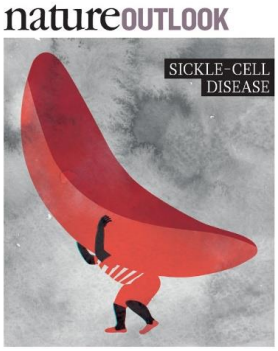

Transfusion Strategies in Sickle Cell Disease: Making Every Unit Count

Courtney E. Lawrence, MD, MS

American Red Cross

June 22nd, 2022 HAABB 2022 HAABB Virtual Summer Meeting

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Disclosures

I have no relevant financial or nonfinancial relationships to disclose.

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Objectives

- Transfusion pathophysiology in sickle cell disease
- Indications for transfusion therapy in SCD
- Benefits and risks of different modalities of transfusion
- Evidence for transfusion goals and procedure parameters
- Current challenges in meeting these goals
- Dual role of transfusion medicine specialists

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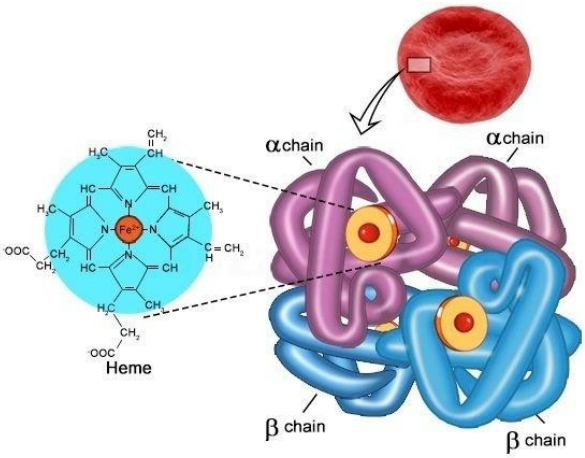
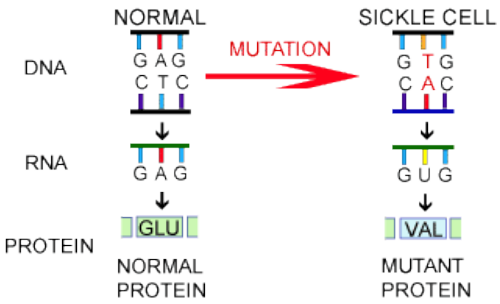
Sickle Cell Disease: Hgb S





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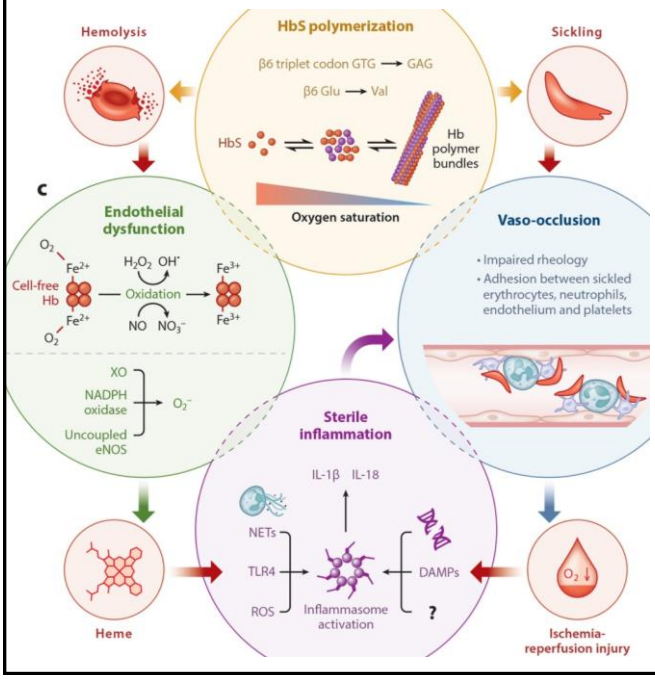

Deoxygenation → Hgb S polymers

RBCs have decreased deformability

<u>Consequences</u>

- Hemolysis → Anemia
- Vasoocclusion: obstruction of blood flow
- Blood vessel dysfunction
  - Free heme
  - Sickle damage
  - Inflammation

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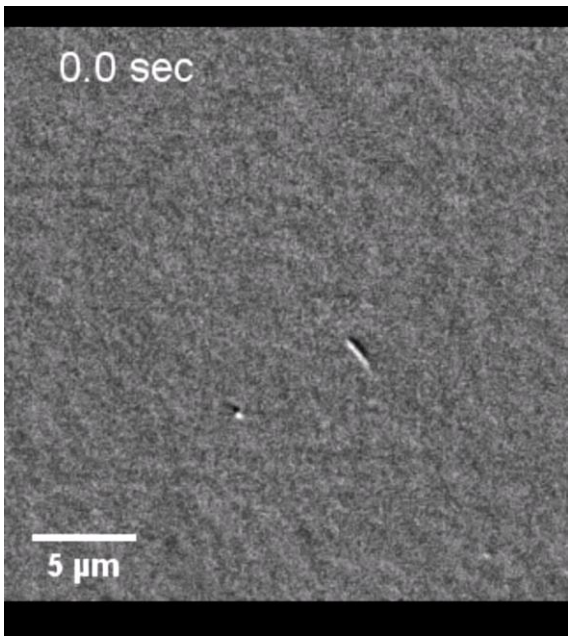

Castle BT, Odde DJ, and Wood DK. Sci Adv 2019 March 13; 5(3): eaau1086

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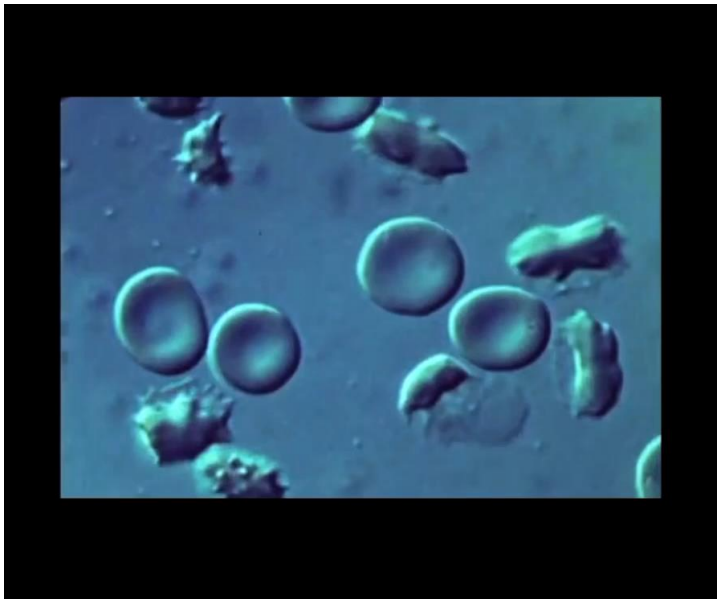

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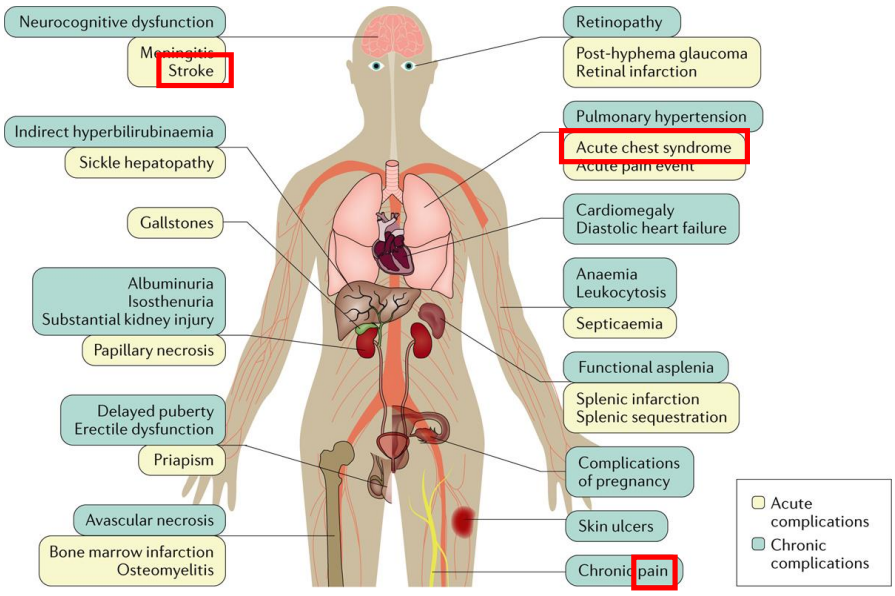

Kato, G. J. et al. (2018) Sickle cell disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2018.10

Nature Reviews | **Disease Primers**

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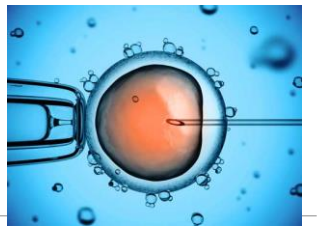
Future of Sickle Cell Disease?

- Preventative
  - Preimplantation testing and embryo selection
- Curative
  - Bone marrow transplant
  - Gene therapy



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Hydroxyurea As A Mainstay Therapy

- Increases fetal Hgb (Hgb F) in RBCs → resist sickling
- Suppression of bone marrow → lower white blood cell count
- Decreases hospitalizations, episodes of painful VOC, acute chest syndrome, number of transfusions needed
- Decreases mortality in children and adults
  - In adults, seen after 5-10 years of treatment
- Generally low side effect profile
  - Fertility concerns

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Emerging SCD Therapies

- Newer therapies:
  - Crizanlizumab (Advakeo)
  - Voxeletor (Oxbryta)
  - L-glutamine (Endari)
- Clinical outcomes data is modest at best

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"We need to transfuse this patient with sickle cell disease…"

- What is the clinical indication?
- What are the goals of transfusion?
- What modality of transfusion is the best option?
- What procedural parameters should we set?

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Why Do We Transfuse?

- ↑ **Hgb** = ↑ O2 carrying capacity of the blood
  - To alleviate poor perfusion to organs
  - To decrease intolerable symptoms of anemia
  - To decrease demand on the heart
- **Dilution of sickle cells → reduce vasoocclusion**
- **Suppress patient's own RBC production***

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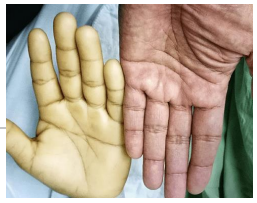
Considering the Effect of Anemia

- Tolerance of anemia? Depends on medical conditions.
- Body finds ways to compensate for anemia over time
  - Heart: Increases stroke volume (heart rate & contractility)
  - Increased red cell production
  - Vasoconstriction to divert from non-critical organs
- Intolerance of stressors (exercise, illness)
  - Fatigue, shortness of breath



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Goals of Transfusion

- Increase total hemoglobin/hematocrit
  - **Hgb 10 – 12 g/dL (Hct 30 – 36%)**
  - Avoid too high (blood gets viscous)
- Decrease number of patient's own sickle RBCs
  - **Hemoglobin S <30% for critical illness**
  - Diluting them out or taking them out
  - Taking them out

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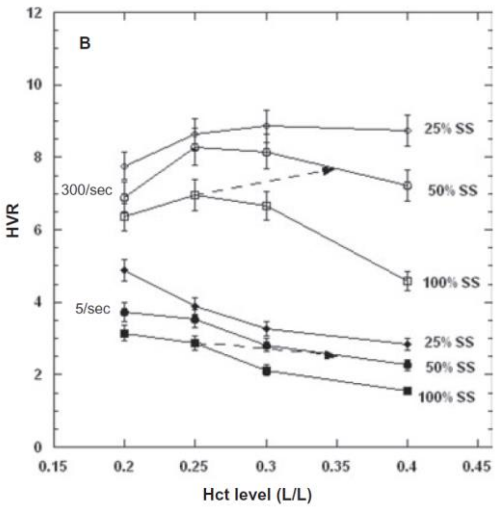
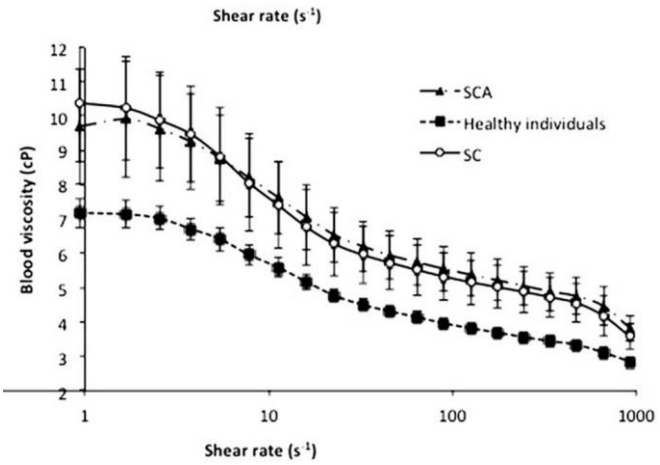
Viscosity Is A Limiting Factor



Alexy et al. 2006. Transfusion



Connes et al. 2016. Blood Rev

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Does This Patient Need A Transfusion?

- Right now?
  - Acute end organ compromise
    - Vasoocclusion, Hypoxemia
  - Acute drop in hemoglobin ***resulting in symptoms of anemia***
  - Impending risk/high risk of developing either

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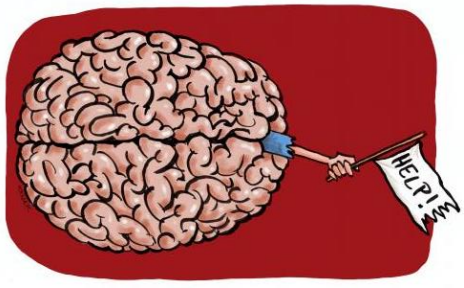
Indications For *Acute* Transfusion Therapy in SCD

Generally accepted indications

- Acute ischemic stroke
- Acute chest syndrome
- Acute splenic sequestration
- Acute hepatic sequestration
- Acute intrahepatic cholestasis
- Aplastic crisis
- Multisystem organ failure
- Pregnancy complications
- Pre-operative

Not generally accepted

- Painful vasoocclusive episode
- Priapism



Adapted from: Chou, Fasano. 2016. Hematol Oncol Clin N Am.

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Does this patient need *regular* transfusions?

- On-going risk for acute complications
  - Stroke history
  - Suboptimal response from other medical therapies
- Persistent symptoms from chronic anemia

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Indications For *Chronic* Transfusion Therapy in SCD

Generally accepted indications

- Primary stroke prevention
- Secondary stroke prevention
- Recurrent acute splenic sequestration until splenectomy*

Individualized indications

- Recurrent acute chest syndrome
- Recurrent painful vasoocclusive crises or chronic pain
- Pulmonary hypertension
- Pregnancy without complications
- Recurrent priapism

Adapted from: Chou, Fasano. 2016. Hematol Oncol Clin N Am.

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Major Clinical Trials for Transfusion in SCD

Transfusion parameters

- Total Hgb > 9 g/dL pretransfusion
- Hgb S <30% pretransfusion

Primary Stroke Prevention

- STOP: Tx after abnormal TCD
- STOP2: Tx after normalization of TCD
- TWITCH: HU vs. tx after 1 y

Secondary Stroke Prevention

- SWITCH: HU vs. tx after overt stroke

Silent Cerebral Infarct

- SIT: 3 yr tx vs. obs

Chou. 2013. Hematol Am Soc Hematol Educ Program.

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Major Clinical Trials for Transfusion in SCD

Acute chest syndrome

- **NACSSG: Acute management in adults >20 yo**
- STOP: Pediatric patients, not primary outcome
- Hydroxyurea?: BABY HUG, Multicenter Study of HU

Preoperative management

- **TAPS: Transfusion vs. no transfusion before low-med risk surgery**
- The Preop Transfusion in SCD SG: Simple vs. aggressive transfusion

Pregnancy

- Prophylactic RBCs vs. prn transfusion only

Chou. 2013. Hematol Am Soc Hematol Educ Program. / Koshy et al. 1998. N Eng J Med. / Malinowski et al. 2015. Blood.

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Evolving Evidence

Recurrent VOC / Chronic Pain

- STOP, SIT, SWiTCH: secondary outcomes
- Hilliard (2018):
  - Simple transfusions, pediatric
  - Hgb S maintained at 30-50%
- Tsitsikas (2016-17):
  - Automated transfusions, adult
  - Average Hgb S ~44%
- Outcomes focus on hospitalization (inpatient, ER)

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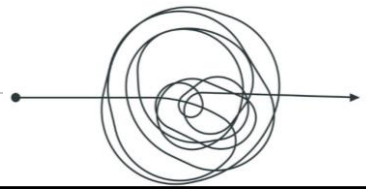
Do They Need An Automated Exchange?

- Simple transfusion
- Partial manual exchange transfusion
- Manual exchange transfusion
- Automated red cell exchange
- ***Limited data on picking the appropriate modality***



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When Can We Simple Transfuse?

- Symptomatic anemia
  - Hgb <9 g/dL
  - Avoid hyperviscosity
- Non-critical illness (no organ compromise, no rapid deterioration)
- Delay in exchange
- Available RBC units

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BBC, 2017, "**What it's like to be 17 and living with sickle cell disease**"

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Why Do An Automated Exchange?

Acute considerations:

- Achieve goal Hgb S and target Hgb/Hct quickly
- Avoid hyperviscosity
  - Once Hgb S consistently <30-50%, less of a concern
- Euvolemic

Long-term considerations:

- Poor Hgb S suppression with simple transfusions
- Iron neutrality

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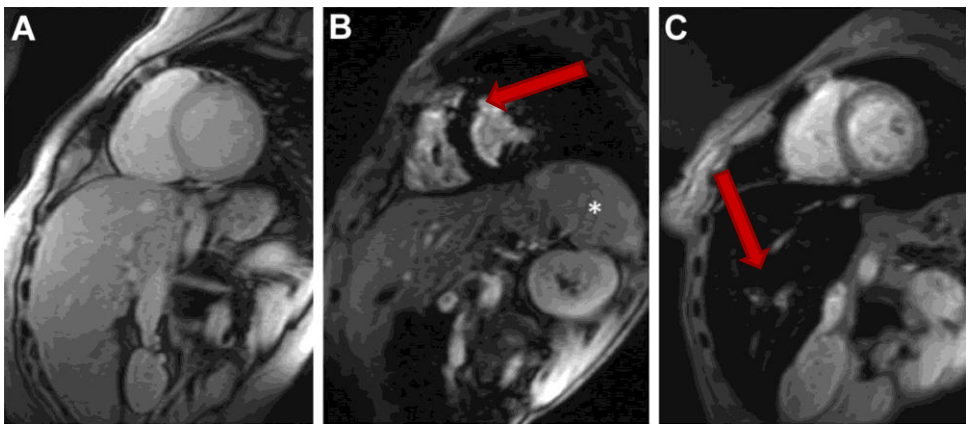
Iron Overload



Hoffbrand et al. (2012). Blood.

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Iron Burden

- Patients started on ARCE without iron overload generally do not become iron overloaded*
- Case series show decreased iron burden with ARCE
- Limitations
  - Not all studies reported the mean increment in Hgb or Hct
  - Those that did showed <1 g/dL Hgb increase, average pre-transfusion Hgb >9
  - Most were on concurrent iron chelation therapy

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Stanley et al. 2016. Ped Blood Cancer. / Fasano et al. 2016. Transfusion. / Kim et al. 1994. Blood. / Singer et al. 1999. J Clin Aph.

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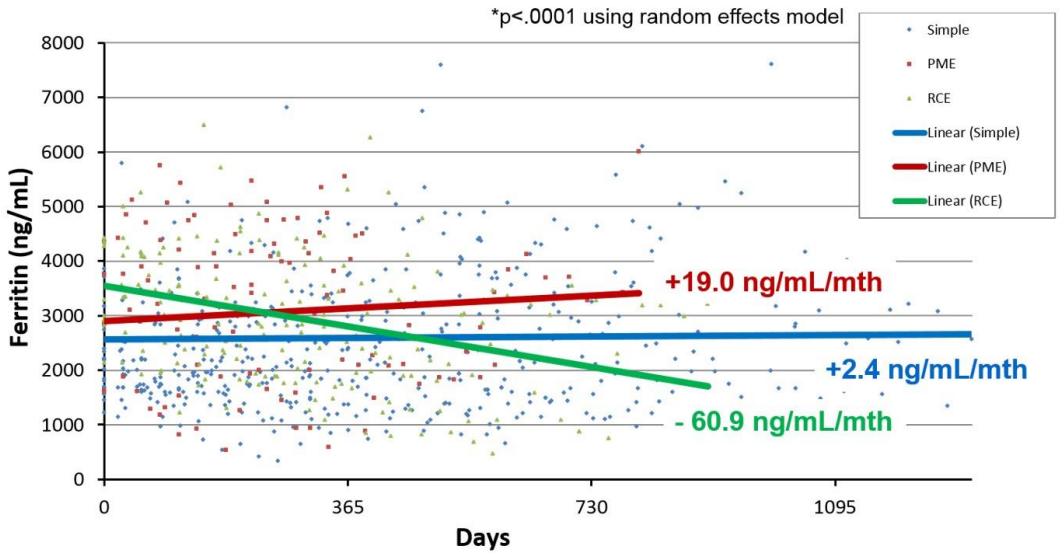

Fasano et al. 2016. Transfusion

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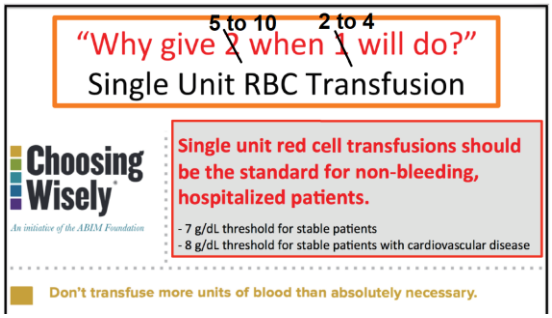
Challenges With Automated Exchange

- Procedurally related
  - Temporary or permanent central line
    - Infection, thrombosis
    - Bleeding, anesthesia risk
- Blood utilization
- Hospital resources
  - Specialty staff



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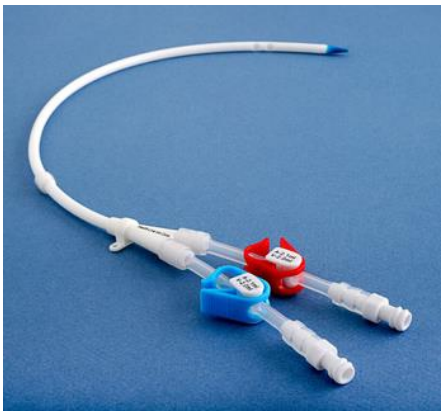
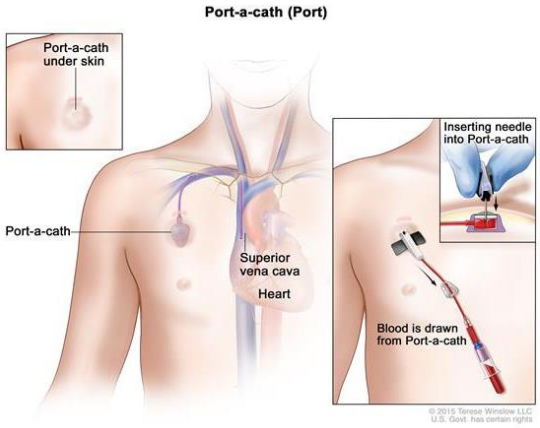
Line Access





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Dual Realities

- Patients with SCD and access to specialty care are living longer
  - More comorbidities, more vulnerable
  - Transfusion studies have focused on pediatric and younger adult populations
- Blood remains a finite resource
  - Need to access donors who are more likely to match our patients

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Where Can We "Stretch"?

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FCR → Goal Hgb S?

- Neuro risk patients: Hgb S <30%
  - Select patients may need lower
    - Recurrent events (moyamoya)
    - Cardiopulmonary bypass
  - Over time, patients may tolerate higher Hgb S
- ….everyone else?
  - Increasing evidence in some areas (e.g. pain) that Hgb S maintained 40-50% is impactful

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Goal End Hematocrit?

- Most clinical outcome studies: Hct >27-30%
- With exchange, low Hgb S can be achieved without relying on suppression
- Nifong: ARCE improved SpO2 without increase - or a decrease - in Hct (end Hct 23-27%)
- End Hct <30% ok for patients with low HgbS?
  - May lose some suppression effect – monitor Hgb S and interval

Nifong, Domen. 2002. Therapeutic Apheresis.

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Isovolemic Hemodilution

- Potential benefit:
  - ~ 1 unit RBCs saved
  - Or can improve the FCR with same volume
- Considerations
  - Can patient tolerate temporary Hct 3-6% decrease
    - Caution in patients who may be vulnerable to anemia
    - Acutely ill, cerebral vasculopathy
  - Limited case series data, focused on cost-savings
  - Challenges to monitoring safety & efficacy

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Patient with SCD: 5'10, 70 kg male with Hct 25%

• Goal Hct 30%	Goal Hct 25%
• FCR 30%: 2697 mL (8-9 units)	2459 (7-8)
• FCR 40%: 2053 (6)	1871 (5-6)
• FCR 50%: 1553 (5)	1415 (4-5)
• IHDepletion first to 20% prior to Exchange	
• FCR 30%: 2438 (7-8)	2215 (6-7)
• FCR 40%: 1855 (5-6)	1686 (5)
• FCR 50%: can't get to Hct	1275 (4)

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Finding The Right Target

- Risk:benefit of who receives exchange modality
  - Acutely: Very ill or at high risk
  - Chronically: Most vulnerable brains
  - Gray zone: Almost everyone else
- %Hgb S and total Hgb/Hct does not have proven precise correlation with most symptoms in sickle cell populations
  - Who can tolerate lower Hgb/Hct? Higher Hgb S?
  - Iron status, procedural tolerance are key factors long term
  - Are some patients candidates for simple transfusion?
  - Can we integrate newer therapies?

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Summary

- Patients with SCD are living longer with more complex medical needs.
- Transfusion remains a cornerstone of acute and chronic management.
- Limited clinical trials evaluating transfusion parameters in patients with SCD, particularly in adults.
- Limited resources (blood, staffing) do not make it feasible to select the most aggressive transfusion strategies (ARCE Hgb S<30% and Hct 30%) for all chronic transfusions.
- Limited published data is suggestive that good clinical outcomes are achieved with less aggressive transfusion strategies.
- We need **partnership** with our clinical colleagues!

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Thank you!

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