Sickle Cell Disease: To Exchange or Not to Exchange in the Setting of Acute Stroke

Andrew Jones, MD

April 2018

Objectives

- Review and apply the ASFA criteria for red cell exchange (RBCX) in acute stroke sickle cell patients.
- Discuss blood bank methods for rapid diagnosis of sickle cell disease.
- Discuss role of TPA and RBCX in the management of acute stroke, and optimal timing for RBCX.
- Explore calculation of replacement volumes in morbidly obese RBCX patients.

Presentation

- 34 year old African American woman
- Riding a bus with sudden left eye vision loss

History of HbSS Disease

- HbSS disease
  - Multiple prior crises
  - Avascular necrosis of bilateral hips (date unknown)
  - Several episodes of acute chest syndrome, requiring intubation
  - Prior transient L eye vision loss (4y ago)
  - Frequent pain crises
- Status post cavernous carotid fistula coiling

Additional History

- Morbidly obese (BMI: 50.9 kg/m^2)
- Recently moved from out of state to Sacramento, has not established care
- Last RBCX 1y ago

Next Steps?

- Admission and evaluation by neurology
- Imaging (MRI preferred)
- Maintain 0_2 above 95%
- IV NS at 1-1.5x maintenance rate
- Simple transfusion to raise Hgb to 10 g/dL
- Monitor blood pressure
- Evaluation for other causes (pneumonia, meningitis, sepsis, etc)

Uptodate. "Acute stroke in sickle cell disease." Mar 2018

Home medications

- Hydroxyurea
- Folate

Allergies

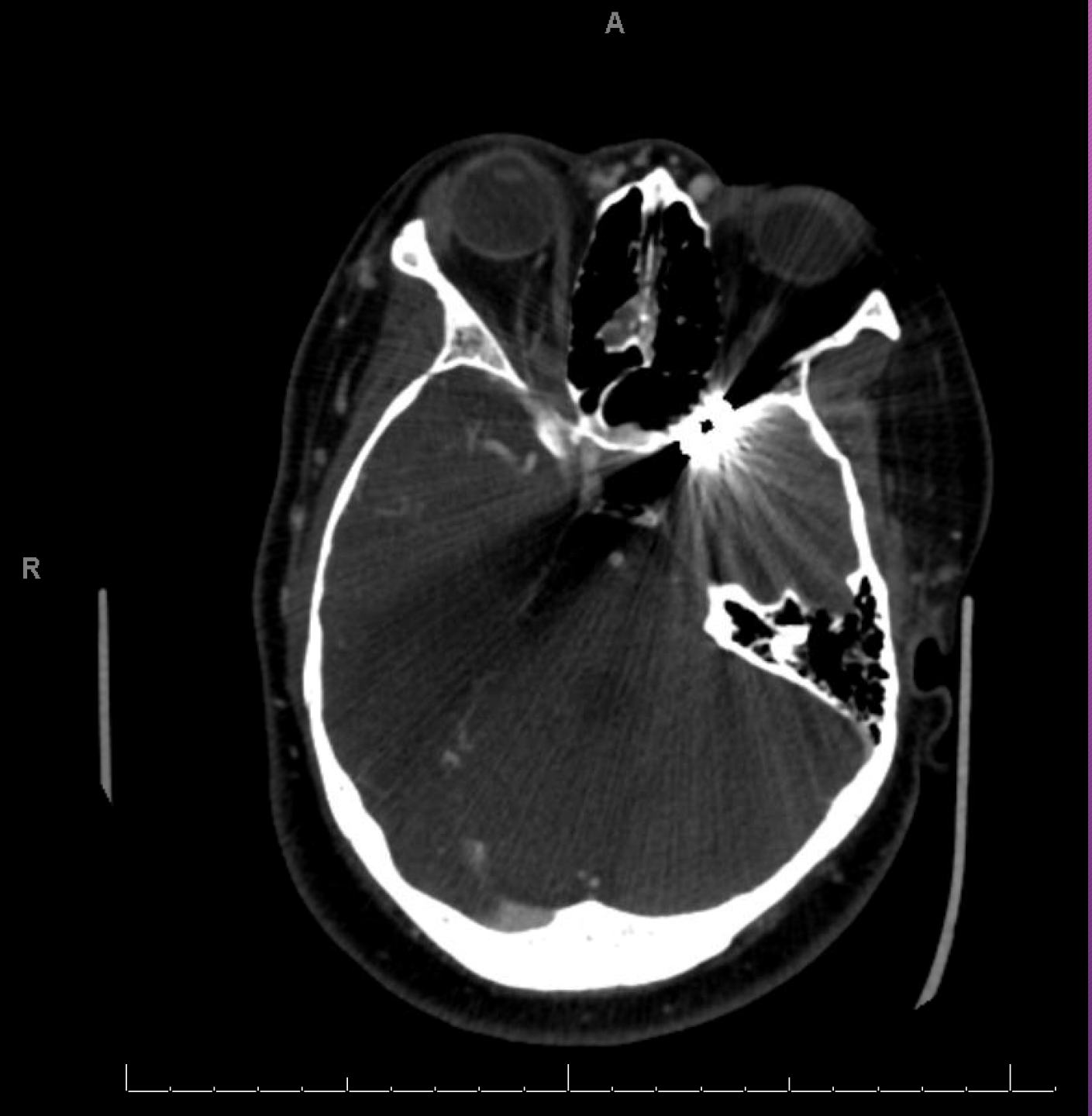
- Toradol (hives)
- Tramadol (hives)
- Morphine (hives)

Physical Exam

- Courtesy of Neurology:
  - CN 2: Pupils equal and reactive to light 3 =>2 mm OU slightly sluggish. Monocular vision tested. Visual fields intact to finger counting OD. No vision detected (peripheral or central) to finger counting, finger wagging, or to light OS. No intraocular hemorrhage visualized
  - CN 3 – CN 12: grossly normal

Imaging

- MRI contraindicated
- CTA Head:
  1. No acute infarct or hemorrhage.
  2. No high-grade stenosis or occlusion of the intracranial vasculature.
  3. Dilated left superior ophthalmic pain which drains into a dilated angular vein along the nasal ridge and facial vein more inferiorly. **Metallic artifact within the region of the left orbital apex likely correlates with prior treatment of the cavernous carotid fistula** and obscures evaluation of the adjacent cavernous sinus. Although, a dilated superior ophthalmic vein can be seen after carotid cavernous fistula treatment this finding is expected to decrease over time and comparison with outside studies is needed to assess for this interval change with is not currently available. A persistently dilated superior ophthalmic vein raises concern for persistent carotid cavernous fistula.



CT Angio

Next Steps

Pathogenesis of Hypercoagulability in HbSS

- Intrinsic
  - Increased platelet activation
  - Depletion of normal anticoagulant proteins
  - Increased expression of Tissue Factor
  - HbSC & HbSβ+thal > HbSS & HbSβ^{0}thal
  - Autosplenectomy
  - RBC membrane abnormalities
- Extrinsic
  - Increased hospitalizations
  - Indwelling catheters
  - Orthopedic surgeries / avascular necrosis
  - Pregnancy

Naik. *J Thromb Thrombolysis*. 35(3). 2013.
Noubouossie. *Blood Rev.* 30(4). 2016.

RBCX

- ASFA Category I (Grade 1C)

TABLE II. Category Definitions for Therapeutic Apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

ASFA Guidelines

Categories

Schwartz. *J Clin Aph.* 31. 2016.

TABLE III. Grading Recommendations Adopted from Guyatt et al. [4,9]

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

ASFA Guidelines

Grades

Schwartz. *J Clin Aph.* 31. 2016.

RBCX

- ASFA Category I (Grade 1C)
- Goal:
  - Reduce percentage of HbS to ≤ 30% of total hemoglobin
  - Total hemoglobin approximately but not greater than 10 g/dL

RBCX in HbSS Acute Stroke

Pros

- Treats underlying disease etiology
- Strong evidence
- Has role in prevention (Category 1 / Grade 1A)

Cons

- Requires high-throughput venous access
- Requires multiple RBC units
- Often requires antigen matching
- Extensive BB workup for new patients
- Delay in treatment
- Not available everywhere

Hulbert ML. *J Pediatr* 2006; 149:710.

Coexistent Sickle Cell Disease Has No Impact on the Safety or Outcome of Lytic Therapy in Acute Ischemic Stroke

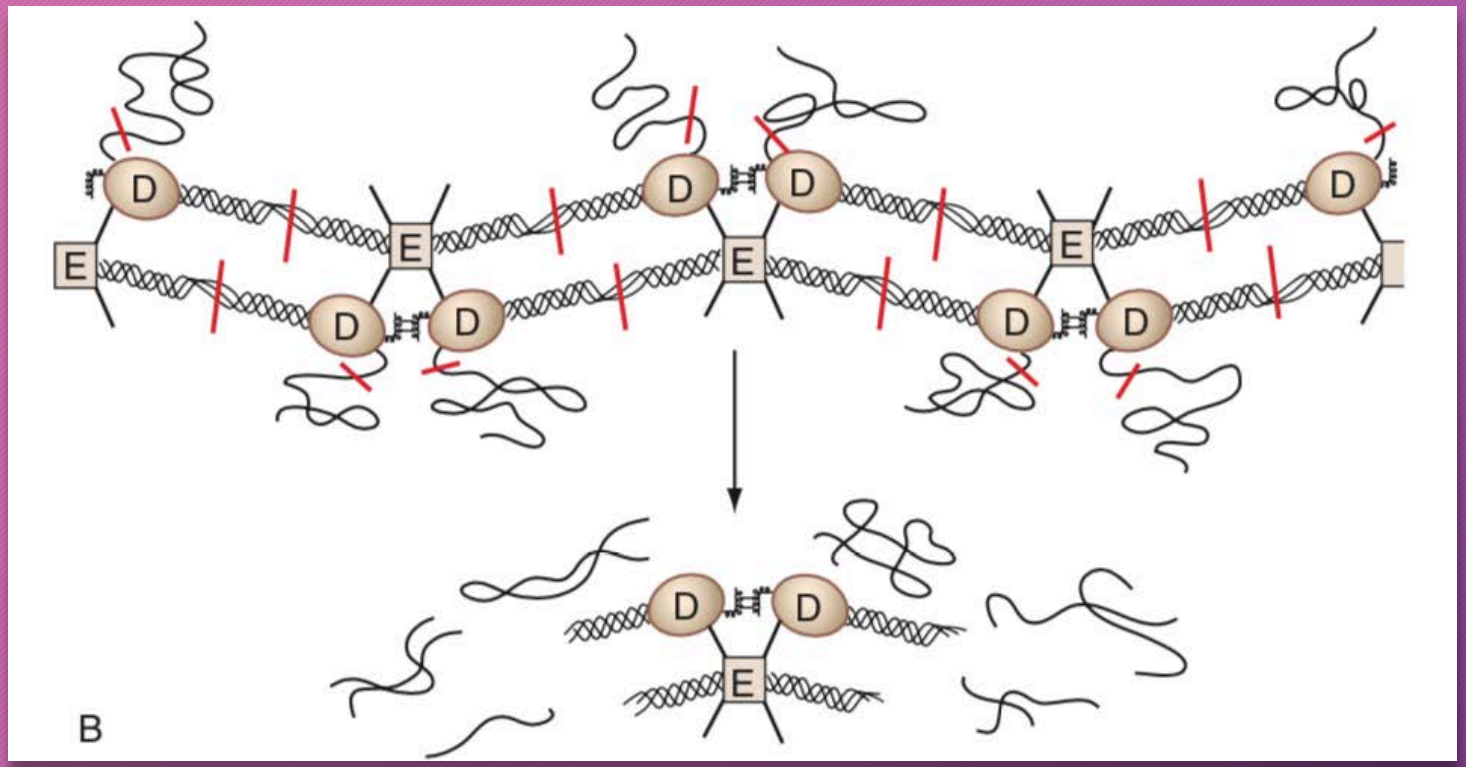
Findings From Get With The Guidelines-Stroke

Robert J. Adams, MS, MD; Margueritte Cox, MS, MGIST; Shelly D. Ozark, MD; Julie Kanter, MD; Phillip J. Schulte, PhD; Ying Xian, MD, PhD; Gregg C. Fonarow, MD; Eric E. Smith, MD, MPH; Lee H. Schwamm, MD

Stroke. March 2017

tPA

- Useful only in **ischemic** strokes
  - HbSS have more hemorrhagic (26%) when compared with controls (18%; $p \leq 0.001$)
  - Ischemic are overall more common for HbSS and controls



MOA of tPA

Henry's. 22nd ed, 2011.

Adams et al Findings

- HbSS are more likely to:
  - Arrive without ambulance
  - Longer time since symptom onset at presentation
  - Have previous stroke
  - Have prosthetic heart valve
  - Present to teaching hospital
- HbSS are less likely to:
  - Have DMII, HTN
  - Smoke

Adams et al Findings (2)

Table 2. Lytic Therapy and Safety Among SCD and Non-SCD Cohorts, After Matching on Age, Sex, and Black Versus Nonblack Race

Variable	SCD (n =832)	Non-SCD (n =3328)	*P* Value
Thrombolytic therapy			
Any thrombolytic therapy, n (%)	61 (8.2)	290 (9.4)	0.3024
Thrombolytic therapy types among patients receiving thrombolytic therapy, n (%)			0.9818
Intravenous tPA only	46 (82.1)	223 (81.1)	
IA tPA only	8 (14.3)	42 (15.3)	
Both intravenous tPA and IA tPA	2 (3.6)	10 (3.6)	
Onset to treatment time in min, median (25th–75th percentile)	148 (100–179)	145 (115–171)	0.6602
Door-to-needle time in min, median (25th–75th percentile)	73 (52–99)	79 (58–101)	0.3891
Arrive by 2 h, treat with intravenous tPA by 3 h	32 (78.1)	189 (79.1)	0.8814
Complications of thrombolytic therapy*			
Symptomatic ICH	3 (4.9)	9 (3.2)	0.4502
Life-threatening systemic hemorrhage	0 (0.0)	2 (0.7)	1.0000
Other serious complication	1 (1.6)	7 (2.5)	1.0000
Any serious complication	4 (6.6)	17 (6.0)	0.7732

IA indicates intra-arterial; ICH, intracerebral hemorrhage; SCD, sickle cell disease; and tPA, tissue-type plasminogen activator.

RBCX vs tPA

- No clear guidance
- Case and institution dependent
- RBCX requires apheresis catheter or port

Clinical Course

- tPA given
- No immediate change in vision
- Patient admitted
- Line could not be placed for ≥ 6h following tPA
- Patient insisted on GA for line placement

Call from Blood Bank

- O Rh positive
- Partial phenotype:
  - Kell: mixed field
  - E: mixed field
  - C: mixed field
- Antibody screen: negative

From CareEverywhere

- 2016

CLINICAL INFORMATION	33 y.o. female with a reported history of sickle cell disease who presents with sudden onset of vision loss, who subsequently left hospital AMA.
FINAL DIAGNOSIS	- Normal HPLC - Normochromic anemia
HPLC INTERPRETATION	

Hemoglobin	Results	Normal Range
Hgb A_2	2.4%	2.0 – 2.9%
Hgb F	0%	0 – 1.1%
Hgb A	97.6%	(96 – 97.9%)
Hbg S	**0%**	

MICROSCOPIC DESCRIPTION	- RBCs show a degree of anisocytosis, with hypochromic and normochromic forms. No sickle cells are noted. - WBCs appear normal. - Platelets appear normal and are present in normal numbers.

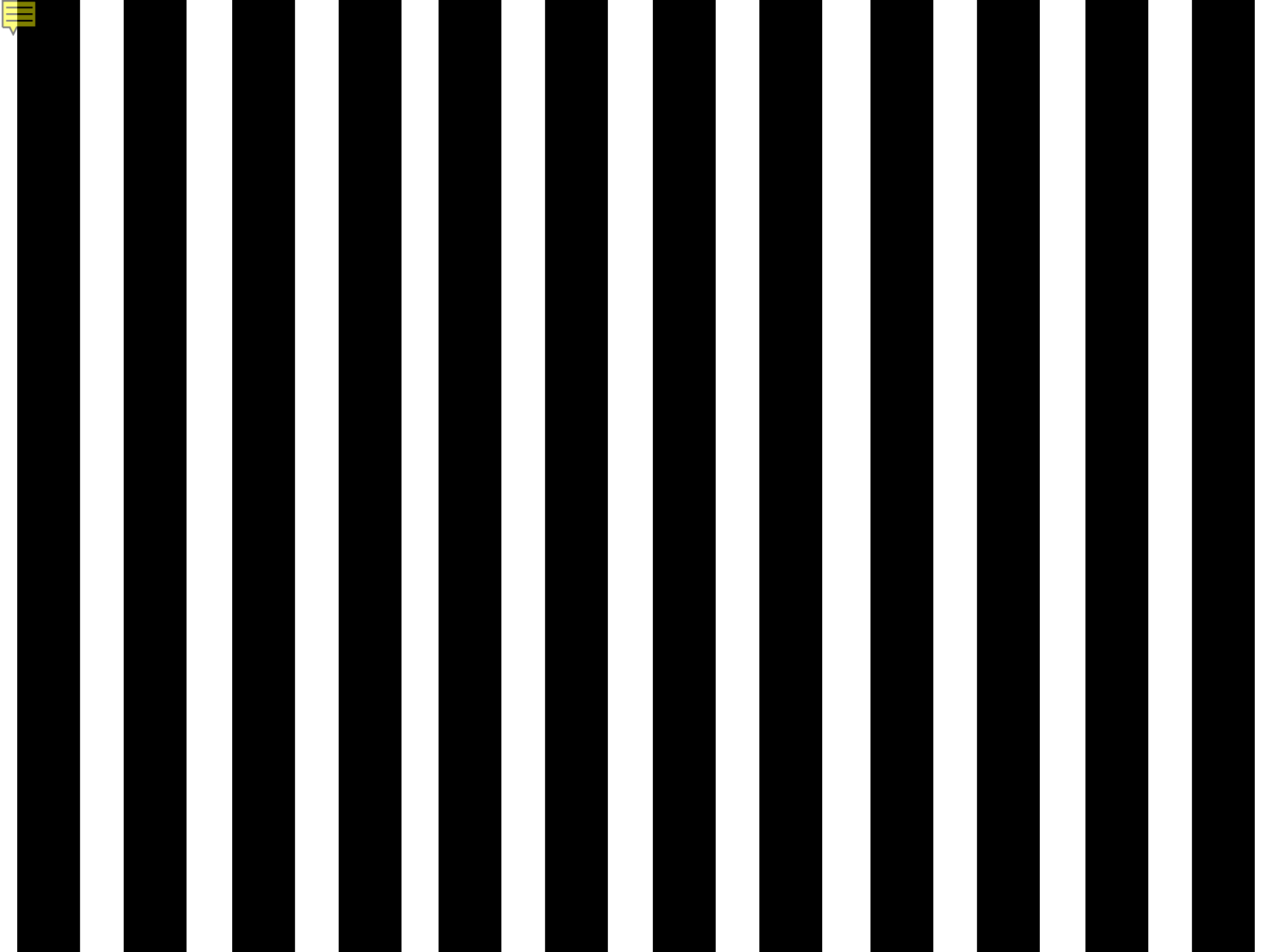
From CareEverywhere

- 2017

Component Name	Value	Ref Range
RBC Count	3.0 (L)	3.80 - 5.10 M/uL
Hemoglobin	9.0 (L)	11.7 - 15.5 g/dL
Hematocrit	26.5 (L)	35.0 - 45.0 %
MCV	88.1	80.0 - 100.0 fL
MCH	30.0	27.0 - 33.0 pg
RDW	18.9 (H)	11.0 - 15.0 %
Hemoglobin A1	97.6	GREATER THAN 96.0 %
Fetal Hemoglobin	0.0	LESS THAN 2.0 %
Hemoglobin A2,Quant	2.4	1.8 - 3.5 %
Interpretation	SEE NOTE Comment: Note Normal phenotype.	

Summation

- No history of HbSS found
- Multiple interventions for presumed HbSS
- Multiple CareEverywhere notes regarding drug-seeking and malingering
- Patient left AMA



Remaining questions

- Should HbSS patients with no history receive benchtop HbSS screening?
  - Peripheral smear
  - Metabisulfite test / SICKLEDEX

Remaining questions

- Should adjusted weight vs actual weight be used when calculating RBCX volume?
- Weight: 135 kg
  - Actual: 135 kg * 65 mL/kg = 8,775 mL
  - Adjusted: 135 * 50 mL/kg = 6,750 mL
  - Terumo App: 6,218 mL
- With FCR of 30% and Hct of 29%, need:
  - Terumo App: 3,585 mL (~12 units)

Br J Anaesth. 2000; 85:91±108

Questions

Thanks to Dr. Suchi Pandey & Dr. David Unold