Transfusion Support for Sickle Cell Disease

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Laboratory Medicine & Pathobiology
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TRANSFUSION MEDICINE 101
CAMP WITH THE BANK

Disclosures

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Learning objectives

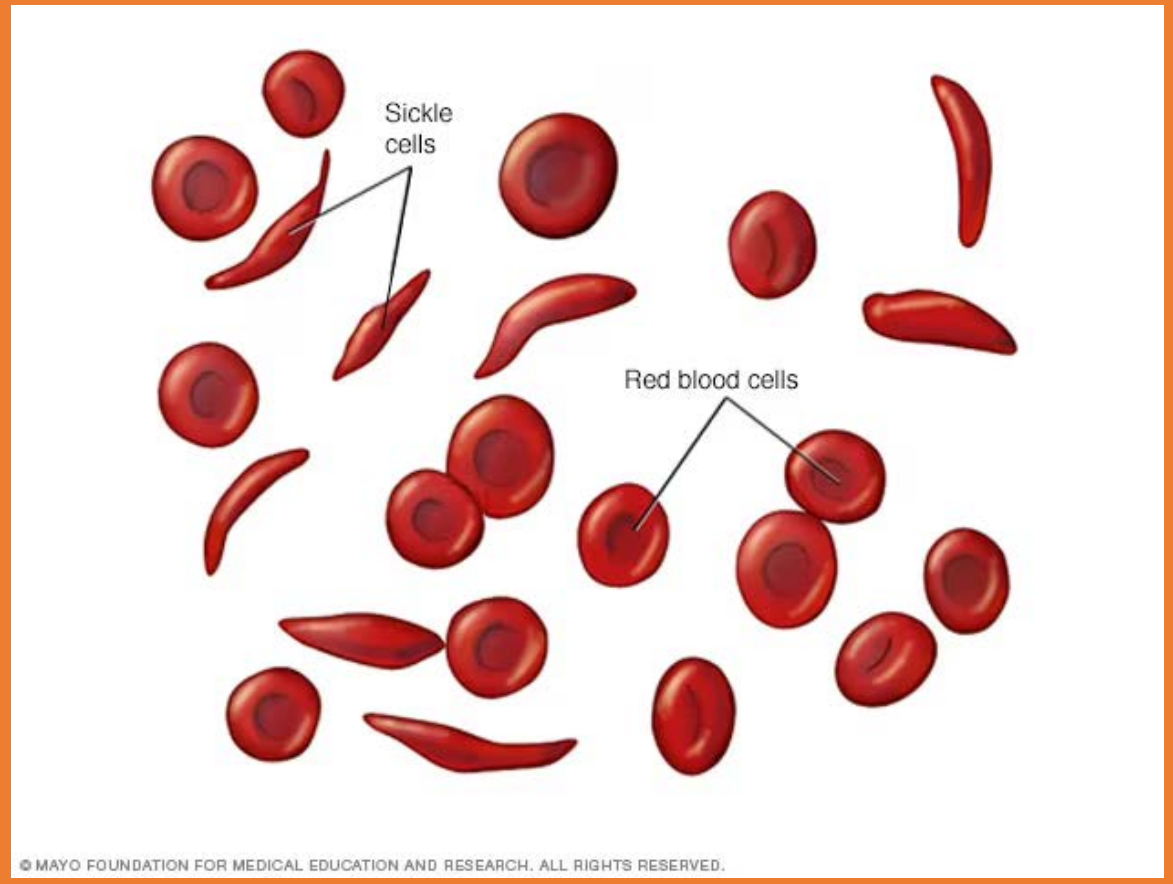
1. Outline the principles of RBC transfusion in sickle cell disease

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

Learning objective #1:

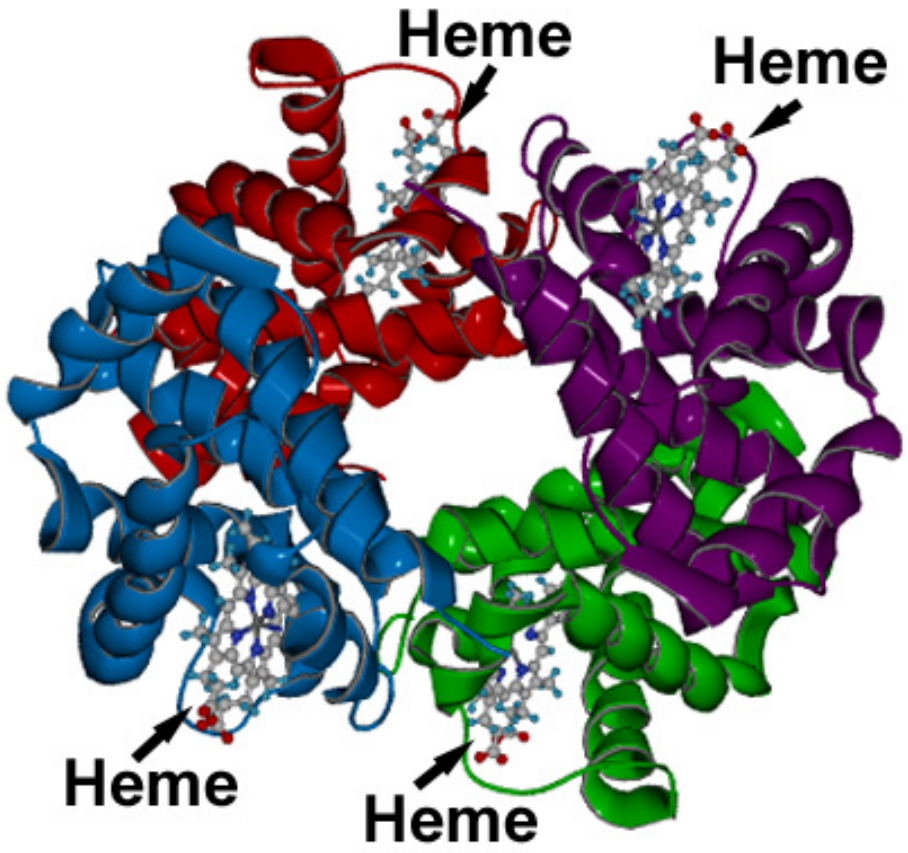
Outline the principles of RBC transfusion in sickle cell disease



What is Sickle Cell Disease?

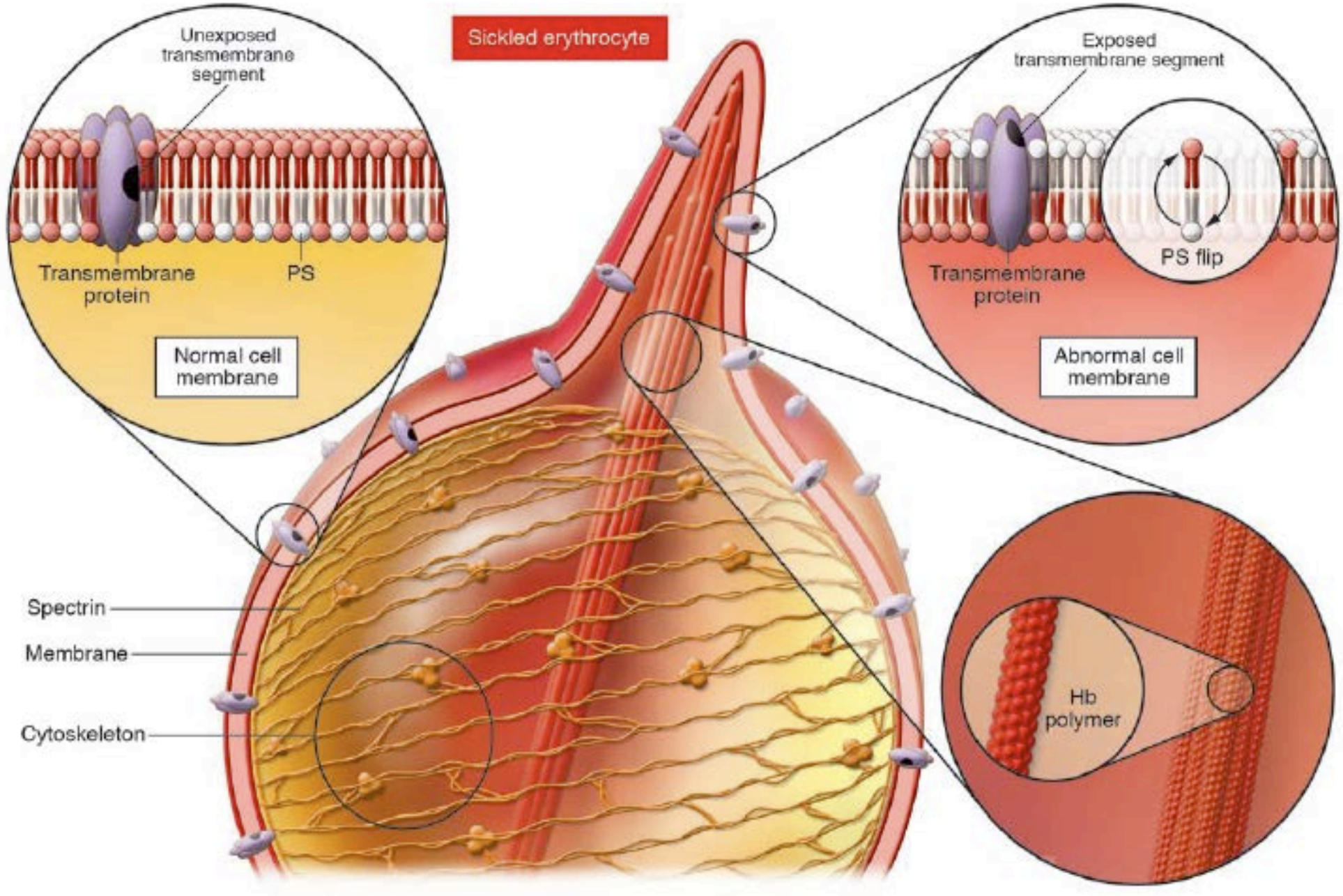
Hemoglobin: An Overview

- Structure of hemoglobin
  - 4 globin chains (2 x alpha and 2 x beta), each containing a heme group within a protected pocket
  - When deoxygenated, Hgb in “taut” configuration, beta globin chains held apart with ionic bonds
  - With oxygen binding, ionic bonds broken, beta globin chains move together and Hgb adopts ”relaxed” configuration



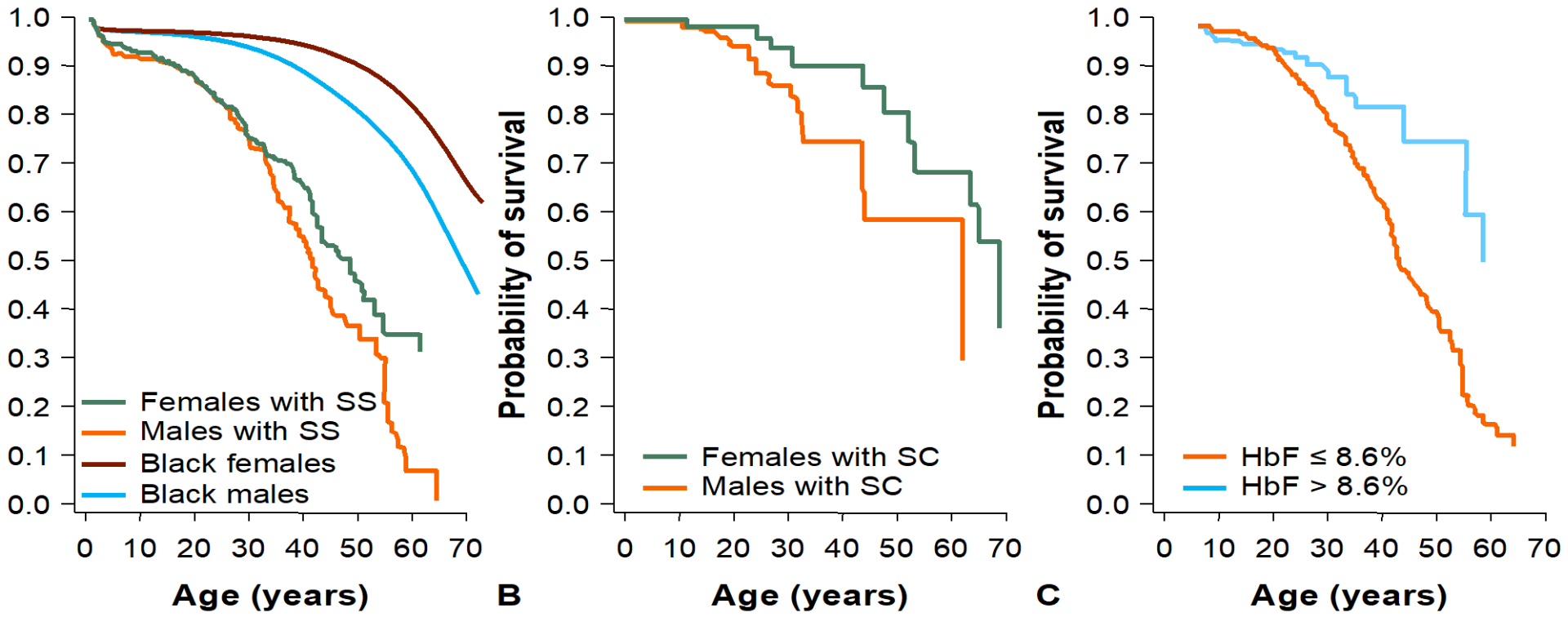
Sickle Cell Disease: Pathophysiology

- Due to specific point mutation in sixth codon of ß-globin gene
- Resulting HgbS has a **hydrophobic domain** which predisposes to precipitation when deoxygenated
- HgbS polymerization results in formation of elongated fibres which stretch and deform the erythrocyte
- Membrane damage results in cellular dehydration, rigidity, adhesiveness/thrombogenicity
- Net result: **hemolysis, vaso-occlusion**



Frenette P, J Clin Invest 2007;117:850

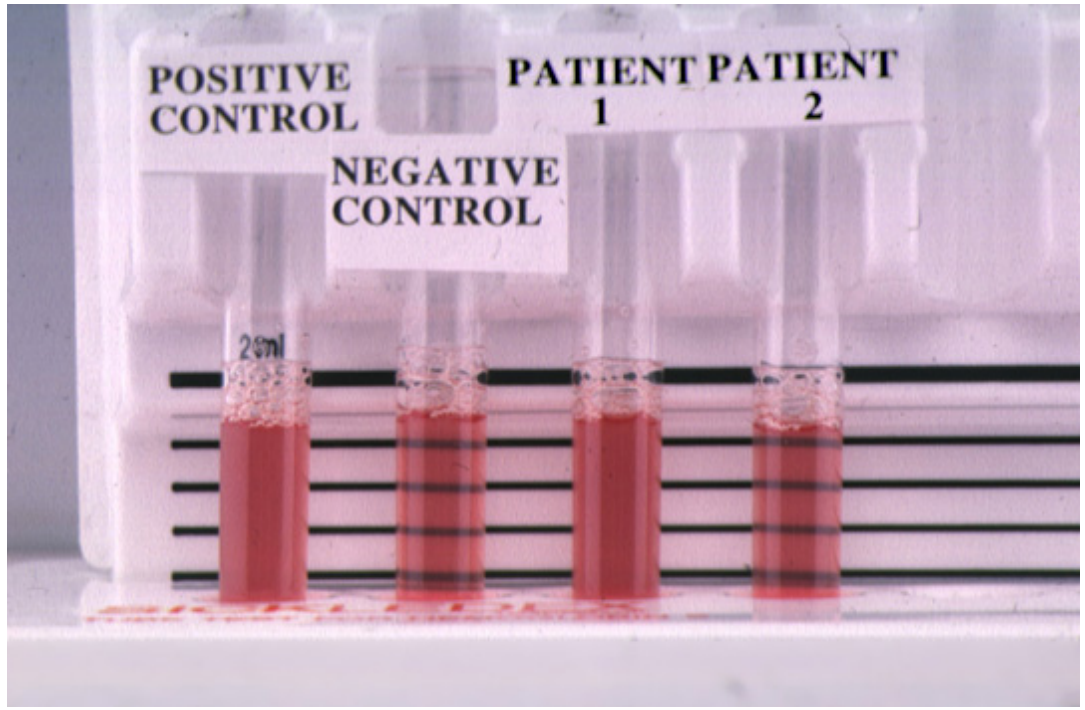
Genotype	HgbS	Typical clinical severity
$ß^S/ß^A$	HgbS: 20-30%	Asymptomatic
$ß^S/ß^C$	HgbS: 50%	Mild-moderate
$ß^S/ß^+$	HgbS: 70-85%	Moderate
$ß^S/ß^o$, $ß^S/ß^S$	HgbS: 90-95%	Severe



Platt O, NEJM 1994;330:1639

A note on screening

- After 6 months age, sickle cell solubility testing (Sickledex®) will detect all sickling syndromes (HgbSS, Sß, SC, etc) AND HgbAS (sickle cell trait)
- Patients with a positive solubility test must undergo confirmatory testing by hemoglobin electrophoresis/high-performance liquid chromatography



A note on screening

- Is it necessary to screen at-risk ethnicities (African, Greek, Southern Italian, Turk, Arab, Indian) for sickle cell disease prior to surgery?
- Consider the following:
  - >95% of patients will have already manifested clinically by age 10
  - Universal newborn screening in place in Ontario since 2006
  - Diagnosing sickle trait (50x more common than sickle cell disease) pre-operatively may create needless delays in care
- **Careful history and physical/early referral to hematology of known SSD cases probably much more important than routine pre-operative lab screening**

O'Leary, Can J Anesth 2013;60:54

Which homozygote sickle cell disease patient warrants an exchange transfusion?

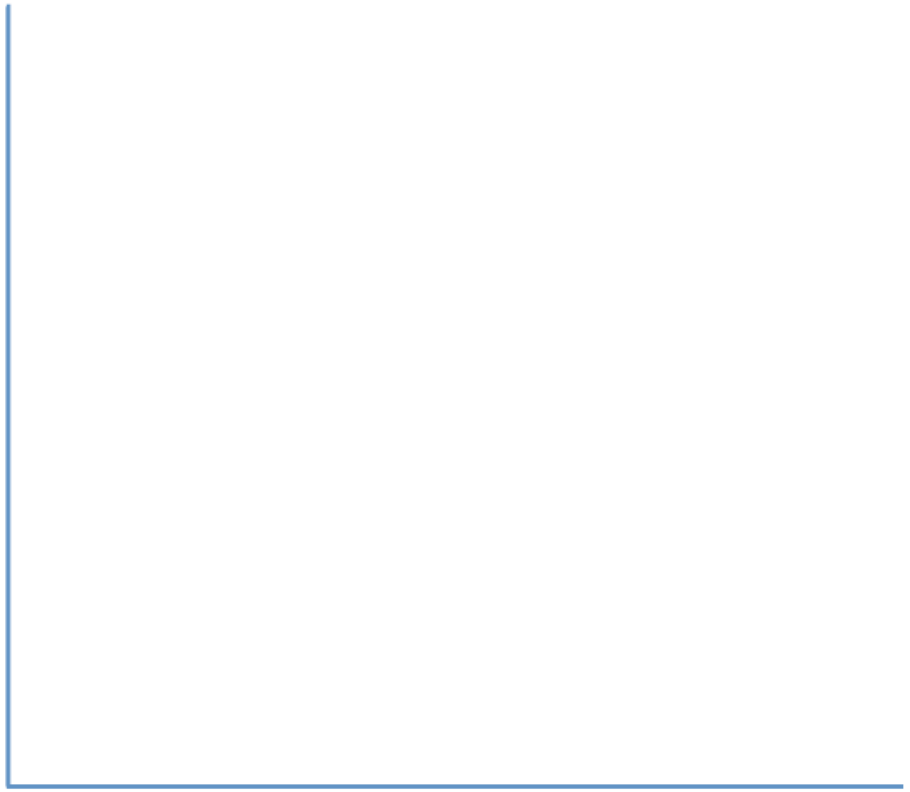
28 year old female G1P0, 25 weeks pregnant with Hgb 70g/L

45 year old woman with Hgb 34g/L with an aplastic crisis

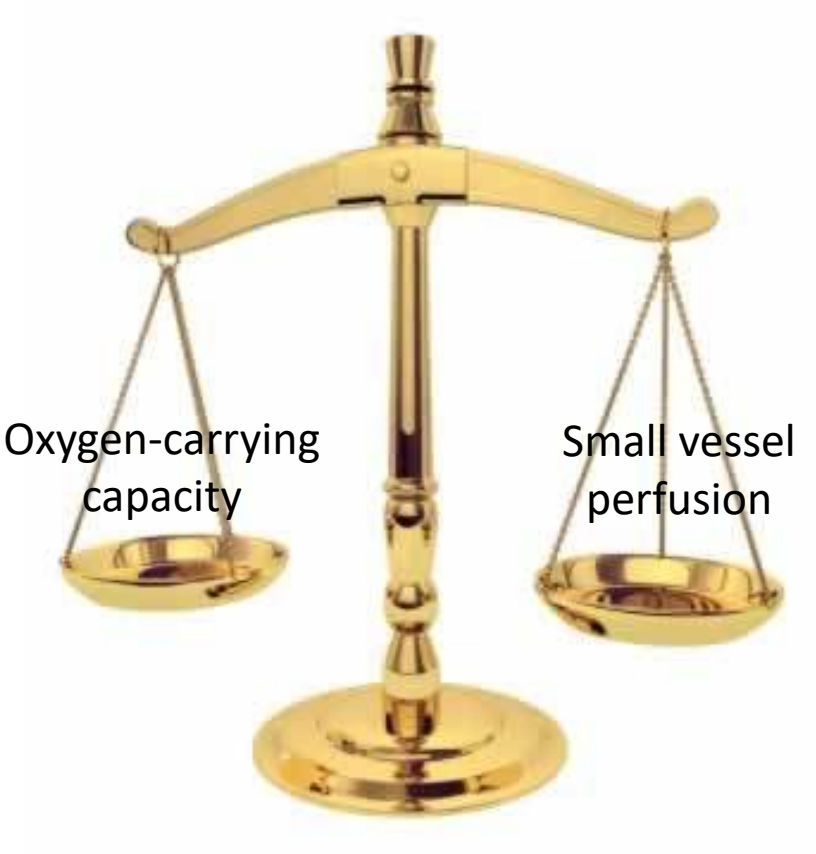
21 year old female with vaso-occlusive crisis and Hgb 70g/L

20 month old girl going for cholecystectomy with Hgb 80g/L

38 year old female with acute chest syndrome requiring mechanical ventilation



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

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

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

↓

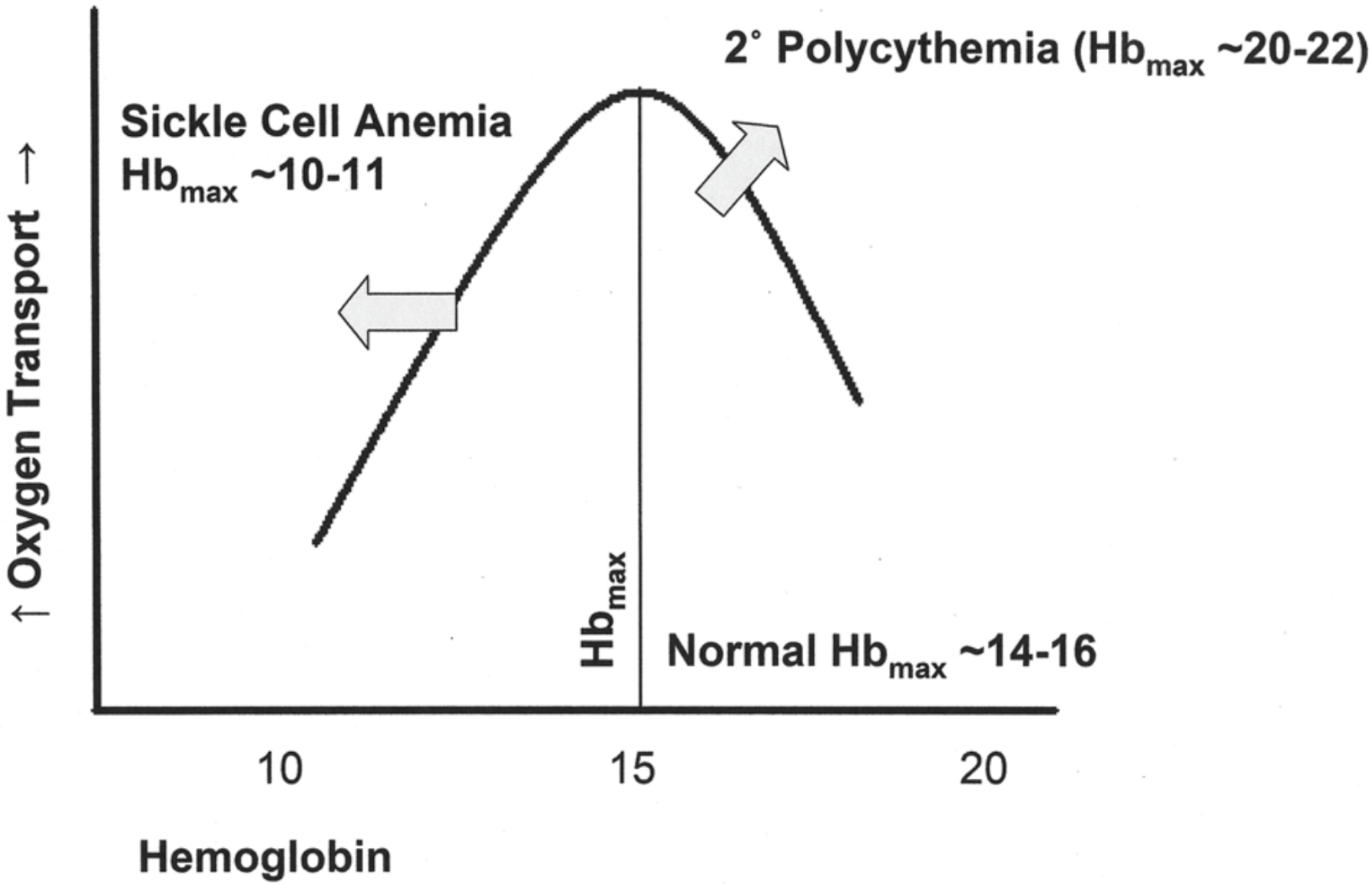
Predominantly determined by hematocrit

↓

Lower flow = lower oxygen delivery

↓

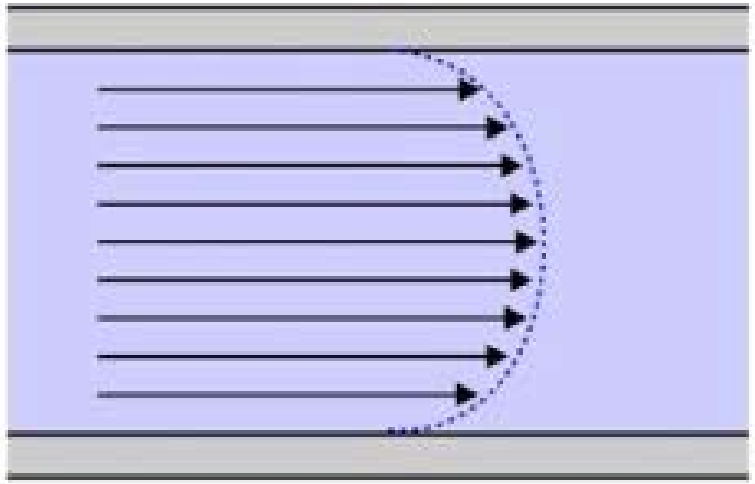
Higher Hgb = <u>Less</u> Oxygen Delivery



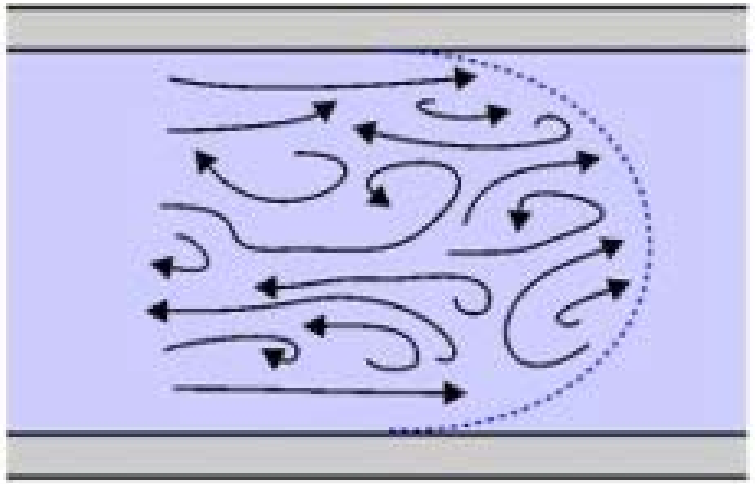
Swerdlow, Hematology Am Soc Hematol Educ Program. 2006;48

Factoring in Fluid Dynamics

- Blood is a shear-thinning fluid
- In post-capillary venules, as shear stress drops and flow becomes more turbulent, blood viscosity increases significantly due to cell-protein interactions



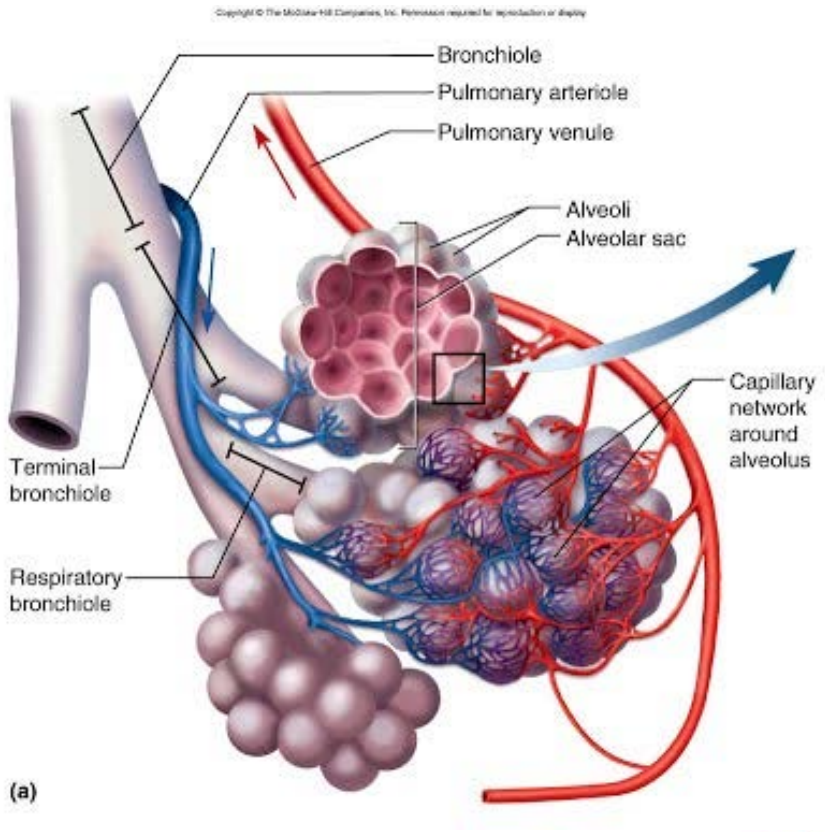
High-shear stress (arterioles)
= laminar flow



Low -shear stress (venules)
= turbulent flow

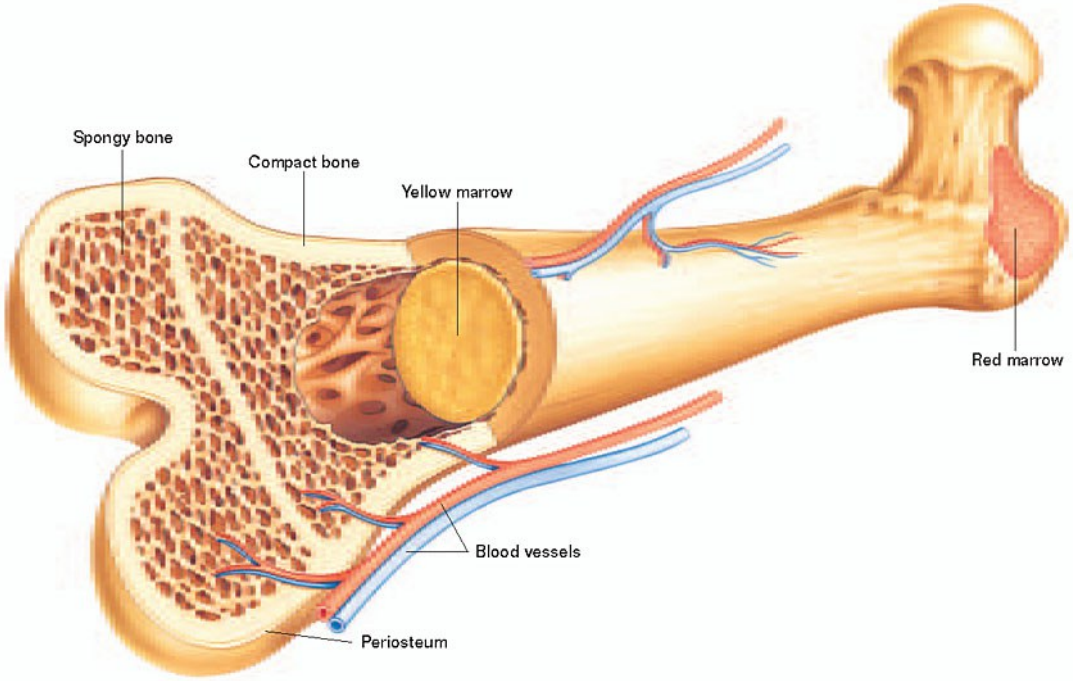
Implications of Viscosity Studies

- In vascular beds with high shear (eg., brain, lungs), oxygen delivery may be optimized by transfusion, but there is likely little benefit and possibly harm of exceeding a Hgb of 100-110 g/L
- This would suggest that transfusing may be helpful to treat ischemic stroke or acute chest syndrome
- Greatest benefit achieved by replacing viscous sickle blood with non-viscous donor blood (eg., decreasing the HgbS%)



Implications of Viscosity Studies

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



Rules of Thumb

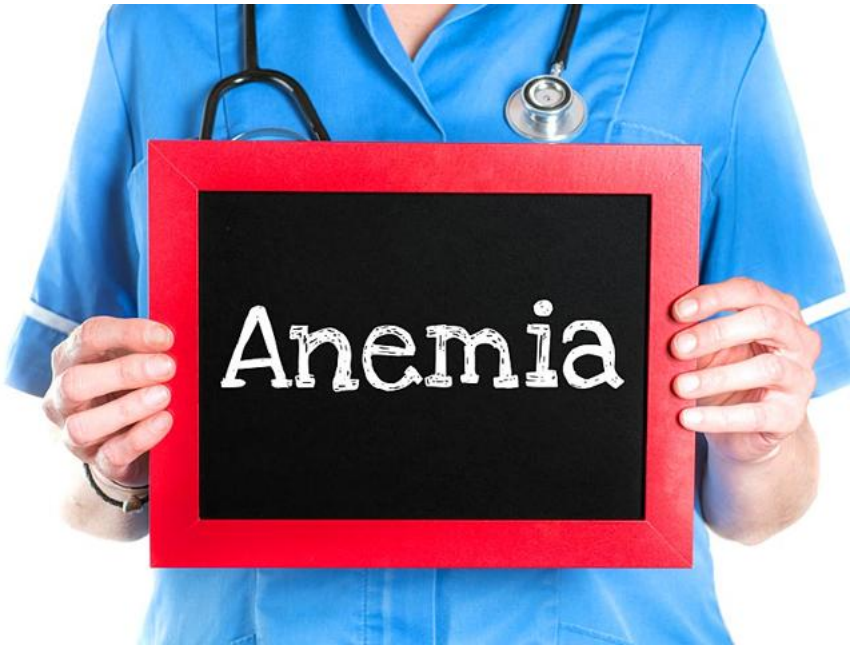
1. In most cases, the benefits of transfusing a patient with sickle cell disease will come from decreasing the viscosity of their blood rather than by increasing the oxygen-carrying capacity
   - **Goal of transfusion is to decr HgbS%, not incr total Hgb**
2. Transfusing a patient with sickle cell disease 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***

Learning objective #2:

Define accepted indications for RBC transfusion in sickle cell disease

https://www.blood.co.uk/news-and-campaigns/the-donor/the-life-changing-power-of-exchange-transfusions/

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)."

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 (parvovirus 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)
- As fall in hemoglobin occurs over days, plasma volume has time to increase in compensation
- Transfusions therefore risk volume overload; administer slowly and consider prophylactic diuretics

Smith-Whitley, Blood 2004;103:422

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
- If untreated, can cause death from hypovolemic shock/anemia; hepatic sequestration rarer and less severe
- ~25% incidence in pts with sickle cell disease, most common first 2 years of life, very rare after puberty
- Goal of transfusion is to buy time for splenectomy
- Post-transfusion hemoglobin levels often higher than expected, suggesting *autotransfusion*: sequestered RBCs released back into circulation.
- Transfusions therefore risk hyperviscosity; use small volumes

Owusu-Ofori, Cochrane Database 2002; CD003425.

Hyperhemolysis

- Defined as a rapid hemoglobin decline to below pretransfusion level, accompanied by rapid decline of posttransfusion HbA%
- Cases typically present as fever and pain 5-10 days after transfusion, with rapid fall in hemoglobin observed shortly after
- One third of cases have no evidence of serologic incompatibility

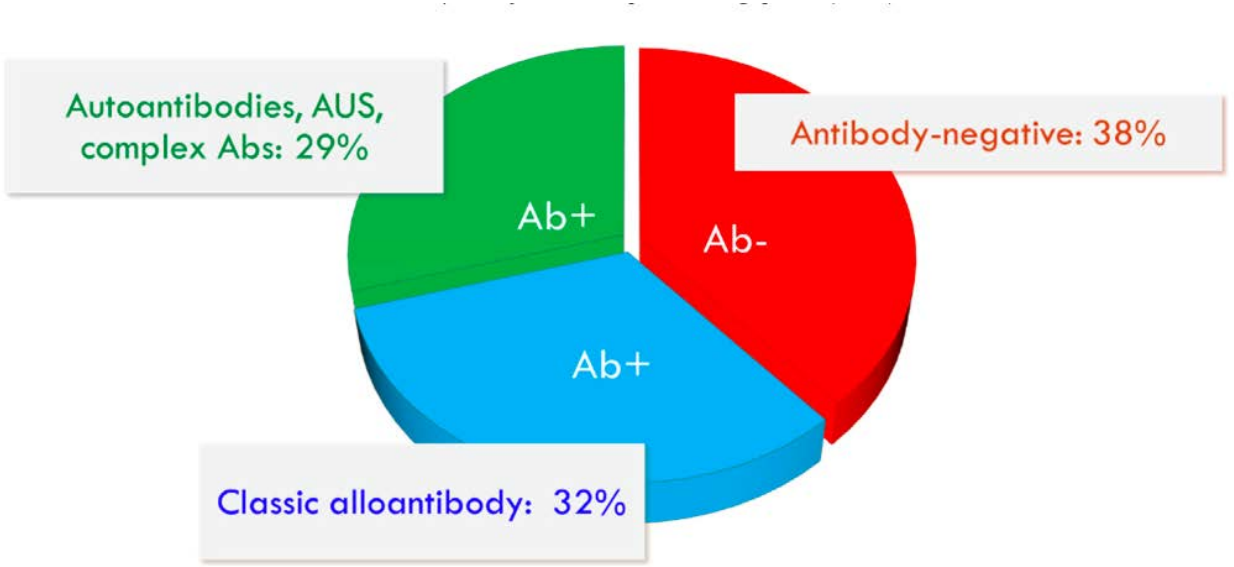
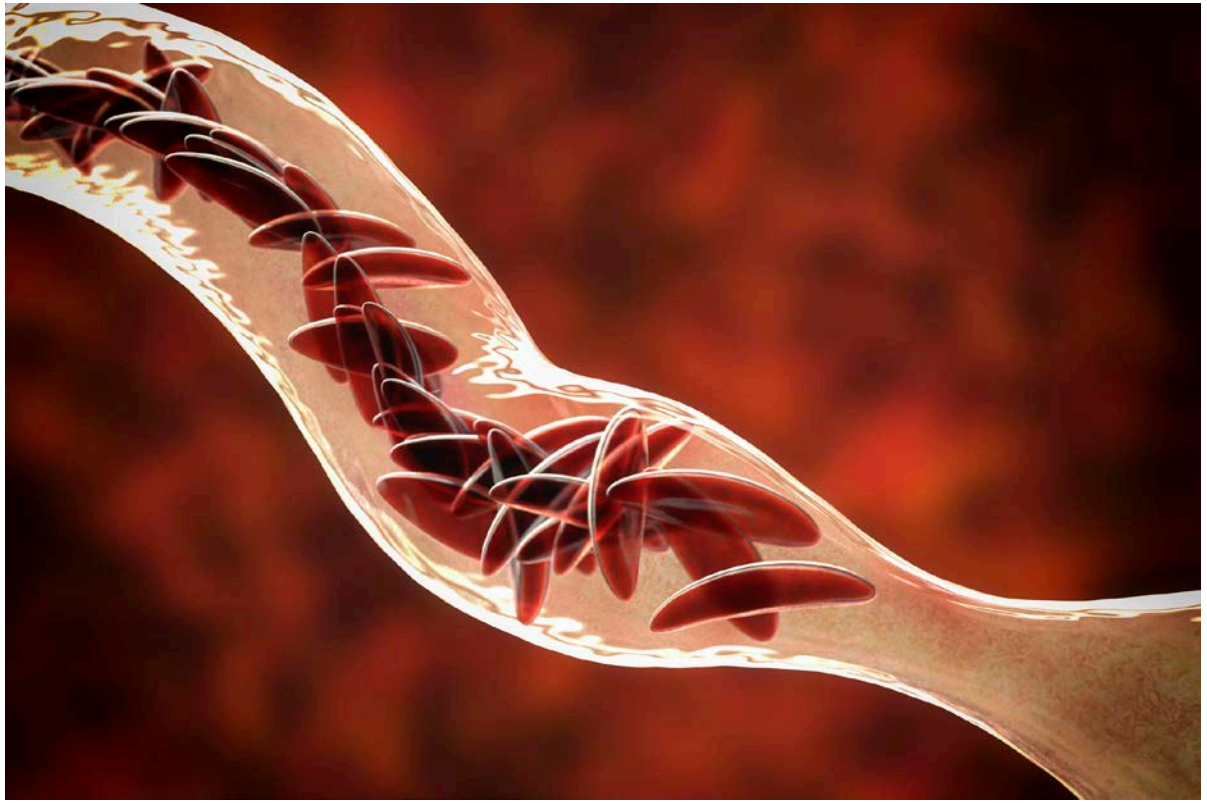


Figure 2. Immunohematological Characteristics of DHTRs in patient with SCD.

Fasano, Transfusion Clinique et Biologique 2019;26:94

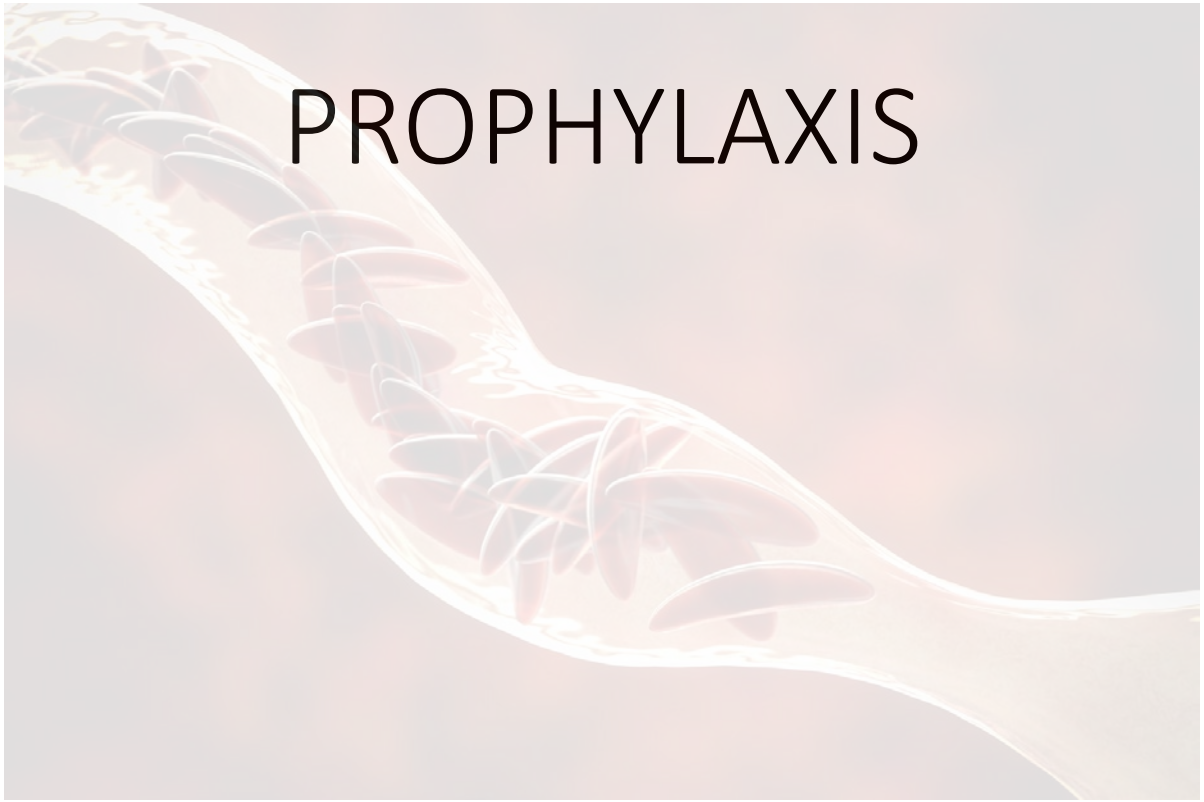
Transfusing to Decrease Whole Blood Viscosity



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

Pregnancy

- Single RCT performed 30+ years ago concluded that initiating a chronic transfusion program for a pregnant HgbSS patient will:
  - Have no effect on fetal outcomes
  - Decrease incidence of sickle complications in the mother
- However, many caveats:
  - Underpowered (only 36 patients each arm)
  - Sickest patients excluded (eg., chronic disease of brain, kidney, liver, lung, or coagulation)
  - Transfusions started relatively late in first trimester (ie., too late to prevent placental insufficiency)
  - Incidence of neonatal abstinence syndrome not reported

Koshy, NEJM, 1988;319:1447

Perioperative

- Landmark 1995 RCT showed no difference in perioperative outcomes between HgbSS patients randomized to
  - “Conservative” transfusion: Hgb maintained at 90-110 g/L
  - ”Aggressive” transfusion: HgbS maintained at < 30% and total Hgb 90-100 g/L
- However, even though all procedures were low-moderate risk, and all patients received careful supportive care, post-operative complications still occurred in both arms
  - 10% risk of acute chest syndrome, 11% of which required intubation, typically on post-op day 3

Vichinsky, NEJM 1995;333:206

Perioperative

- TAPS Trial: Patients with HgbSS/Sß^0 undergoing low-moderate risk surgery randomized to two different perioperative transfusion strategies
  - 33 pts to supportive care only (no transfusion)
  - 34 pts to pre-op transfusion within 10d of procedure: top-up if Hgb < 90 g/L, partial exchange if Hgb > 90 g/L (goal of HgbS < 60%)
- 81% mod risk (eg., cholecystectomy, joint replacement), 19% low risk (eg., adenoidectomy, inguinal hernia repair)

Howard, Lancet 2013; 381: 930

Perioperative

- Trial stopped early due to increased rate of serious adverse events in untransfused arm (33% vs 3%)
  - Most significantly acute chest syndrome: 9/33 in untransfused, 1/34 in transfused
  - Only 1 patient developed acute chest syndrome after low-risk surgery
- Median time to post-operative complications = 2.5 d
- Of patients in untransfused arm, 12% were transfused intraoperatively anyway, another 27% post-operatively (most for sickle complications, e.g. ACS)

Howard, Lancet 2013; 381: 930

Perioperative

- Surgeries without pre-op transfusion complicated by post-operative acute chest syndrome (9 of 33 patients)
  - Adenoido-tonsillectomy (3)
  - Laparoscopic cholecystectomy (2)
  - Tonsillectomy (1)
  - Laparoscopic splenectomy (1)
  - Umbilical hernia repair (1)
  - Shoulder arthroplasty and subacromion decompression (1)
- A 10th patient developed intra-operative bleeding requiring conversion of laparoscopic to open cholecystecomy, followed by acute chest syndrome
- 2/10 patients required ICU admission

Howard, Lancet 2013; 381: 930

Perioperative

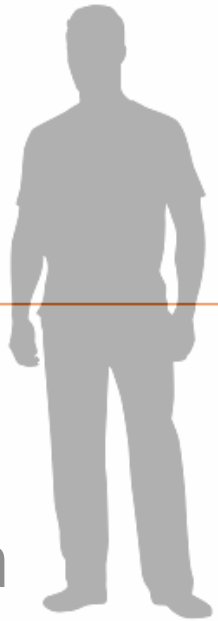
Risk	Example	Pre-op transfusion
Low	• Skin, eyes, nose, ears, dental • Distal extremities • Perineal, and inguinal areas	Not required
Intermediate	• Abdominal or orthopedic procedures • Oropharyngeal procedures	Top-up transfusion to 100 g/L (approx HgbS 60%); exchange if Hgb > 90g /L
High	• Intracranial, 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

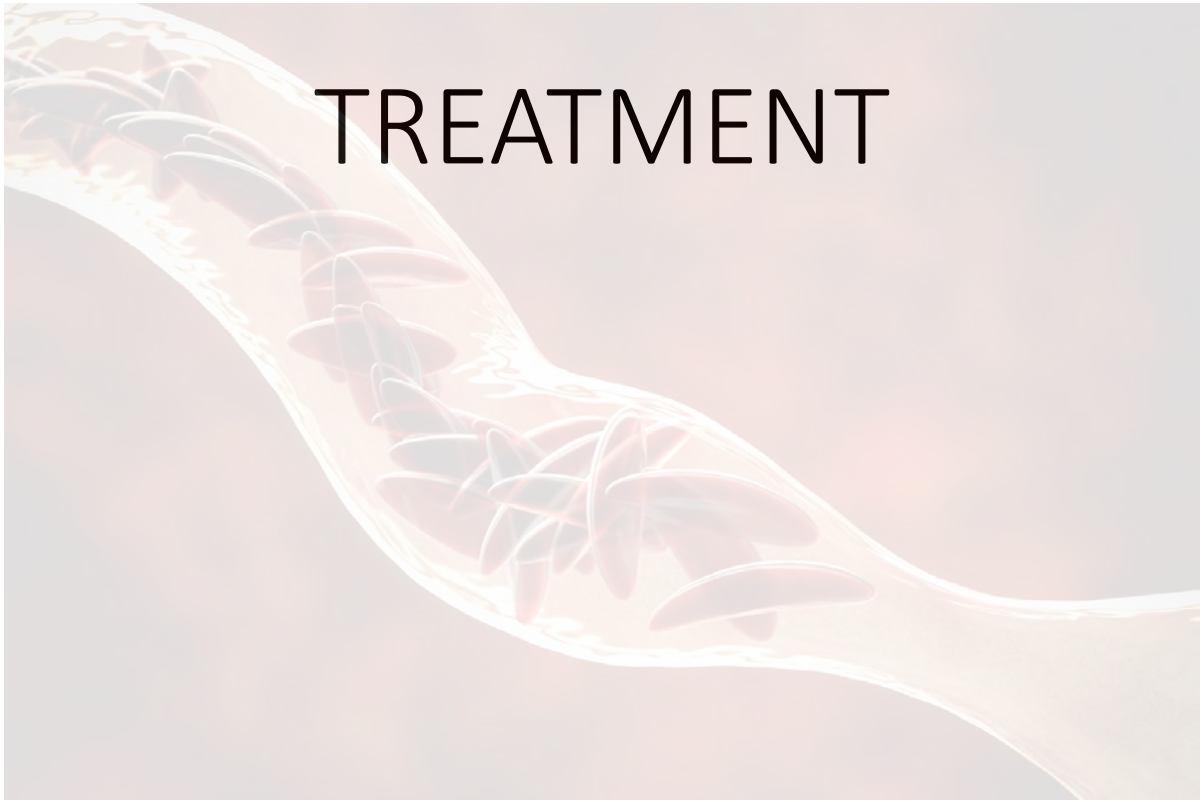
Adams, NEJM. 1998;339:5
Adams, NEJM. 2005;353:2769
Ware, Blood. 2012;119:3925
DeBaun, NEJM. 2014;371:699
Ware, Lancet. 2016;13;387

Stroke prevention



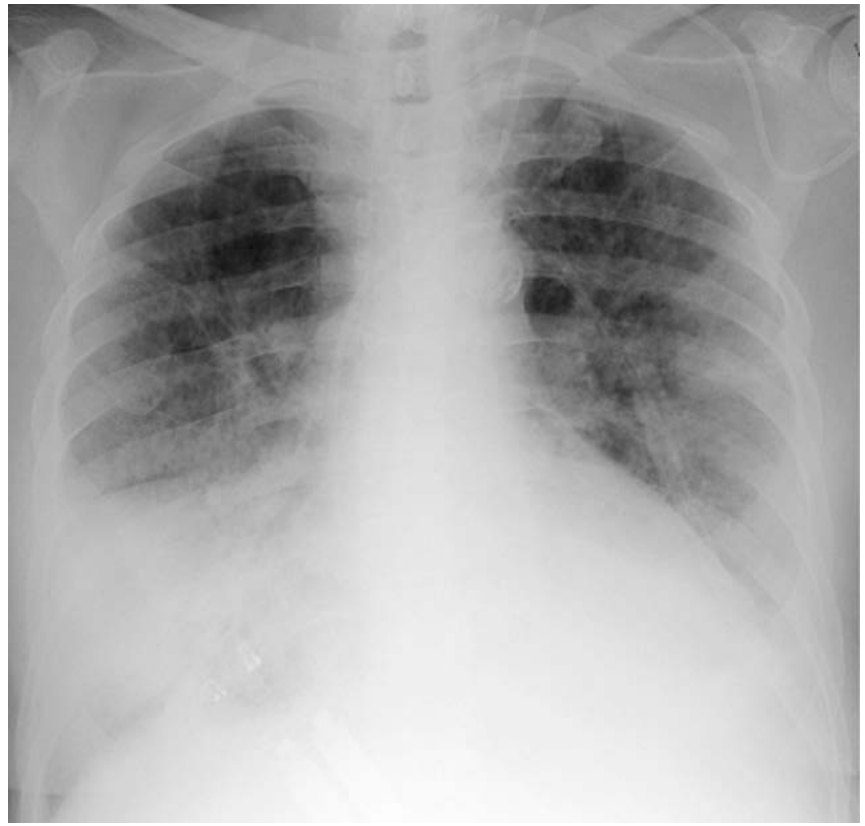
- In adults with sickle cell disease, very little evidence to base practice on
- If no obvious other explanation (eg., vasculopathy apparent on angiogram and no evidence of cardio-embolism) usual practice is to initiate chronic transfusion support following new onset symptomatic stroke
  - With first presentation of *ischemic* stroke, transfusion should be initiated within 2 hours
  - With *hemorrhagic* stroke, may be prudent to wait until bleeding has stopped before initiating transfusion

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

- Largest observational study of 671 episodes noted[1]
  - 72% of pts received transfusions, ~2/3 of them top-up transfusions
  - Transfusion associated with improvement in gas exchange (PO_2 68 ➔71 mmHg and SpO_2% 91% ➔94%)
  - Simple and exchange transfusions resulted in “similar” improvements (data not shown)
- However, an earlier case series reported that 40% of patients referred for exchange transfusion for ACS had failed earlier attempt at top-up transfusion.[2]

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

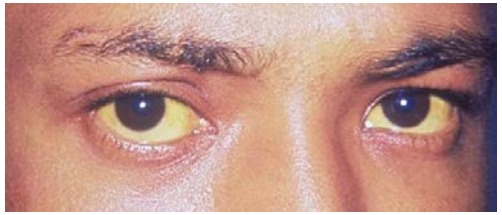
Acute Chest Syndrome

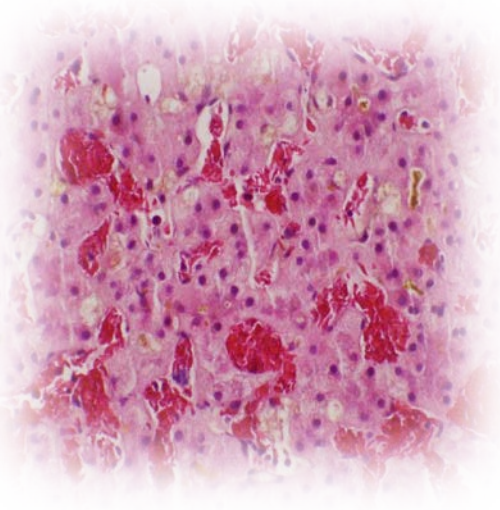
- In absence of RCT evidence, guidelines recommend transfusions for all but mildest cases, and exchange transfusions for patients with poor prognostic markers

  - 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 vent 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

Other Indications for Therapeutic Transfusion

- Sickle cell intrahepatic cholestasis (sickle hepatopathy)
  - 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

Other Indications for Therapeutic Transfusion

- In absence of good evidence, many advocate transfusion for specific complications only if standard-of-care, non-transfusion approaches have failed:
  - *Priapism*: voiding, hydration, analgesics, heat, vasodilators, aspiration/irrigation, adrenergic agents. Beware of ASPEN syndrome (Association of SCD, Priapism, Exchange transfusion, and Neurologic events)
  - *Malleolar ulcers*: wound care, antibiotics, compression stockings
  - *Proliferative retinopathy*: phototherapy, cryotherapy, vitrectomy, scleral buckling
  - *Avascular necrosis*: physiotherapy
  - *Renal dysfunction*: ACE-I
  - *Pulmonary hypertension*: vasodilators (confirm pre-capillary cause)
- Hydroxyurea and/or phlebotomy should also be considered for the above and may be safer than transfusion

"What's the takeaway on all this?"

Overview of Transfusion Indications

Generally Accepted

- 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

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

With regard to transfusion of patients with sickle cell disease, which is true?

Unlike patients transfused for thalassemia, SCD patients are not at risk of developing iron overload

Transfusion triggers are the same for patients with and without sickle cell disease

Delayed haemolytic transfusion reactions are common unless phenotypically matched blood is provided

Units for transfusion should be irradiated

Alloantibody development occurs rarely in the transfused SCD patient.

Learning objective #3:

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

Prevention of Alloimmunization

- Approx 25% of patients with SSD will become alloimmunized from transfusion
- Traditionally assumed to represent differences in antigen expression between typical donor and sickle cell patient
- Context of transfusion appears to be important as well (eg., higher risk with intermittent vs chronic transfusion)

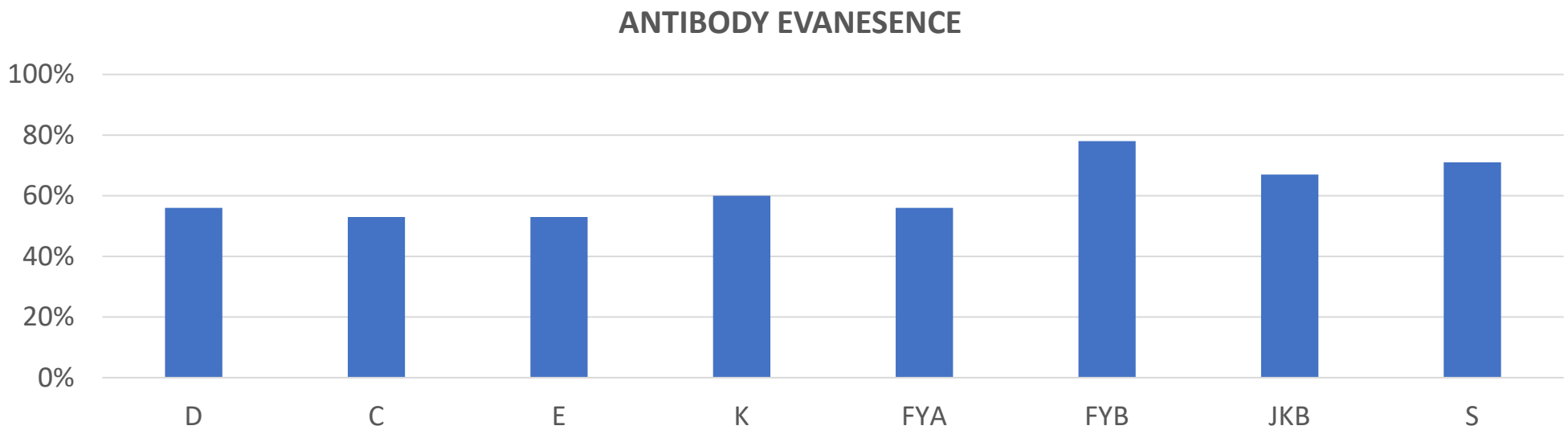
Table 3. Average Frequencies of RBC Alloantibodies Made By Transfused Patients With SCD

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

Prevention of Alloimmunization

- Over 80% of sickle patients with alloantibodies will test negative for that antibody at least once
- Episodic transfusions in different hospitals increases risk of DHTRs and hyper-hemolysis
- Prophylactic matching therefore important

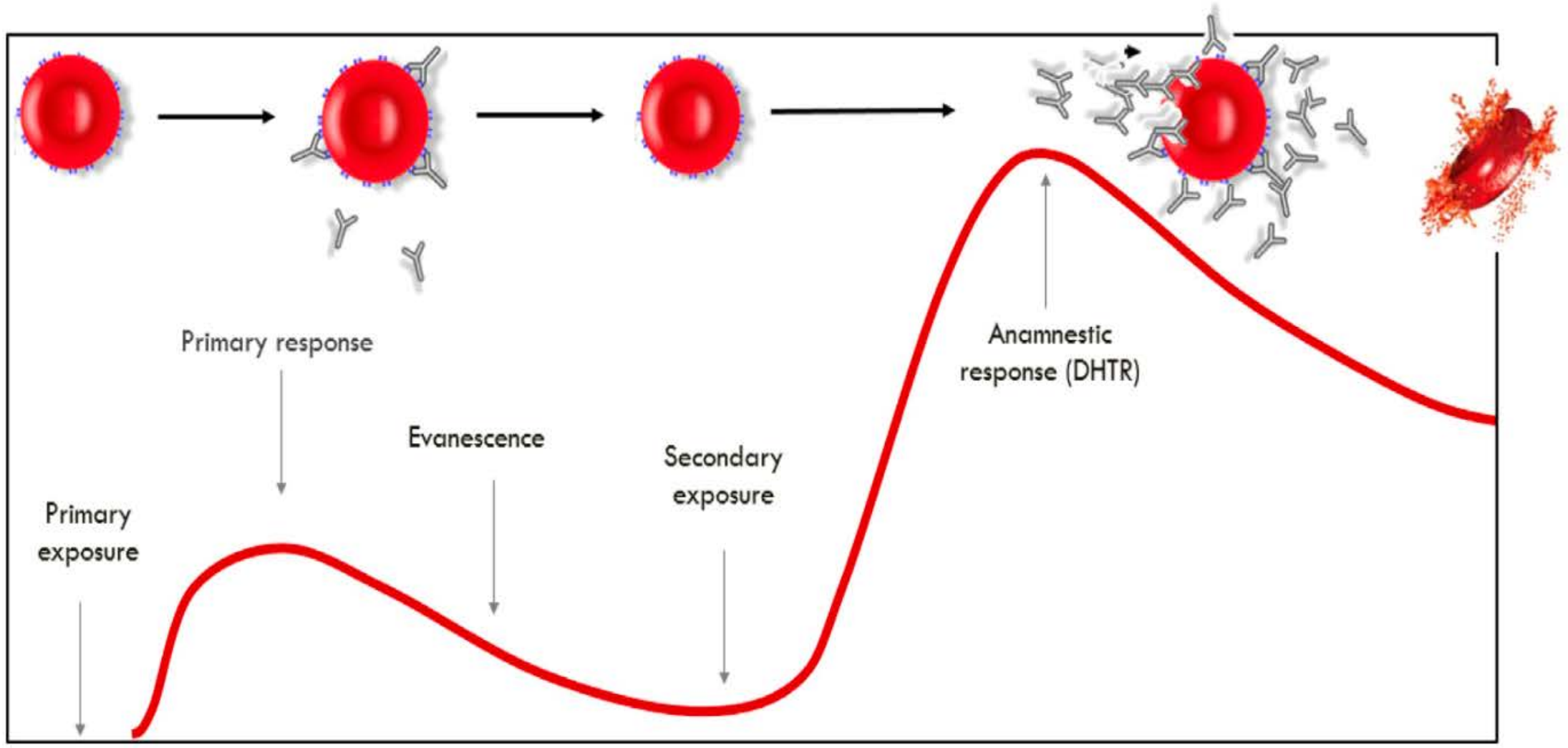


Williams, South Med J. 2016 Sep;109:588

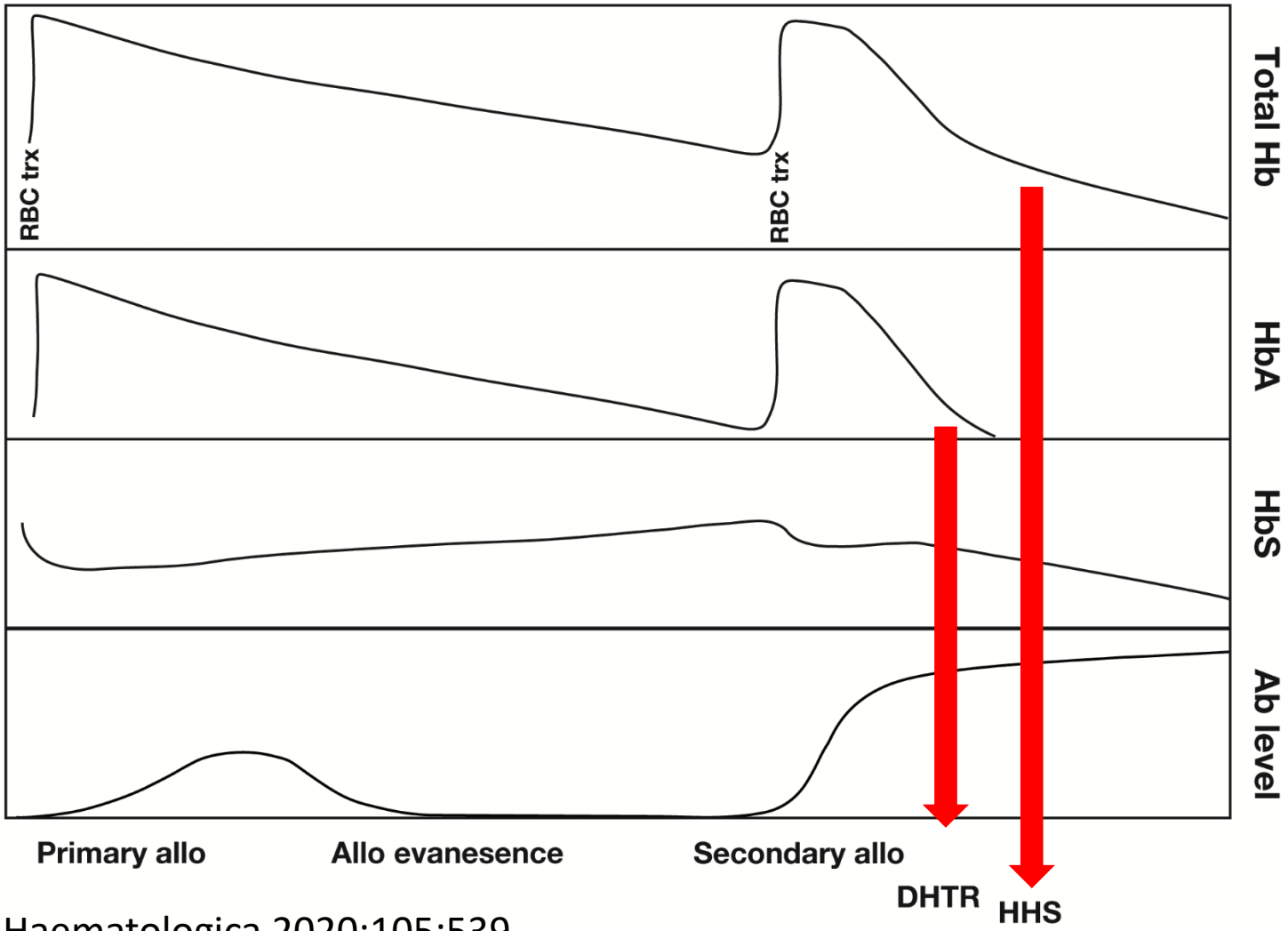
Reasons for Failure of Prophylactic Matching

- Laboratory/transcription error in phenotype of either donor or recipient
- Failure to notify blood transfusion service of patient diagnosis
- Inability to source antigen-typed units for urgent transfusion
- Genotype/phenotype discrepancy (eg., partial Rh antigens)

Delayed Hemolytic Transfusion Reactions



Hyperhemolysis



When **total** hemoglobin falls below pre-transfusion levels, suggests an accompanying fall in autologous HgbS cells, indicating hyperhemolysis

With sickle cell disease, a delayed hemolytic transfusion reaction is best indicated by rapid fall in HgbA cells

In either case, an anamnestic antibody response not always observed

Thein, Haematologica 2020;105:539

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 reticulocytopenia
- In cases accompanied by acute organ failure, or if first line therapy has failed, current guidelines now recommend adding
  - Eculizumab (to interrupt complement-mediated lysis)
  - Rituximab (to prevent further antibody formation if rescue transfusion required)
- Once diagnosed, hyperhemolysis is a relative contraindication to all future transfusions

ASH, Blood Adv. 2020;4:327

Hyperhemolysis

1. Perform HgbEP within 48 hours following every RBC transfusion
   - Especially important in patients only transfused episodically
2. Repeat both a group and screen and HgbEP with every subsequent presentation with VOC symptoms, symptomatic anemia or dark urine during the next 25 days
3. If >30% decrease in post-transfusion Hgb, or > 50% decrease in HgbA% observed, admit to hospital

In one study, even with prophylactic matching, this protocol revealed a 4.2% incidence of DHTR following episodic transfusion, 35% without new antibodies, and an overall mortality rate of 11.5%

Narbey, Am J Hematol. 2017;92:1340

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***
- Genotyping of donors allows for more careful selection of RBCs than traditional phenotyping and should be performed in all patients

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**

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