PROGRAM FACULTY DISCLOSURES

- I have no relevant financial relationships to disclose.
- I will not discuss products in my presentation.

AGENDA

- Overview of SCT
- Pathophysiology of SCT complications
- SCT and Athletes
- Case Studies
- Exercise Recommendations
- Risk Mitigation/ Prevention strategies
- Closing
Overview of SCT

- Common hemoglobinopathies
- What is Sickle Cell Trait (SCT)?
- How is SCT inherited?
- Diagnosis
- Complications

Common hemoglobinopathies: Populations Affected and Outcomes

<table>
<thead>
<tr>
<th>Abnormal Hb Type</th>
<th>Population Affected</th>
<th>Prevalence (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbS</td>
<td>African American, Hispanic, Africa, Mediterranean, South Asia, and Middle East.</td>
<td>1 in 12/ 1 in 500</td>
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<tr>
<td></td>
<td>Hispanic: 1 in 100/ 1 in 36,000</td>
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<tr>
<td></td>
<td>SCT/SCD: African American</td>
<td>1 in 12/ 1 in 500</td>
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<tr>
<td></td>
<td>Hispanic: 1 in 100/ 1 in 36,000</td>
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<tr>
<td></td>
<td>SCT (HbAS): No symptoms</td>
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<tr>
<td></td>
<td>SCD/SCD: Severe complications</td>
<td></td>
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<tr>
<td>HbC</td>
<td>African American, People of West African descent</td>
<td>2.3% of African Americans</td>
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<tr>
<td></td>
<td>HbC trait (HbAC): No symptoms</td>
<td></td>
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<tr>
<td></td>
<td>HbC/HbCC: Mild hemolytic anemia, mild to moderate splenomegaly</td>
<td></td>
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<tr>
<td>HbE</td>
<td>Southeast Asian descent</td>
<td>About 30% in Southeast Asia</td>
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<tr>
<td></td>
<td>HbE trait (HbAE): Asymptomatic</td>
<td></td>
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<tr>
<td></td>
<td>HbE disease/ HbEE disease: Mild hemolytic microcytic anemia and mild splenomegaly</td>
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<tr>
<td>HbSC</td>
<td>African Americans and people of West African descent</td>
<td>N/A</td>
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<tr>
<td></td>
<td>N/A</td>
<td></td>
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<tr>
<td></td>
<td>Milder symptoms</td>
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<tr>
<td></td>
<td>HbSC/HbSC disease: Milder symptoms</td>
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</tbody>
</table>

BACKGROUND

- Sickle cell disease (SCD) – substitution of glutamic acid by valine on position 6 of the β chain of hemoglobin S (HbS), (β^{Glu->Val}).
- Autosomal recessive disorder.
- HbAS or sickle cell trait, SCT - a copy of the HbS allele and one normal HbA allele
- Asymptomatic carriers - spared the serious complications associated with possessing two copies of the mutant allele (i.e. HbSS).
What is Sickle Cell Trait (SCT)?

- One sickle cell gene and one normal gene.
- Heterozygous carriers of an abnormal β-globin gene
- Production of an abnormal hemoglobin, Hb S.
- 300 million people worldwide with SCT
- Approximately 30% to 40% in sub-Saharan Africa.


How is SCT inherited?

Offspring of SCT parents:
- 50% chance of inheriting the SC gene.
- 25% chance of SCD
- 25% chance of not having SCD or SCT

Asymptomatic carriers, but they can pass SCT on to their children.

www.cdc.gov/ncbddd/sicklecell/traits.html
Screening Techniques

- Sickle solubility testing,
- Hb electrophoresis,
- High-performance liquid chromatography (HPLC), and
- Iso-electric focusing (IEF),
- DNA analysis
- Multiplexed POCT using RIA

Definitive diagnosis

Two main methods:
- Hb separation and quantitation methods or
- Analysis of β-globin genes.

Additionally,
- Presence of HbA (principal) and HbS in an individual
- No transfusion in preceding >= 3 months

Other methods may be necessary for proper identification.

COMPLICATIONS

- Usually none
- Rare cases/ extreme conditions (Heat, dehydration, increased barometric pressure & hypoxia):
  - Pain crises – VOC
  - Splenic infarction
  - Exertional rhabdomyolysis,
  - Renal complications,
  - VTE, and
  - Exercise-associated sudden death.

(Bonham et al., 2010; Naik and Haywood, 2015)
SCT Complications

**PATHOPHYSIOLOGY**

- SC: Polymerization of the deoxygenated HbS.
- May be irreversible
- Increased fragility (distortion) of the rbc → Microvasculature occlusion → Hemolysis
- HbS polymerization dependent on [Intracellular HbS] and non-S Hb type
- HbF inhibits HbS polymerization
- Higher HbA > HbS is protective from sickling & asymptomatic

HbS Polymerization is also affected by:
- Oxygen saturation.
- Intracellular pH and
- 2,3-diphosphoglycerate (2,3-DPG) levels.
- Interplay of genetic and environmental moderators in SCT carriers.
Pathophysiology

Genetic Moderators of clinically symptomatic HbAS:
1. Genetic modifiers co-inherited with HbS;
2. Rare & dominant forms of HbS alleles;
3. Heterozygosity for HbS that may be misleading; and
4. Non-Mendelian inheritance of HbS.

Xu and Thein, Haematologica 104(6) 2019

SCT and Athletes: Timeline of major HbS discoveries and SCT screening mandates

American Society of Hematology

SCT and Athletes

Robert I. Liem, Balancing exercise risk and benefits: lessons learned from sickle cell trait and sickle cell anemia, Hematology Am Soc Hematol Educ Program, 2018, Figure 1.
Case Study 1

O/E:
• altered consciousness,
• later alert and restless
• RR – 55 breaths/min
• ECG: Hyperkalemia

RX:
• IV Dextrose, Insulin, & sodium bicarbonate.

Key findings:
• Metabolic panel: [Na+] – 148mEq/L, (R: 133-145)
• [K+] – 5.6mEq/L, (R: 3.3—5.1).
• [HCO3⁻] – 8 mEq/L, (R: 22—32), and
• AKI [Cr] – 1.98 mg/dl (R: 0.5—1.2).
• Imaging: CT brain scans, C-spine, chest, cervical spine, abdomen, & pelvis – unrevealing.

Later:
• c/o diffuse myalgias.
• Repeat [K+] – 9.9 mEq/L, Lactic acid – 19.9 mmol/L, [Ca] – 2.5 mmol/L.
• [Cr] – 2,271 IU/L & Repeat [Cr] – 7,500 IU/L within 2 hr.

Day 2:
• Diagnosis of severe exertional rhabdomyolysis with renal failure made.
• [CK] and [K+] gradually worsened.
Day 2 (contd.)
- Significant bilateral pedal edema.
- Compartment syndrome (bedside fasciotomies)
- Bloody stool and elevated bladder pressures.
- Postop bleeding ensued from all surgical sites (imminent DIC).
- [Hb] fell from 11–6.3 g/dl (R: 11.2–15.7) and Fibrinogen was 55 mg/dl (reference range 180–400).

Day 3 on admission:
- Developed severe ARDS (PaO₂ in mmHg: FiO₂ was as low as 54).
- Neuromuscular blockade, inhaled nitric oxide and positive end-expiratory pressure (PEEP) titration guided by esophageal balloon improved the patient’s oxygenation. PaO₂/FiO₂ ratio increased to 245.
- Hemorrhage continued with ongoing transfusions and vasopressor support.
- CT revealed cerebral edema,
- Repeat TEE showing depressed LV function and fluid overload.
- [K+] & [Cr] continued to rise
- Intermittent Bradycardia, Asystolic cardiac arrest, and eventual demise.

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Chest radiograph from hospital Day 2 demonstrating clear lung fields (left panel). Comparison film from hospital Day 3 revealing pulmonary vascular congestion and bilateral opacities consistent with acute respiratory distress syndrome (right panel).
Conclusions from Case Study 1 (Murugappan et al., 2018)

• SCT predispose carriers to exertional rhabdomyolysis
• Risk of exertional death is significantly higher.
• Pathophysiology is unclear.
• Dehydration and electrolyte imbalances associated with drastic and rapid weight loss pose a greater risk to combat sports athletes with SCT.
• Management of multiorgan failure resulting from severe exertional rhabdomyolysis is quite challenging.

Case Study 2

- 20-year-old previously healthy African-American male college student.
- Severe leg pain, fatigue, and inability to finish the 1.5 mile run of his military fitness assessment.
- Completed push-ups & sit-ups effortlessly.
- Symptoms did not abate following hydration & rest.
- Distressing thigh and hamstring pain persisted with impairment of mobility.
Case Study 2

- Drug history - unremarkable.
- Success in past mandatory half-yearly military fitness tests.
- 1.5 mile runs executed under 11 mins, maximum sit-ups, & push-ups in 1 minute.
- Intramural soccer player.
- Recurrent bilateral muscle cramps in the lower extremities following physical exertion for over 2 years.

Case 2

- Excessive tenderness in both quadriceps and hamstrings to palpation.
- Pain with knee flexion > 80°, and full extension.
- Preliminary tests: CK - 5,662 IU/L, LDH - 1,332 IU/L, and no RBC on urinanalysis.
- Initial diagnosis of exertional rhabdomyolysis (ER)
- Following hydration with saline IV, symptoms improved.
- Discharged home

Symptom resolution continued at home.

- Pain in the quadriceps noticed at 1 wk follow-up.
- Repeat labs showed reduction in [CK] to 1,351 IU/L, with slight increase in liver enzymes
- Arduous activities were restricted for another week.
- Missed follow-up visits (3 weeks)
- Second fainting episode during a make-up fitness assessment with acute onset excruciating leg cramps.
Second fainting episode

Environmental temperature ideal.

? Hydration status

Thirst, micturition, and weight loss observed a week prior.

Pain on passive stretching and significant quadriceps tenderness on palpation.


IVF and ICU transfer.

Hours later – leg stiffness, weakness, & hypoesthesia.

Became normoglycemic, but acidotic with raised [K+], [PO4-], and reduced [Ca2+].

Myoglobinuria

Vigorous IV hydration, HCO3-, Diuretics, and Insulin.

Reduced urine output.

Day 2 on Admission - Case study 2

DIC

Massive transfusion with blood and plasma products.

Multicompartment fasciitis of lower extremities.

Even with renal dialysis, acidosis and hypotension persisted.

Global compartment syndrome with further fasciitis and edema.

DIC worsened → Renal failure
Day 23 on Admission

- CK peaked at 9 million IU/L
- Attempts to salvage viable tissue with hyperbaric oxygen not successful.
- Loss of brainstem reflexes
- CT & MRI - Diffuse Infarction (Upper cervical cord, brainstem, midbrain, and subcortical regions)
- With family consent, ventilatory support withdrawn.
- Several infarcts in brain, spleen, kidneys confirmed by postmortem.
- Autopsy confirmed multiple infarcts throughout the brain, spleen, and kidneys, consistent with sickling.
- SCT also verified via postmortem genetic testing.

Pathophysiology of ECAST

- Controversial
- Profound lactic acidosis → extreme hypoxemia in contracting muscles → muscle hyperthermia → local red blood cells dehydration.
- Increase in epinephrine release following a rise in physical exertion may predispose the red cells of SCT to become sticky.
- Explosive rhabdomyolysis → fatal metabolic emergency.
- Terminal common pathway involving hyperkalemia is implicated.

Loosemore et al., 2012; Quattrone et al., 2015
Exercise Risks

Retrospective study of nearly 48,000 active duty, African American soldiers.

Findings:
- SCT was not associated with a higher risk of death but
- Associated with a significantly higher risk of exertional rhabdomyolysis. (Kurina et al., 2016)
- SCT is associated with exertional death in NCAA football players with a rate of 1:827 in Division I football athletes.
- The death rate is 37 times higher in football athletes with SCT than those without. (Harmon et al., 2012)

ECAST Survival Chain

O'Connor et al., ACSM & CHAMP 2012

RTDP Guidelines

- Resolution of all symptoms.
- Full restoration of end-organ functions (biomarker tests).
- Thorough medical history and complete physical examination (Drug hx, family hx etc.).
- Individualized and progressive RTDP regimen under medical supervision.
- Patient education on risks of recurrence of ECAST

O'Connor et al., 2012; Quattrone et al., 2015
Risk Reduction Approach

• Individualized strength and conditioning programs.
• Periodization of the training program.
• Extensive recovery times between repeated high intensity events.
• All activity should be stopped if athlete has any symptom.
• Athlete and Coach education

Quattrone et al., 2015; Liem, 2018

REFERENCES

CLOSING

- Questions and Comments