibodies
  - Delayed (>7 days post-transfusion): new antibodies often detected in serum or eluate


Hgb (g/L)
Retics (x 10exp9/L), Bilirubin (µmol/L), LDH x 10exp-1 (U/L)
Days
Epo
Hydroxyurea
Epo
Steroid
IVIG
Ritux
RBC
RBC
RETICS
LDH
HGB
BILI
Other labs:
Anti-N by group and screen
Direct antiglobulin test negative
Platelets 60 X 10exp9/L
Ferritin 3962 µg/L
C3 0.26/C4 0.06 g/L
Lactate 6.6 mmol/L
PaO2 29 mmHg

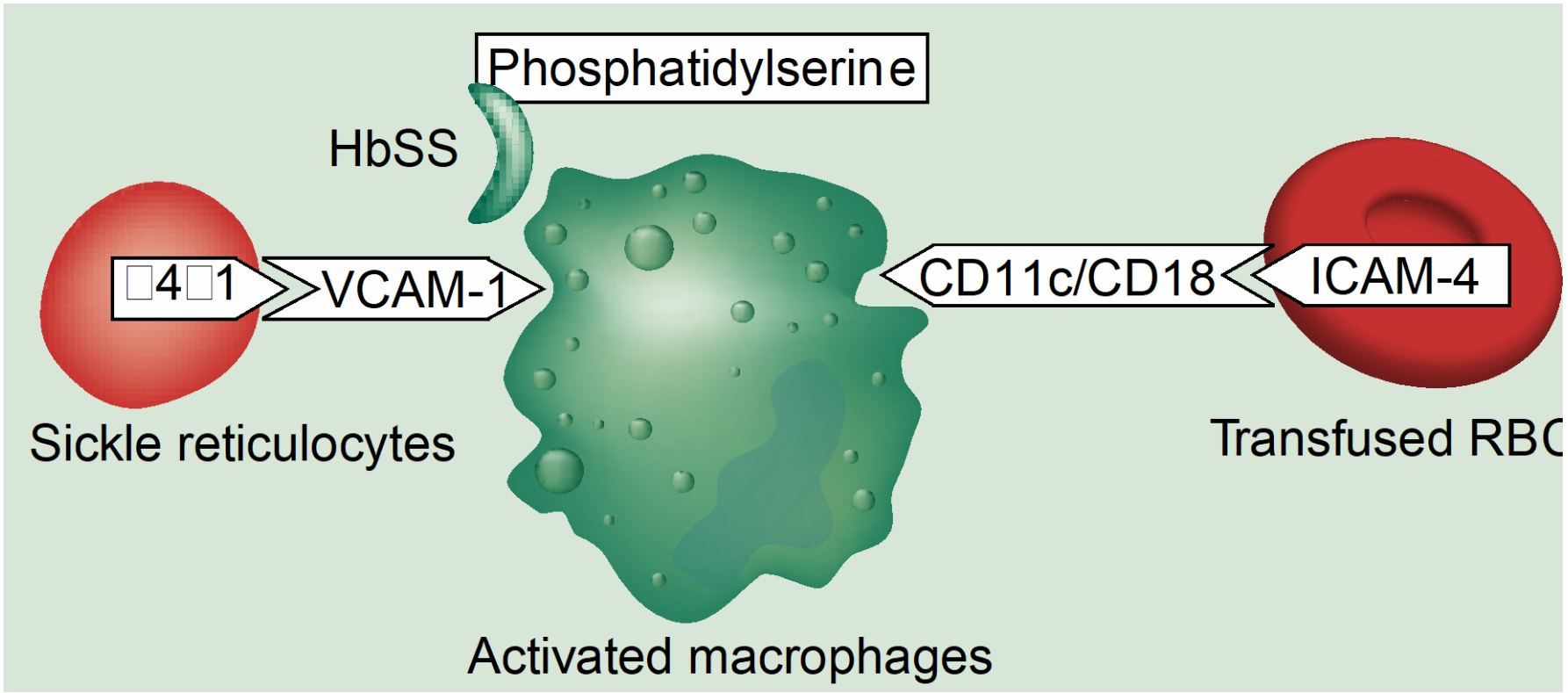
Hyperhemolysis

Traditional Model of Delayed Hemolytic Transfusion Reaction



Hyperhemolysis

Proposed Non-Serologic Mechanisms of Hemolysis



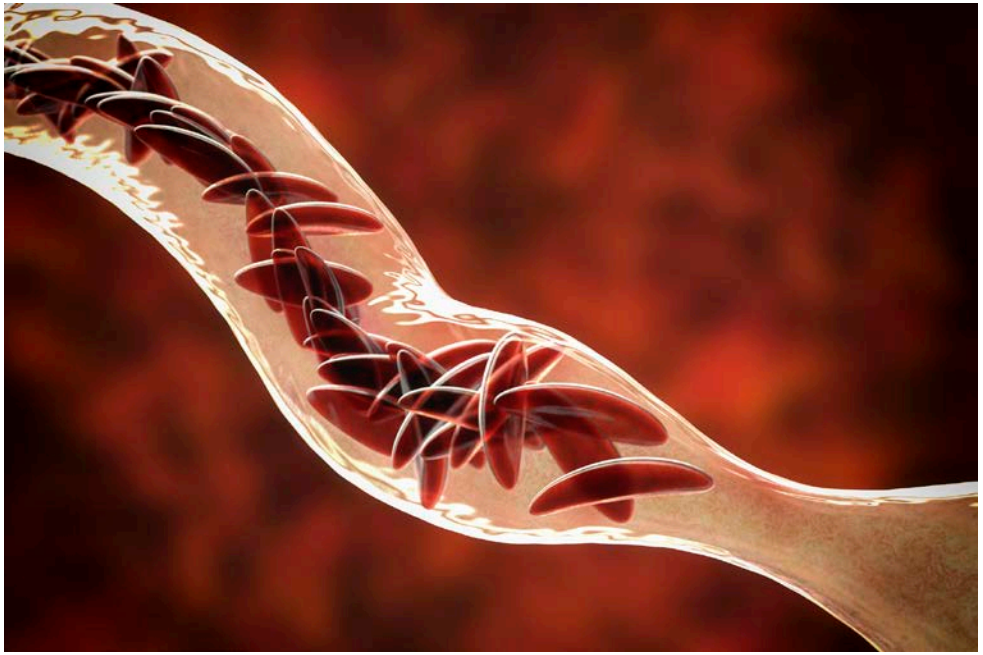
Win, Expert Rev. Hematol. 2009;2:111

Hyperhemolysis

- Once diagnosis made, immediately initiate treatment with immunosuppressive therapy
  - First line: IVIG (2 g/kg over 2-5 days) and high-dose steroids (eg., prednisone 1 mg/kg/day)
  - Add Epo if if reticulocytopenia
- In cases accompanied by acute organ failure, or if first line therapy has failed, some have advocated
  - Eculizumab (to interrupt complement-mediated lysis)
  - Rituximab (to prevent further antibody formation if rescue transfusion required)
- Once diagnosed, hyperhemolysis is a relative contraindication to <u>all future transfusions</u>

1. Anderson, Trans Med Rev 2007;21(S1):S9 2. Win, Trans Med Rev 2010;24:64
3. Pirenne, Blood 2018;131(25):2773

Transfusing to Decrease Whole Blood Viscosity



Transfusing to Decr HgbS%

- Traditional goal of therapy is to decr HgbS to < 30% while keeping total Hgb < 110 g/L
  - In patients with HgbSC, preferable to state goal as HgbA > 70%
- Available RCT evidence limited to ability of transfusion to **prevent** complications in variety of high-risk settings:
  - Pregnancy
  - Perioperative
  - Stroke prevention
- Guidelines for **treatment** of complications based largely on observational studies and case series
  - Acute chest syndrome
  - Sickle hepatopathy

Transfusing to Decrease Whole Blood Viscosity

Pregnancy

- Current guidelines discourage *routine* provision of transfusion support to pregnant women, but still support it for those with:
  - History of severe SCD-related complications before current pregnancy (including during previous pregnancies)
  - Additional features of high-risk pregnancy (eg, multiple pregnancy, nephropathy, other comorbidities)

ASH, Blood Adv. 2020;4:327

  - UK Guidelines: women previously on hydroxyurea because of severe disease

BCSH, Br J Haem 2017;176:192

Perioperative: General Guidelines

Risk	Example	Pre-op transfusion
Low	• Skin, eyes, nose, ears, dental • Distal extremities • Perineal, and inguinal areas	Not required
Intermediate	• Abdominal or orthopedic procedures • Oropharyngeal procedures	Top-up transfusion to 100 g/L (approx HgbS 60%); exchange if Hgb > 90g /L
High	• Intracranial, cardiovascular, or intrathoracic procedures • Scleral buckling • Intermediate-risk procedures in patients with significant comorbidities (eg., chronic pulmonary disease), *or with baseline Hgb > 90g/L*	Exchange transfusion to HgbS of 30% (HgbA 70%)

Stroke prevention

- RCTs in children with SSD have shown that
  - Transfusion remains first line therapy for both primary and secondary stroke prevention
  - In patients being transfused for *secondary* prophylaxis, must maintain HgbS% of <30% indefinitely (and continue monitoring: may not be sufficient to completely prevent progressive disease)
  - In patients being transfused for *primary* prophylaxis, careful transition to hydroxyurea after > 1 year of transfusion may be feasible
  - For patients with silent infarcts (25-35% prevalence!), transfusion decisions should be made case-by-case

Adams, NEJM. 1998;339:5
Adams, NEJM. 2005;353:2769
Ware, Blood. 2012;119:3925
DeBaun, NEJM. 2014;371:699
Ware, Lancet. 2016;13;387

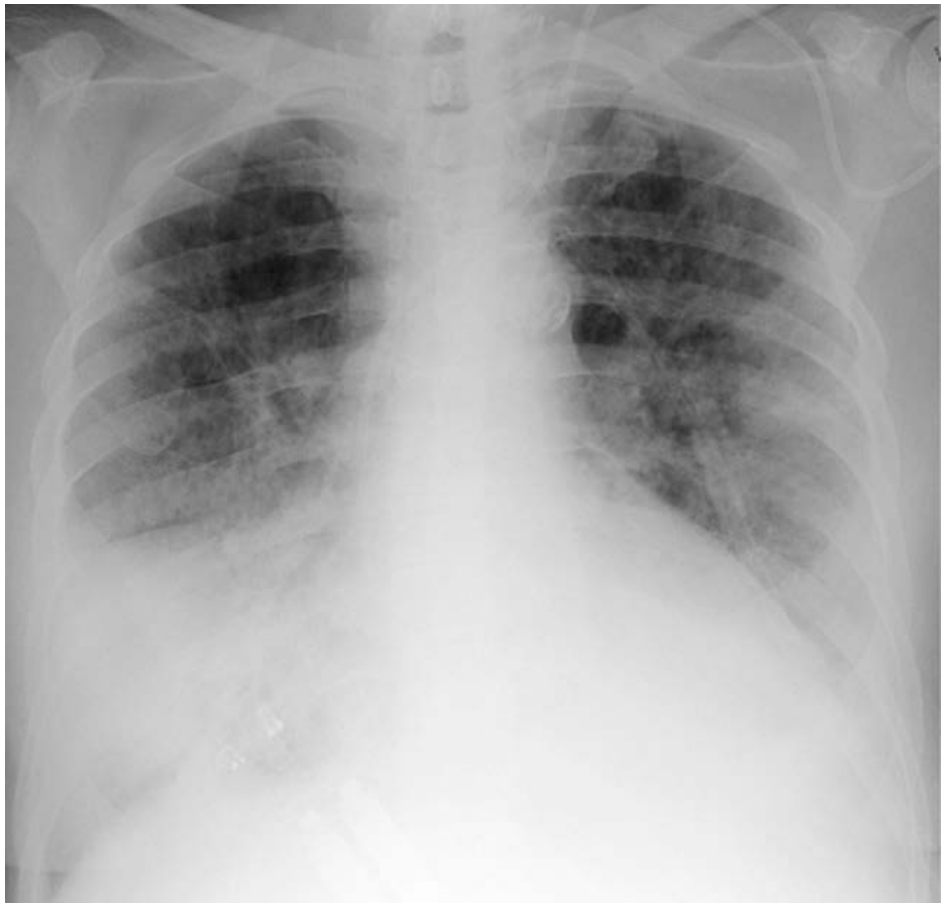
Stroke prevention

- In adults with sickle cell disease, very little evidence to base practice on
- If no obvious other explanation (eg., vasculopathy apparent on angiogram and no evidence of cardioembolism) usual practice is to initiate chronic transfusion support following new onset symptomatic stroke
  - In presence of *hemorrhagic* stroke, may be prudent to wait until bleeding has stopped

Transfusing to Decrease Whole Blood Viscosity

Acute Chest Syndrome

- Standard definition encompasses a broad range of disease severity: *new pulmonary infiltrate on CXR accompanied by fever and/or resp symptoms*
- May be triggered by infection or marrow embolism; specific cause not identified in ~60% of cases despite extensive investigations



www.radiology.vcu.edu

1. Vichsinky, NEJM 2000;342:1855
2. Wayne, Blood 1993;l811109

Acute Chest Syndrome

- In absence of RCT evidence, guidelines recommend transfusions for all but mildest cases, and exchange transfusions for patients with poor prognostic markers

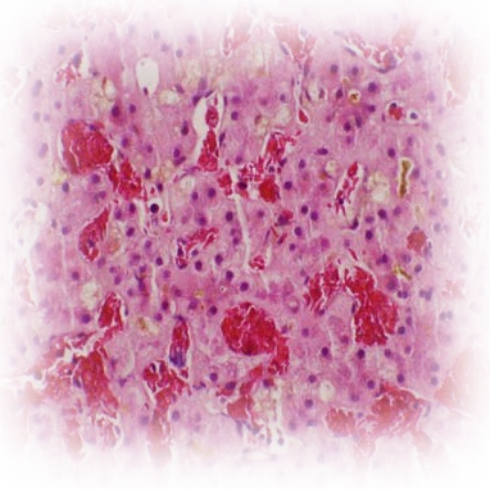
- Physical exam
  - Altered mental status
  - Persistent HR > 125/min
  - Persistent RR > 30 or other evidence of incr work of breathing
  - Temp > 40C
  - Hypotension vs baseline

- Lab/radiologic findings
  - Arterial pH < 7.35
  - SpO2 persistently < 88% despite aggressive ventilatory support
  - Serial decline in SpO2% or A-a gradient
  - Hgb decr by ≥ 20 g/L
  - Plts < 200/fL
  - Elevated BNP or troponin
  - Evidence of multiorgan failure
  - Pleural effusion
  - Progressive pulm infiltrates

Johnson, Hematol Oncol Clin N Am 2005:19;857

Sickle Hepatopathy

- Sickle cell intrahepatic cholestasis
  - Severe RUQ pain, acute hepatomegaly, coagulopathy, extreme hyperbilirubinemia (predominantly conjugated), only moderately elevated liver enzymes
  - Occasionally progresses to acute liver failure
  - Chronic (benign) form more common in children; in adults may progress to severe liver dysfunction requiring transplant
  - Acute forms (accompanied by sequestration) may occur in setting of VOC and be precipitated by intercurrent infection or exposure to hepatoxin: DO NOT BIOPSY
  - Case reports of improvement from exchange transfusion



Gardner, Blood. 2014; 123:2302

"What's the takeaway on all this?"

Overview of Transfusion Indications for SSD

Generally Accepted	Possibly Effective	Not Indicated
• Acute cerebrovascular accident • Primary and secondary stroke prevention • Retinal artery occlusion • Acute and recurrent splenic sequestration • Intrahepatic cholestasis • Acute chest syndrome • Aplastic crisis • Pre-operative for moderate to high-risk procedure • Hemorrhage (eg., splenic rupture) • Prevention of pain crises	• Recurrent or persistent priapism • Pulmonary hypertension • Progressive renal failure • Pregnancy with exacerbation of anemia or evidence of placental insufficiency • Severe sepsis	• Compensated anemia • Infections other than aplastic crisis or acute chest syndrome • Treatment of uncomplicated pain crisis • Pre-operative for minor procedures • Non-surgical management of avascular necrosis • Uncomplicated pregnancy

HEMATOLOGY CONSULTATION

Adapted from Wanko, Hem Onc Clinics of NA 2005;19:803

Selection of RBCs

Prevention of Alloimmunization

- Approx 25% of patients with SSD will become alloimmunized from transfusion
- Due largely to differences in antigen expression between typical donor and sickle cell patient

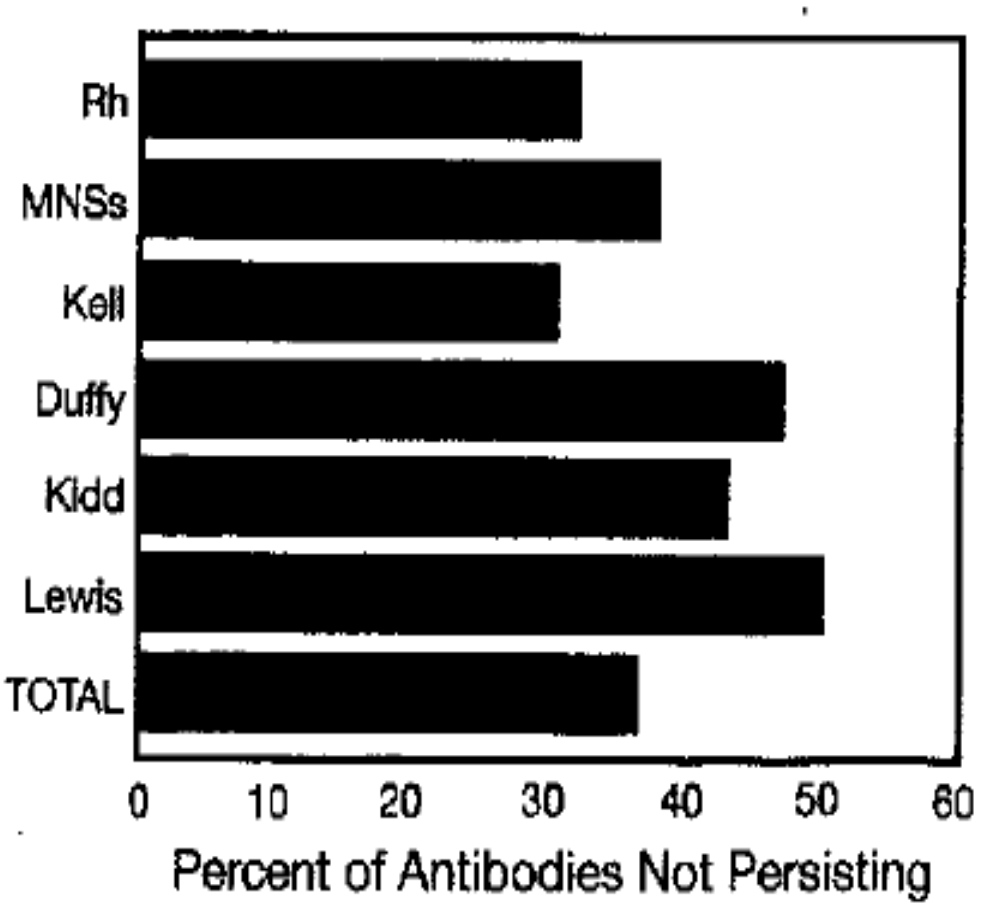
Table 3. Average Frequencies of RBC Alloantibodies Made By Transfused Patients With SCD

Antibody	Average frequency (%)
Anti-E	21
Anti-K	18
Anti-C	14
Anti-Le^a	8
Anti-Fy^a	7
Anti-Jk^b	7
Anti-D	7
Anti-Le^b	7
Anti-S	6
Anti-Fy^b	5
Anti-M	4
Anti-E	2
Anti-C	2

Josephson CJ, TMR 2007;21:118

Detection of Alloantibodies

- In patients with sickle cell disease, 30-50% of antibodies will be detectable on at least one occasion 1 year after they were first observed
- Episodic transfusions in different hospitals increases risk of DHTRs and possibly hyperhemolysis
- **Note, though, that many DHTRs in sickle cell will not be accompanied by evidence of serologic incompatibility**



Vichinsky E, Semin in Hematol 2001;1(S1):14

Prevention of Alloimmunization

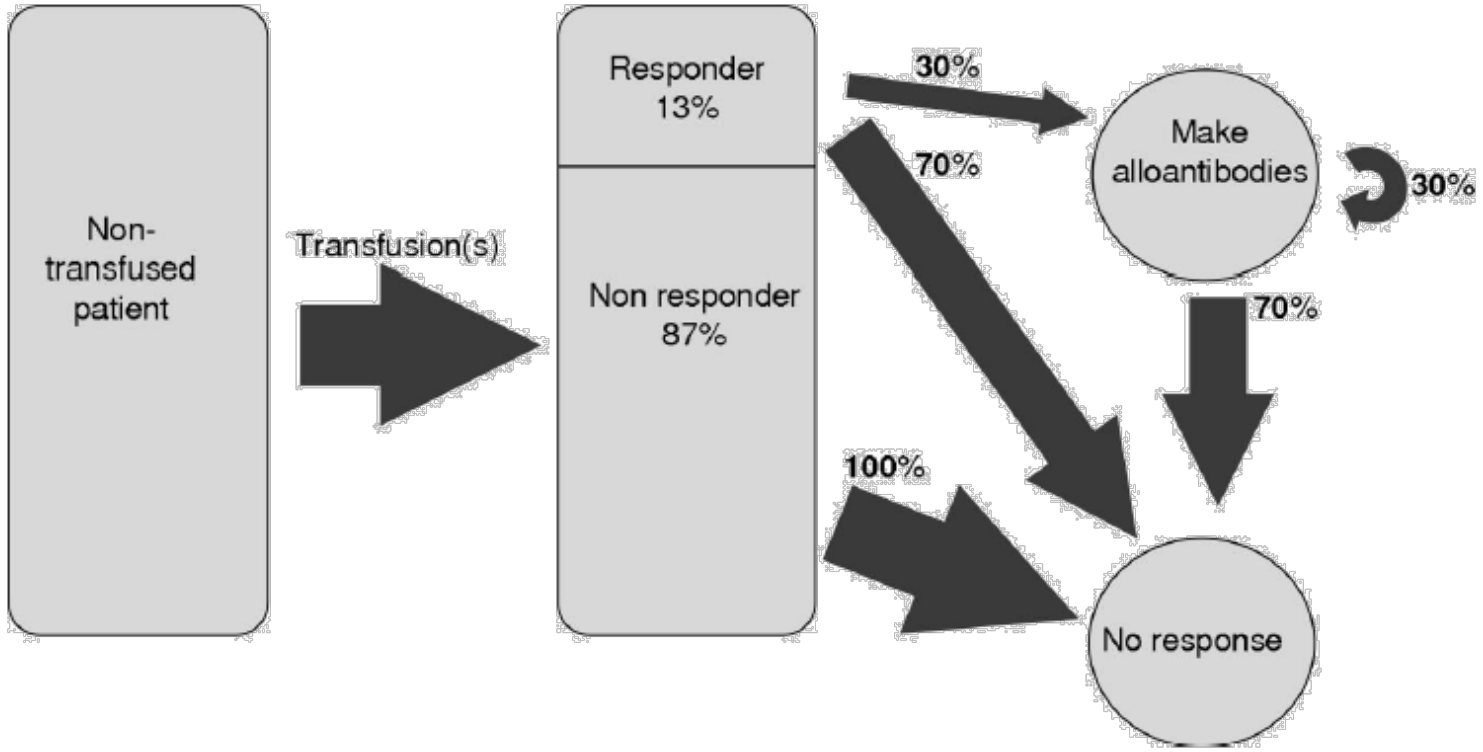
- Extensive matching has diminishing yields

Matching protocol	% of immunizations that would have been prevented beyond ABO/D matching	% of transfused SCD who would never make an antibody	Frequency of required phenotype in Caucasians
Rh (C,c,D,E,e)	37.2%	82.3%	15%
Rh and K	53.3%	87.5%	13.6%
Rh, K and S	55.5%	88.3%	6.1%
Rh, K, S and Fy^a	62.8%	91.2%	2.1%
Rh, K,S, Fy^a, Jk^b	70.8%	93.4%	0.6%

Castro, Transfusion 2002;42:684

Prevention of Alloimmunization

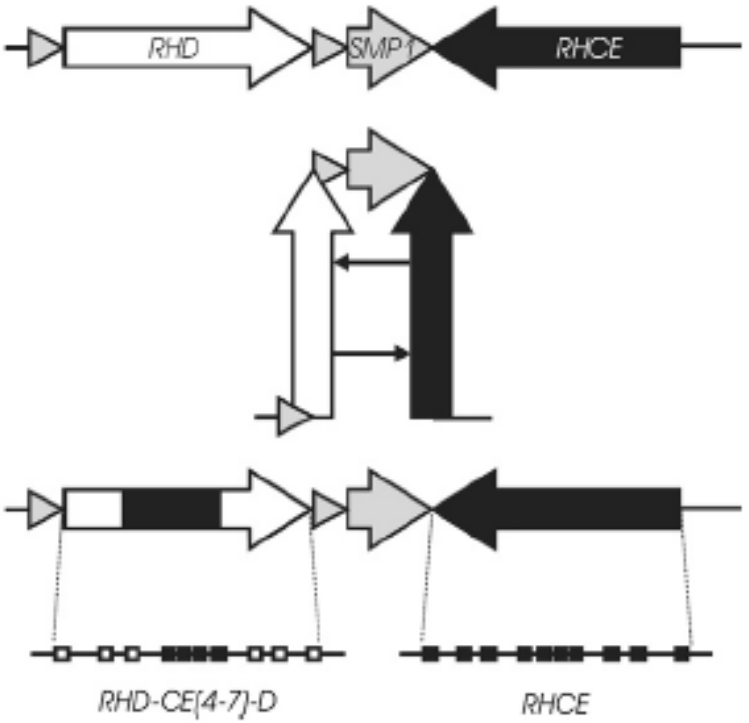
- 13% of transfusion recipients are immune responders; on confronting a foreign antigen, sensitization occurs 30% of the time



Higgins JM, Blood. 2008;112:2546 and 2010;15:4315

The Importance of Genotyping

- 22% of Black individuals carry the RHD variant RHDIIIa-CE(4-7)-D
- Represents transposition of part of a normal RHCE gene into the RHD gene, which both
  - Ablates the D antigen
  - Creates a partial C antigen



Chou, Hematology 2009;178

The Importance of Genotyping

improved transfusion support

Category	% in white donors	% in black recipients
Partial RH antigens		
Partial D among D+	1	7
Partial C among C+	0	30
Partial e among e+	0	2
Low incidence antigens		
VS (RH20)	0.01	26-40
Js^a (KEL6)	0.01	20
Rare blood groups		
U negative (MNS:−5)	0	1
Hr^s negative (RH:−18)	0	0.1
Hr^B negative (RH:−34)	0	0.1
RN (RH:−46)	0	0.1
Js^b negative (KEL:−7)	0	1

Antigens NOT expressed on screening cells used by hospital blood banks

Yazdanbakhsh K, Blood. 2012;120:528

The Importance of Genotyping

- Ironically, the harder we try to match sickle patients for common clinically significant antigens such as C, E, K, Fya, Jkb and S…
- … the greater the likelihood we will be selecting a blood donor who is positive for low frequency antigens such as V, VS, JAL and Js^a
- Thus, safe matching of blood for sickle cell patients may require genotyping donors as well
- Specialized reagents may be required to optimally detect and identify antibodies formed by SSD patients

Other Considerations

- Transfusion of HgbS-containing units (eg, from sickle trait donors) may confound attempts to monitor response to transfusion but does not itself pose any significant harm to patients
- Transfusion of fresh RBCs (eg., < 7-10 days) may prolong interval between transfusions but is not mandatory
- ***The above considerations are of much lesser importance than the provision of antigen-typed units***

QUESTIONS/COMMENTS?

- **PRINCIPLES**
  - Decr HgbS%, generally more important than increasing total Hgb
  - Benefit only with high-shear vasculature
  - Ceiling of Hgb ~100 g/L
- **WEAK EVIDENCE WITH PREGNANCY**
  - Available evidence suggests more benefit for mom than developing fetus
  - There may be exceptions (eg., signs of placental insufficiency, prev IUGR)
- **CAUTION WITH SEVERE ANEMIA**
  - Aplastic crisis: *volume overload*
  - Sequestration: *autotransfusion*
  - Hyperhemolysis: *worsening anemia*
- **GOOD EVIDENCE FOR STROKE PREVENTION**
  - Transfusion indicated for all children with high-risk dopplers and history of stroke
  - Smaller value for children with SCIs
  - Limited evidence in adults; look for other causes, caution with hemorrhagic stroke
- **NUANCED APPROACH FOR SURGERY**
  - Usually not needed for low-risk patient with low risk procedure
  - Indicated for everyone else, top-up vs exchange depends on comorbidity, procedure risk, baseline hemoglobin
- **THERAPEUTIC TRANSFUSION IF ACUTE ORGAN COMPROMISE**
  - Limited evidence, but consensus supports transfusion for acute stroke, acute chest syndrome, sickle hepatopathy
  - Other situations: "if all else fails"
- **SELECTION OF RBCs MUST BE DONE WITH CARE!**
  - Tell your blood bank early that your patient has sickle cell, provide detailed transfusion history

EXTRA SLIDES

Other Considerations

- Improved transfusion support of sickle cell patients still comes primarily from "low-tech" solutions:
  - Judicious ordering of blood products by clinicians (eg., not for asymptomatic anemia or uncomplicated pain crisis)
  - Incr recruitment of donors from ethnic minority groups
  - Better communication between clinicians and laboratory regarding patient diagnosis
  - Better communication between hospital blood transfusion services regarding patient phenotype and antibody history *(tell your blood bank if your patient has ever been transfused elsewhere)*
- **Safest option? Get a hematology consult before you operate on or transfuse a patient with sickle cell disease**