
GEICO

STROKE IN SICKLE CELL DISEASE VSSTF AND VSCC MEETING OCTOBER 14, 2022

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CHKD

DISCLOSURES

- Speakers bureau for Global Blood Therapeutics
- No conflicts of interest relevant to today's talk

SICKLE CELL DISEASE (SCD) AND STROKE

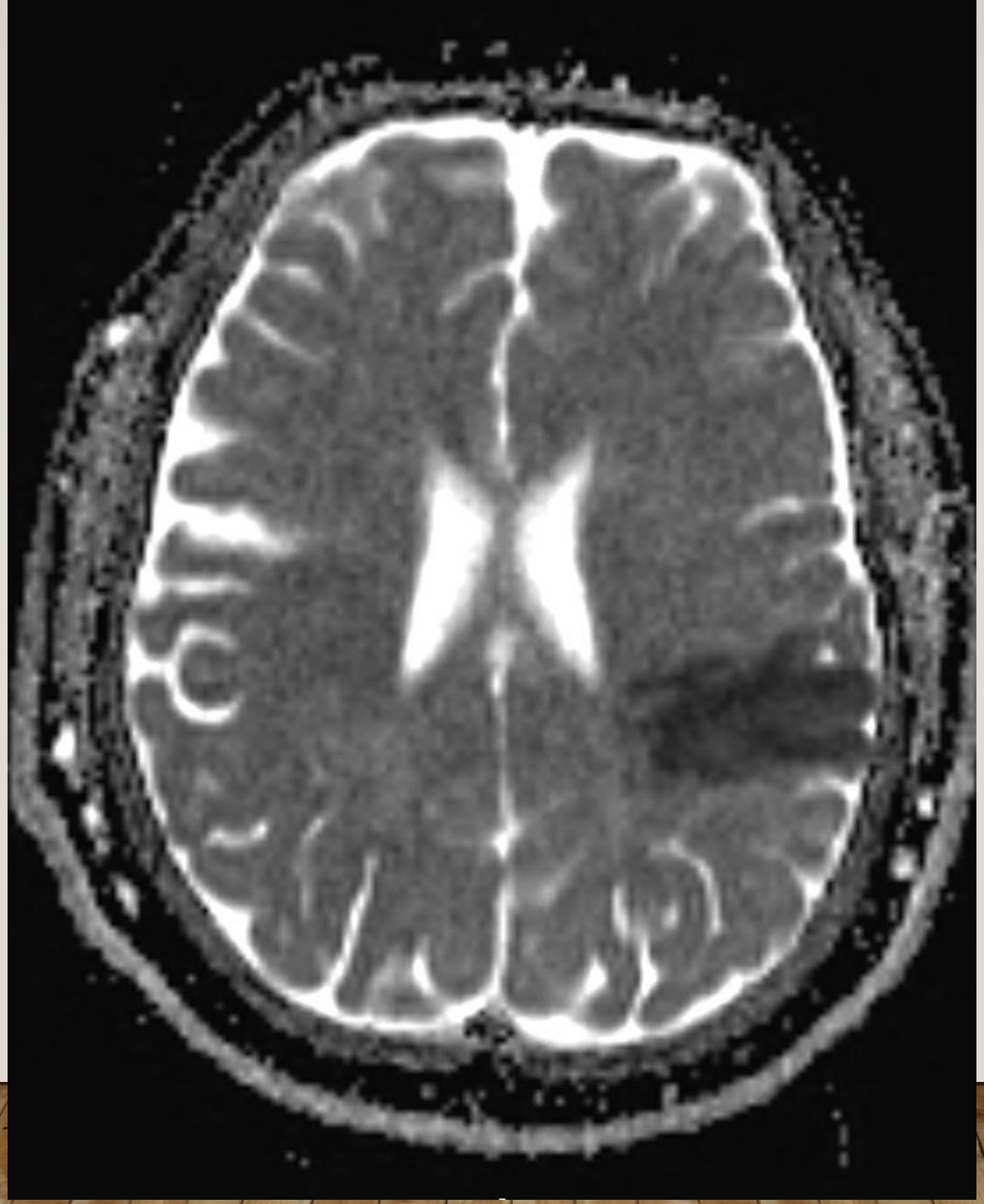
- Stroke, silent infarcts, and cognitive morbidity the are most common permanent problems in children and adults with SCD
- Before 1990, by 40 years of age, 20% of adults with Hemoglobin SS disease had had a CVA (less in SC disease)
- Screening of young children using TCD ultrasound has resulted in a 10 fold decrease in prevalence of stroke in children
- Silent cerebral infarcts remain a problem, occurring in up to 50% of adults by age 30
- Impact on quality of life in sickle cell is huge

SICKLE CELL DISEASE (SCD) AND STROKE

- Recent Case
- Review of sickle cell disease
- Epidemiology of stroke in SCD
- Reasons for stroke in SCD
- Presentation of stroke in SCD
- Acute management of stroke in SCD
- Long term interventions for stroke in SCD
- Primary and Secondary prevention of stroke in SCD
  - TCD screening
  - MRI screening

RECENT CASE

- Contacted by mother of 20 yo with Hemoglobin SS disease with concerns that he had had numbness in this right hand for at least 4 hours. Patient was on rivaroxaban due to PE in 11/2021
- Directed to come immediately to ED (consideration for CHKD versus SNGH); there found to have sensory deficits in right hand, mild asymmetrical strength of right hand vs. left, and difficulty with word finding.
- MRI/A stroke protocol revealed restricted diffusion in the left parietal lobe cortex and white matter consistent with ischemia with a small associated hemorrhagic component.



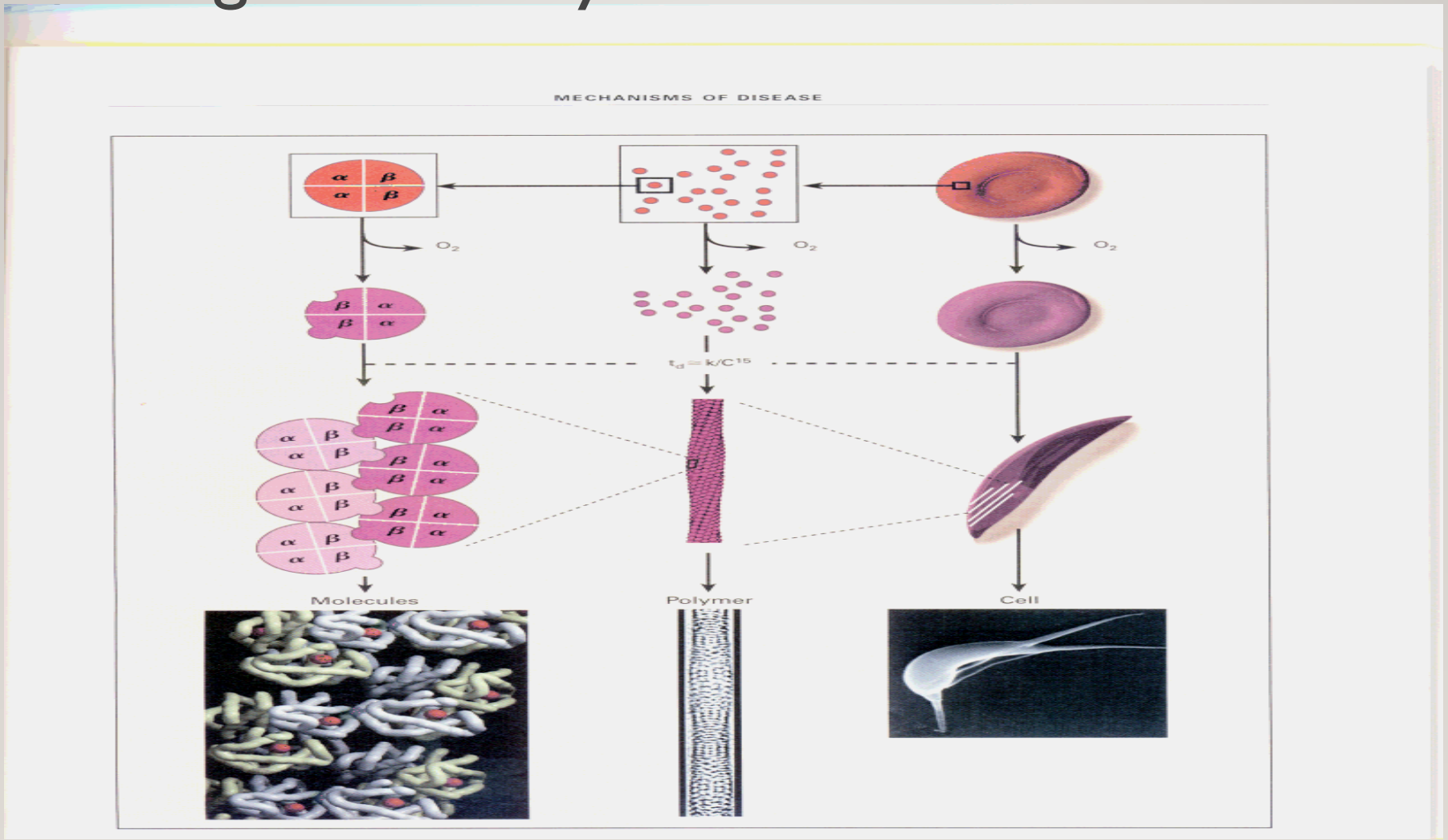
RECENT CASE

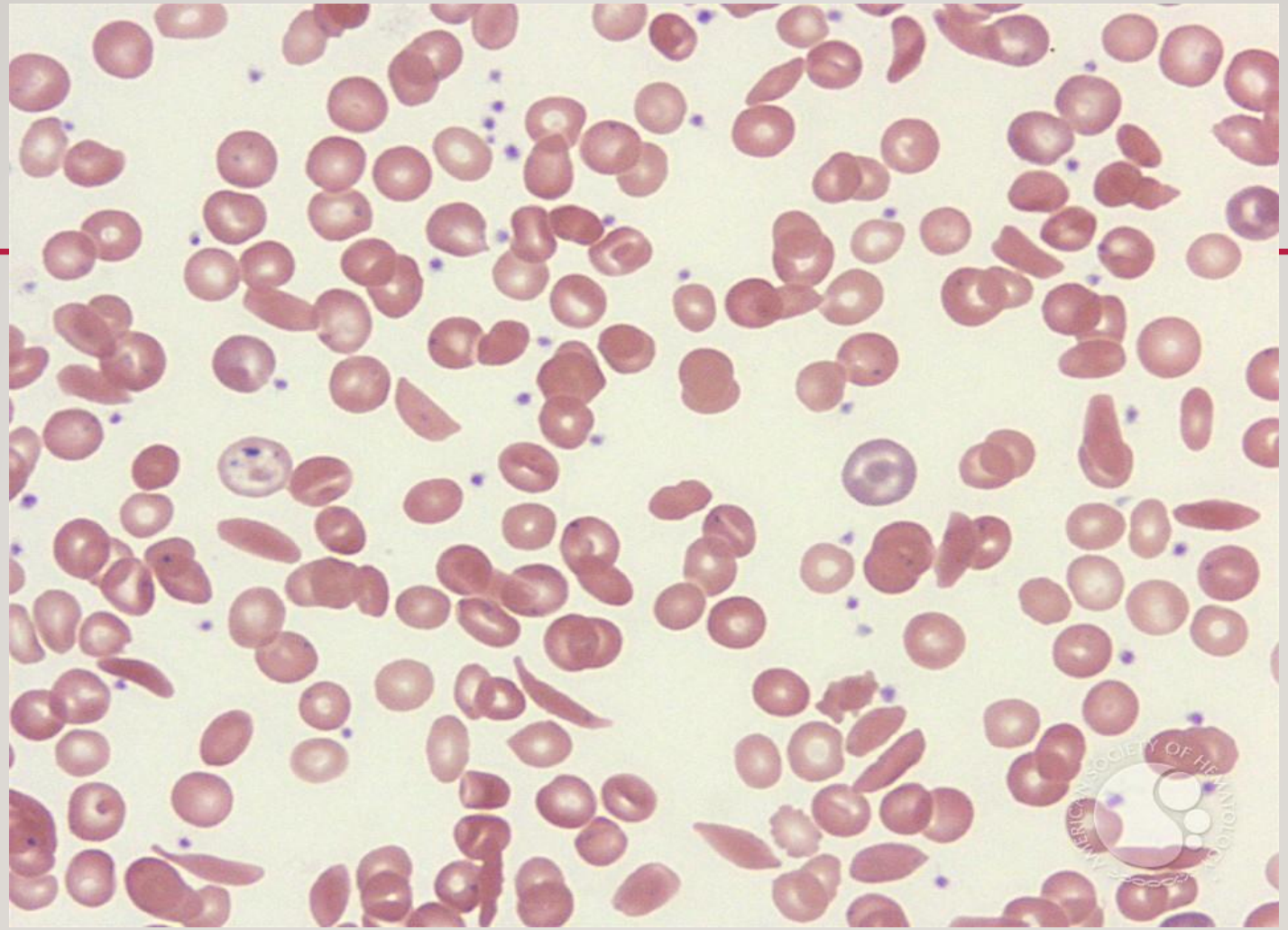
- Presentation: 4.5 hours after onset of symptoms, hemorrhagic component, already on anticoagulant. Hemoglobin 10.5 g/dl.
- Decision made to emergently perform an automated red blood cell exchange aiming for a hemoglobin S level < 30 % post-exchange.
- By the next morning, physical findings of stroke had almost completely resolved.
- Hemoglobin 11.4 g/dl and hemoglobin S = 29.1% post exchange.
- Patient to be placed on chronic transfusional therapy.

SICKLE CELL DISEASE: THE PROBLEM

- Valine for glutamic acid substitution at 6th position of beta chain (classic Sickle cell anemia)
- Results in unstable hemoglobin that polymerizes in times of stress
  - Pyrexia (fever)
  - Hypoxia (low oxygen tension)
  - Acidosis
- Hemolysis (red cell breakdown) with anemia; vaso-occlusion; increased infectious risk

Hemoglobin S Polymer Formation:





SICKLE CELL DISEASE-EPIDEMIOLOGY

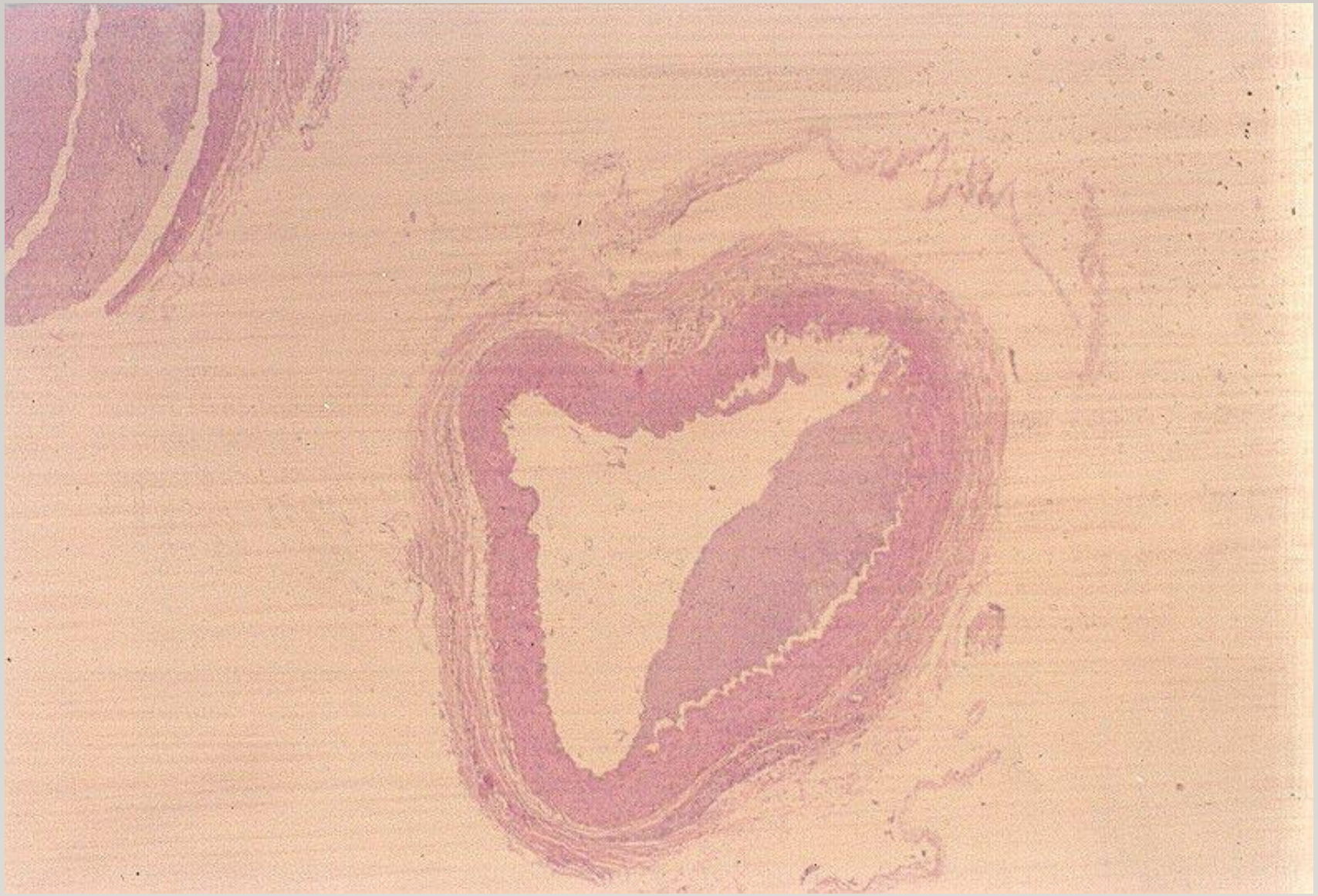
- Genetic blood disorder
- 8% African American population has trait
- 1/400 inherit disease
- Affects approximately 100,000 Americans
- Not only African American!
- Approximately 25-35 new infants with sickling disorders in Hampton Roads area each year

STROKES IN SCD

- Most devastating complications of sickle cell disease
- Prevalence estimates from 7.8% - 24%
- Risks higher at certain ages
  - Ischemic ages 2 – 9 and after age 30 historically
  - Hemorrhagic ages 20 -29 historically
- Recurrence risk 60-80% without intervention; 14-20% even on transfusional therapy historically
- Risks vary according to genotype
  - SS and S Beta zero thalassemia >> SC and S Beta plus thalassemia

REASONS FOR STROKES

- Narrowing of blood vessels
- adhesion of blood cells to damaged lining of blood vessels
- Large vessel occlusion
- growth of new, weaker blood vessels and hemorrhage
- Other causes:
  - Paradoxical emboli
  - Atrial fibrillation
  - Hypertension
  - Diabetes
  - High cholesterol



PRESENTATION OF STROKE IN SCD

- Focal neurological deficit
- Severe headache
- Seizures
- Speech impairment
- Sudden death

DIFFERENTIAL DIAGNOSIS OF ACUTE FOCAL NEUROLOGICAL DEFICIT IN SCD

- Acute ischemic infarct
- Hemorrhagic stroke
- Seizures
- Hemiplegic migraine
- Posterior reversible encephalopathy syndrome
- Cerebral sinus venous thrombosis

DIAGNOSIS AND ACUTE CARE

- Labs:
  - CBC, reticulocyte count, CMP, LDH, PT/PTT/fibrinogen; type and cross

DIAGNOSTIC MODALITIES

- Imaging
  - Pediatric centers frequently utilize MRI/DWI stroke protocols
    - Help to differentiate acute from subacute (and need for exchange transfusion)
    - MRV may be necessary to rule out cerebral sinus venous thrombosis
  - CT's
    - Noncontrast CT
    - CTA (must be careful in sickle cell) and CT perfusion imaging help to determine potential role of endovascular therapy

TREATMENT OF STROKES IN SCD: IMMEDIATE

- Multidisciplinary team: neurologist, hematologist, ED providers, intensivist
- ABC's
- Oxygen/supportive care

TREATMENT OF STROKES IN SCD: IMMEDIATE

- For children and adults with SCD, recommendation is for prompt blood transfusion with preference for acute exchange transfusion
  - Ideally automated
  - Ideally utilize sickle cell negative, phenotype specific pRBC's
  - Ideally begin within 2 hours of presentation
  - Consider simple transfusion if hemoglobin < 8.5 g/dl while exchange transfusion being planned

TREATMENT OF STROKES IN SCD: IMMEDIATE

- For adults with SCD who meet criteria for IV tPA (age > 18, symptoms < 4.5 hours, etc), guidelines suggest management using a shared decision-making approach
  - The administration of IV tPA should NOT delay prompt simple or exchange transfusion
  - Factors that suggest possible benefit from IV tPA: older age, atrial fibrillation, DM, hypertension, hyperlipidemia
  - There are no validated risk stratification or reliable age cutoff criteria to guide the choice of initial therapy
  - Retrospective review showed no significant impact on the safety or outcome of thrombolytic therapy in acute ischemic stroke in patients with SCD versus non-SCD stroke patients
  - IV tPA should NOT be used in children with SCD < 18 yo
  - Multicenter studies need to be done!

CHALLENGES

- Central line access needed for exchange transfusion
- Mobilization of red cell apheresis team
- Blood product availability
- If IV tPA considered, bleeding risks related to line placement

LONG TERM INTERVENTIONS FOR STROKE IN SCD

- Chronic simple or exchange transfusion to keep S level < 30%
  - Reduces risk of second stroke from 65-80% to 15%
- Hydroxyurea
  - Most patients are already on in 2022
  - SWiTCH trial showed 10% risk of second stroke on HU versus 0% risk on transfusions
- Antiplatelet therapy
- Stem cell transplants
  - Studies show CNS protective effects
- Gene therapy
  - Experimental but multiple clinical trials

SWITCH TRIAL

- Patients with primary stroke on chronic transfusions for at least 18 months randomized to transition to hydroxyurea + phlebotomy or to remain on transfusion and chelation.
- 7/67 on the experimental arm had new CVA
- 0/66 on the standard arm had new CVA
- Higher risk in patients with more severe vasculopathy

STEM CELL TRANSPLANTATION

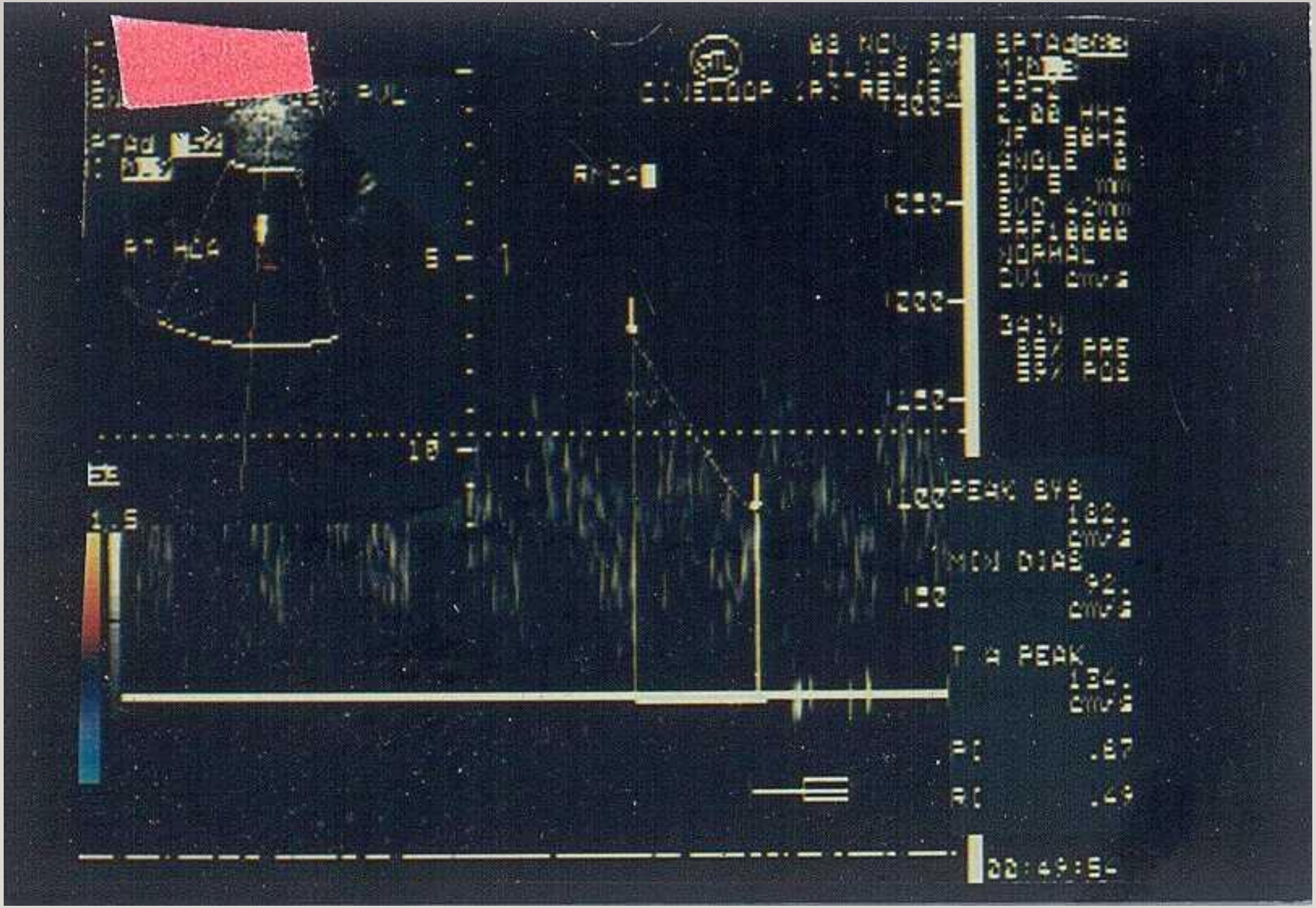
- Only curative therapy for sickle cell at present
- Matched sibling donor transplant data:
  - overall survival for matched sibling transplant: 96+ %
  - > 90% success rate (no more sickle cell disease)
  - Chance of death: 2 – 3%; mainly related to GVHD and infection

GENE THERAPY

- 2001: using lentiviral vectors, sickle phenotype corrected by gene transfer in murine model
- introduced gene contained introns linked to locus control region of beta gene along with anti-sickling variant of human B globin
- Multiple on-going gene therapy trials with one commercial product available.
- Should prevent sickle cell related progressive cerebral vascular disease

PRIMARY STROKE PREVENTION: TRANSCRANIAL DOPPLER (TCD) SCREENING

- Has made a huge impact on reducing CVA's in sickle cell patients
- Screening from ages 2 – 16 y.o.
- Elevated velocities indicate increased risk of CVA
- Risk can be lowered by chronic transfusional therapy (STOP trial)
- Transfusions necessary indefinitely (STOP 2 Trial)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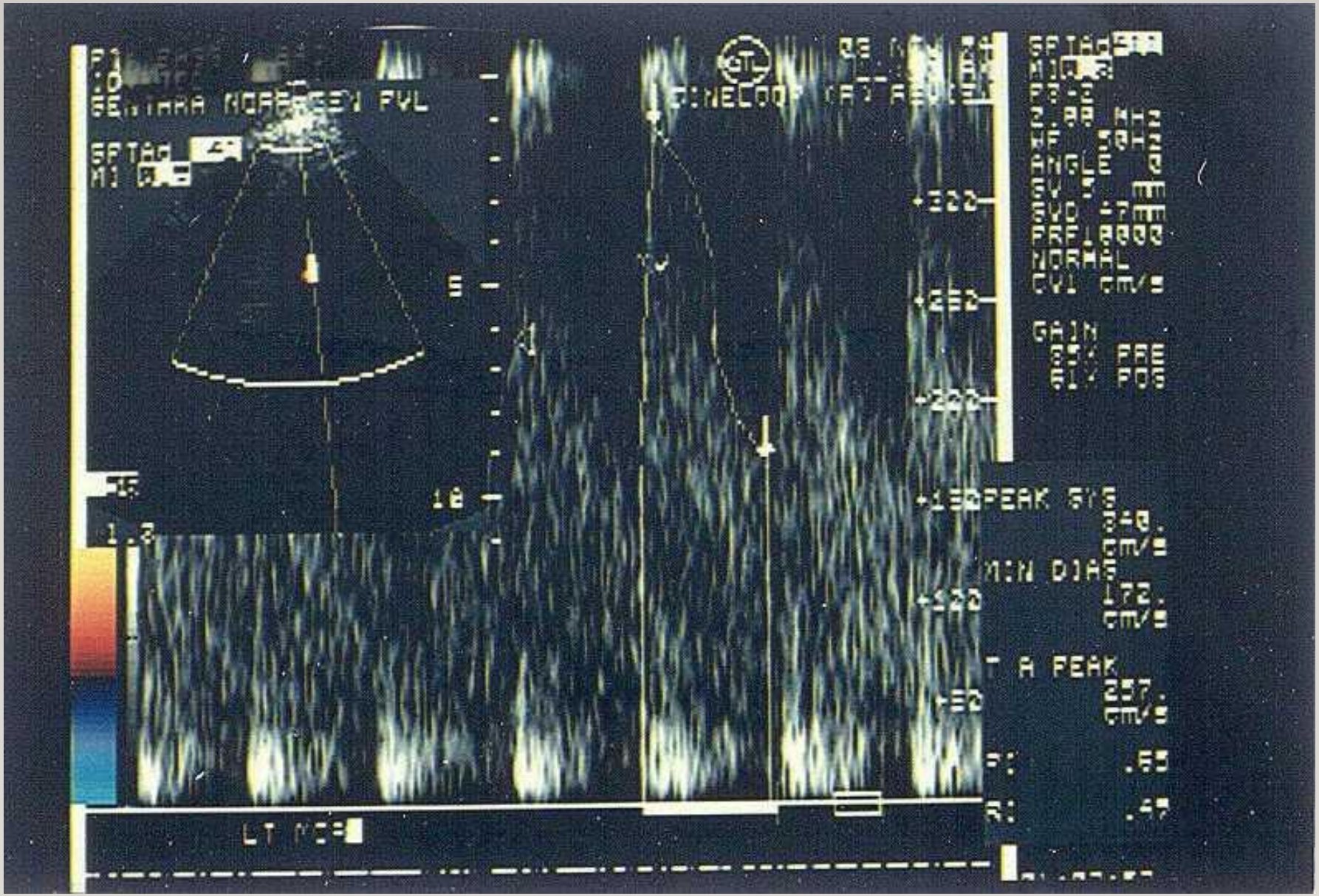
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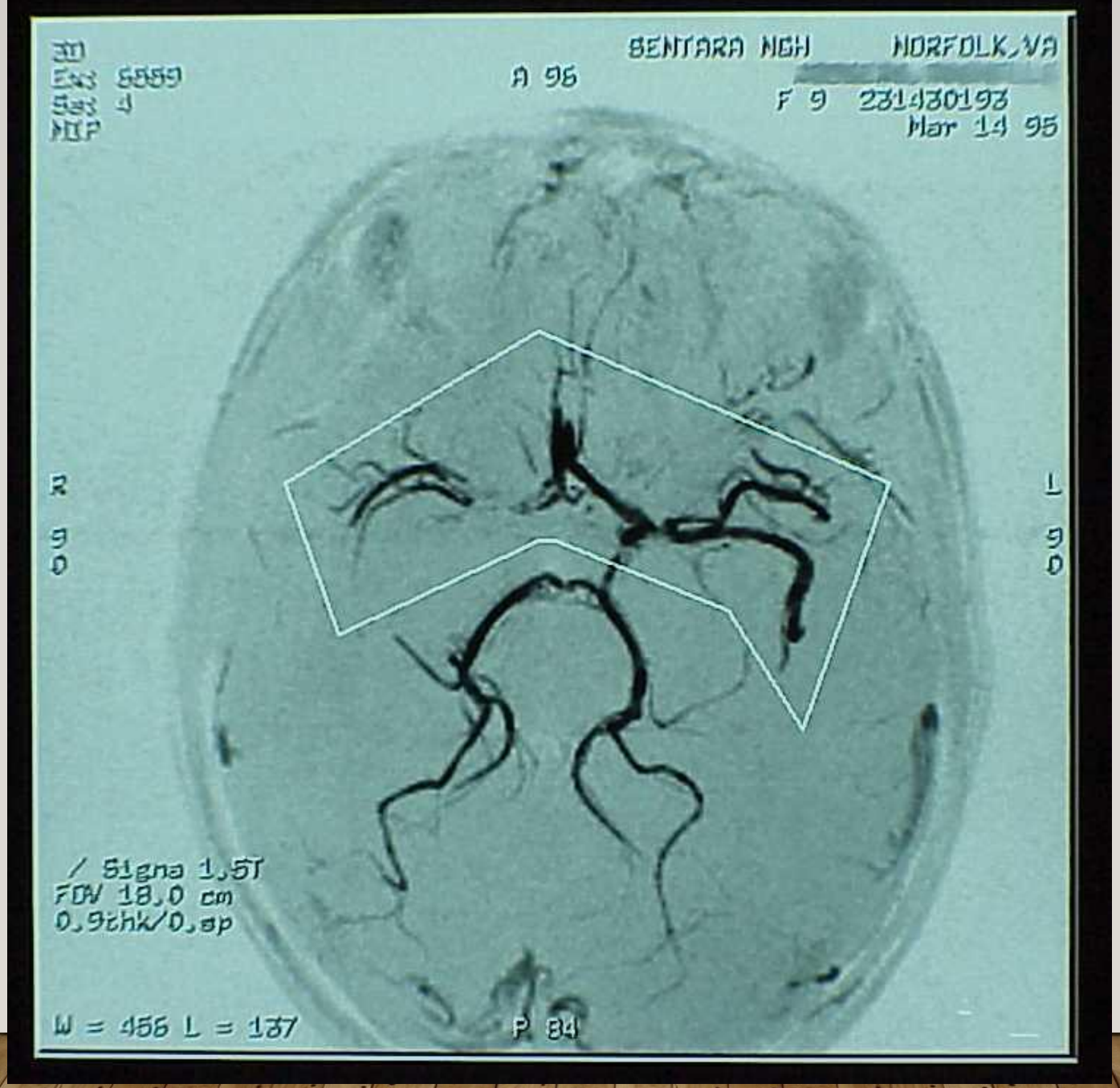
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TWITCH TRIAL

- Primary stroke prevention
- Patients with increased TCD velocity on transfusion therapy for at least 12 months randomized to HU + phlebotomy or transfusion +chelation
- Non-inferiority was shown in terms of TCD velocities
- No strokes in either group

MRI SCREENING FOR SILENT INFARCTS

- High incidence of silent infarcts in children and adults with sickle cell disease
- Consideration of MRI screening in childhood if able to do without sedation
- Consideration of MRI screening in adults
- Consideration of chronic transfusion to decrease risk of overt stroke

SUMMARY

- Patients with SCD are at high risk of stroke throughout their lives.
- True sickle cell related stroke has a unique pathophysiology.
- Intervention to lower the hemoglobin S concentration to < 30 % in an emergent fashion should be the primary goal in stroke management in SCD.
- IV tPA for adult patients with SCD who meet criteria should be considered.
- We are in need of more clinical trials to guide the management of acute stroke in SCD!
- Both primary and secondary stroke prevention strategies can be effective in decreasing the risk of brain injury in SCD.
- Curative therapy for SCD currently exists – this is the ultimate stroke preventative therapy for patients with SCD.

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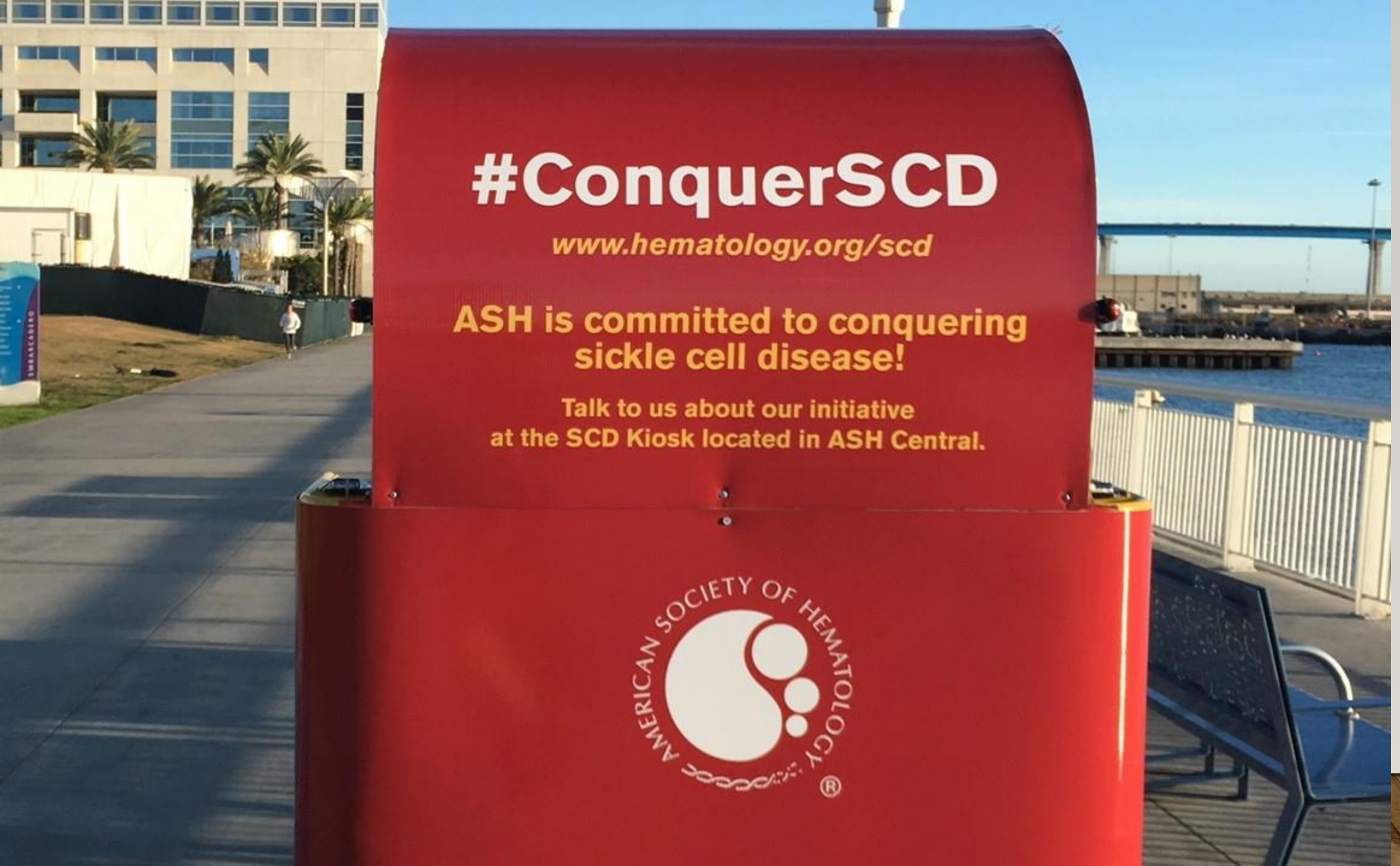
#ConquerSCD
www.hematology.org/scd
ASH is committed to conquering sickle cell disease!
Talk to us about our initiative at the SCD Kiosk located in ASH Central.
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