Pain in children with sickle cell disease
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Objectives

Case Study

AAPT diagnostic criteria

Mechanisms of pain in sickle cell disease

A suggested management strategy
14 year old Male

- DOB: 25 November, 2004,
- Arrived UK September, 2009
- HbS/Beta0; Haemoglobin S due to the 20A>T mutation with concomitant heterozygous beta zero thalassaemia due to the IVS-II-849 A>G beta zero mutation.
## PROGRESS

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>TCD</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td>NORMAL</td>
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<tr>
<td>HOSPITAL ADMISSIONS</td>
<td>5</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
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<tr>
<td>MAJOR COMPLICATIONS</td>
<td>Adenotonsillectomy</td>
<td>Right tibia osteomyelitis, Right orbital sickling</td>
<td>Spine infarction, avascular necrosis humerus</td>
<td>Pyomyositis, Infarction of spine, Re-adenoidectomy</td>
<td>AVN spine</td>
<td>Cervical, thoracic, lumbar AVN (acute on chronic)</td>
<td>Palpitation but NO pulmonary hypertension</td>
<td>Spine insufficiency on MRI but NO cord compression</td>
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<tr>
<td>MAJOR THERAPEUTIC DECISIONS</td>
<td>Referred to Evelina Children’s hospital</td>
<td>Hydroxyurea started</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain protocol designed</td>
<td></td>
<td></td>
<td>Regular Blood transfusion, Deferasirox</td>
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</table>
### Exhibit 1a. Typical Laboratory Findings in Sickle Cell Disease

<table>
<thead>
<tr>
<th>Genotype</th>
<th>$Hb^+$ (g/dL)$^\dagger$</th>
<th>HbS (%)</th>
<th>HbA (%)</th>
<th>HbA2 (%)</th>
<th>HbF (%)</th>
<th>HbC (%)</th>
</tr>
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<tbody>
<tr>
<td>SS</td>
<td>6–9</td>
<td>&gt;90</td>
<td>0</td>
<td>&lt;3.5</td>
<td>&lt;10</td>
<td>0</td>
</tr>
<tr>
<td>$S^0\beta$-thalassemia</td>
<td>7–9</td>
<td>&gt;80</td>
<td>0</td>
<td>&gt;3.5</td>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td>$S^\beta^*$-thalassemia</td>
<td>9–12</td>
<td>&gt;80</td>
<td>10–30</td>
<td>&gt;3.5</td>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td>SC</td>
<td>9–14</td>
<td>50</td>
<td>0</td>
<td>&lt;3.5</td>
<td>≤1.0</td>
<td>45</td>
</tr>
</tbody>
</table>

* Definitions for abbreviations are as follows: $Hb = hemoglobin; HbS = sickle hemoglobin; HbA = normal adult hemoglobin; HbA2 = minor variant of adult hemoglobin; HbF = fetal hemoglobin; HbC = hemoglobin variant that causes manifestations of SCD when paired with HbS

$^\dagger$ The hemoglobin values in this exhibit apply in the absence of a blood transfusion in the last 4 months, are not absolute, and are applicable to adults and children only (not newborns).
Pain in sickle cell disease

• Most common complication
• African Tribal names:  
  - *Chwechweechwe* (relentless perpetual chewing)  
  - *Adep* (beaten up)  
  - *HemKom* (body biting)
• Morbidity, direct and indirect cost, early mortality

Acute vaso-occlusive episodes

- Hallmark manifestation
- Acute Pain (Dactylitis). 6-8 months
- 5 cardinal signs of acute inflammation:
  - rubor (redness),
  - calor (increased heat),
  - tumor (swelling),
  - dolor (pain),
  - functio laesa (loss of function)
- Ischemia- reperfusion physiology (reperfusion injury)
Vaso-occlusion in SCD
A multicellular and multistep model

Zhang et al. Blood 2016
Ischemia-Reperfusion Injury

Two distinct phases of Ischemia/Reperfusion:

• 1. **Ischemia** caused by interruption of vascular supply leads to tissue injury

• 2. **Reperfusion** is associated with resolution of occlusion and resupply of oxygen → inflammatory phase → systemic inflammation → remote organ injury/ multi-organ dysfunction syndrome
### Table 1. Dimension 1: Core Diagnostic Criteria

1. Diagnosis of SCD as confirmed by laboratory testing.
2. Reports of increased pain that lasts ≥2 hours and started in the past 10 days.
3. Must display ≥1 of the following signs:
   a. Palpation of region of reported pain elicits focal pain or tenderness.
   b. Movement of region of pain elicits focal pain.
   c. Decreased range of motion or weakness in region of reported pain.
4. Pain is not entirely explained by specific physical examination findings (leg ulcers, priapism, edema) or imaging abnormalities (bone infarction, osteomyelitis, hepatobiliary [cholecystitis, pancreatitis, hepatic sequestration], splenic sequestration).

Diagnostic modifiers to indicate subtypes of acute pain:

**Subtype 1** – Without comorbid chronic SCD pain: Acute pain that occurs in the absence of chronic pain and is consistent with vaso-occlusion, for example, pain in the extremities, back, abdomen, chest, or head for which no explanation is identified. Dactylitis is included in this modifier.

**Subtype 2** – With comorbid chronic SCD pain: Acute pain that occurs in the presence of chronic pain with or without signs of vaso-occlusion (e.g., lower hemoglobin, increased reticulocyte count, elevated lactate dehydrogenase).

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**ACUTE SCD Pain:**
- Diagnosis of SCD
- ≥ 2 h 10 ≤ days
- Signs:
  - Focal pain/tenderness
  - Pain on movement
  - Decreased range of motion
  - Not explained by other diagnosis

**Modifiers: Acute SCD Pain sub-Phenotypes**

1. *Without* comorbid chronic SCD pain
2. *With* comorbid chronic SCD pain
Multiple Cellular Processes that Lead to Central Sensitization

Effectors:
- Changes in the threshold and activation kinetics of NMDAR and AMPAR
- Changes in the trafficking of AMPA receptors into the membrane
- Alterations in ion channels to increase inward currents & reduce outward currents
- Reductions in the release or activity of GABA and glycine

Cellular processes:
- Increase of membrane excitability
- Synaptic facilitation
- Disinhibition

Central sensitization:
- Development of or increases in spontaneous activity
- Reduction in threshold for activation by peripheral stimuli
- Enlargement of their receptive fields (conversion of nociceptive-specific neurons to wide dynamic neurons that now respond to both innocuous and noxious stimuli)

Transition from Acute to Chronic Pain

Acute pain triggers
For example: stress, weather, infection, activity

Chronic pain modulators
For example: stress, depression, anxiety, sleep disorders

Central Sensitization
Vaso-occlusion with inflammation

Acute pain
Focal

Chronic pain
Generalized
Hyperalgesia
Allodynia

Peripheral sensitization

Field et al. J Pain. 2019
Managing comorbidities

• Psychological co-morbidities are common and can make pain worse in patients with SCD

• Depression, anxiety, poor sleep quality are often present especially in patients with high pain burden

• Certain traits such as catastrophizing in individuals/parents at higher risk for developing chronic pain

• Managing comorbidities is necessary → pain psychology may be helpful
Integrative Pain Clinic for SCD

• Multi-disciplinary clinic held in the division of Hematology
• **Comprehensive Services:**
  • Hematology
  • Pain management
  • Psychology
  • Social work
  • Physical therapy
  • Healing touch
  • Aromatherapy
  • Massage therapy
  • Acupuncture/Acupressure
Vaso-occlusive episodes vs. daily pain

- Quantity, severity of pain vastly underestimated
- Iceberg phenomenon
  - Only tip of iceberg seen by health care providers in EDs, hospitals.
  - Most pain is “submerged” at home or work.
  - Implications vast.

Smith et al Annals Int Med 2008
Acute pain: changes in characteristics with increasing age

• Position
  • Dactylitis 6/12 – 2 years
  • Limb pain in childhood
  • Truncal pain in adulthood

• Incidence
  • Increases during childhood
  • Adults access health care on 3.5% of days
  • Reduced in older adults

• Opiate use
  • 11% of days in young children
  • 57% of days 14-19 yrs
  • > 40% adults take daily opiates

• Pain in adults (PISCES study)
  • 55% have pain over half of days
  • 29% have pain 95% of days

Figure 5.1 Age specific rates of acute painful crisis and other acute complications in the East London Newborn Cohort (data from HbSS children)
Acute SCD Pain (Tentative Definition, AAAPT)

- Patient with SCD by lab testing
- Lasts at least 2 hours
- Started in last 10 days
- One physical sign (palpation, movement cause pain, or decreased ROM)
- Can’t be explained by SCD complication (leg ulcer, priapism, edema, bone infarction, AVN, osteo, hepatobiliary)
- Subtypes
  - 1- No painful comorbidity
  - 2- With painful comorbidity
- May occur with or without chronic SCD pain
  - Joshua J. Field¹, Samir Ballas², Claudia M. Campbell³, Lori E. Crosby⁴, Carlton Dampier⁵, Deepika S. Darbari⁶, Wally R. Smith⁷, William T. Zempsky⁸. AAAPT Diagnostic Criteria for Acute Sickle Cell Disease Pain. Manuscript under review.
Acute Pain: Diagnosis and Assessment

• A patient is having a sickle pain episode when they tell you they are having pain
• Patient may have
  • Swollen painful joint
  • Fever
  • Raised white blood count, CRP
  • Increased haemolysis
  • Worsening anaemia
• BUT examination and investigations may be normal
• Haemoglobin electrophoresis is not helpful
• Pain score, respiratory rate, oxygen saturations, chest examination
Acute Pain: Analgesia

- WHO analgesia ladder
- NICE guidance
- NIH guidelines

- Pain relief within 30 minutes of presentation
- Re-assess regularly until pain free
- Mild to moderate pain: NSAIDS, weak opioids
- Severe pain: Strong opioids
- Personalised pain plan
- Day Unit vs Emergency Room
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose &amp; frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>15mg/kg qds (give 20mg/kg first dose)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1mg/kg tds</td>
</tr>
<tr>
<td>Morphine PO</td>
<td>200-400 micrograms/kg 4hrly</td>
</tr>
<tr>
<td>Morphine IV</td>
<td>10-100micrograms/kg (titrate slowly to effect)</td>
</tr>
<tr>
<td>Diamorphine intranasal</td>
<td>100 micrograms/kg stat dose (max 10mg)</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>0.5-1.0mg/kg qds (max 30mg qds)</td>
</tr>
</tbody>
</table>
Which opioid to use?

1. **Diamorphine**
   1. Parenteral or intranasal (in children)

2. **Morphine**
   - Oral vs sc vs iv
   - PCA or MST plus intermittent immediate release

3. **Oxycodone**
   - Reduced side effect profile
   - Concerns re long term side effects

4. **Fentanyl**
   - Sub-lingual or buccal formulation – works rapidly

5. **Combinations:** eg Oral morphine plus fentanyl (SCAPE trial)

6. Ensure adequate analgesia **BUT** give as low a dose as possible for as little time as possible
1. **Appendix 1: PAIN ASSESSMENT TOOLS:**

2. FLACC Behavioural Pain Assessment Tool (Suggested age group 2 months – 7 years)
   
<table>
<thead>
<tr>
<th>Categories</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FACE</strong></td>
<td>No particular expression/smiling</td>
<td>Occasional grimace/frown.</td>
<td>Frequent/constant quivering chin;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawn disinterested</td>
<td>clenched jaw</td>
</tr>
<tr>
<td><strong>LEGS</strong></td>
<td>Normal position / relaxed</td>
<td>Uneasy, restless, tense</td>
<td>Kicking/legs drawn up</td>
</tr>
<tr>
<td><strong>ACTIVITY</strong></td>
<td>Lies quietly, normal position, moves</td>
<td>Squirming, shifting back and forth/tense</td>
<td>Arched, rigid or jerking</td>
</tr>
<tr>
<td></td>
<td>easily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CRY</strong></td>
<td>No cry awake/asleep</td>
<td>Moans/whimpers. Occasional complaint</td>
<td>Crying steadily, screams/sobs;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>frequent complaints</td>
</tr>
<tr>
<td><strong>CONSOLABILITY</strong></td>
<td>Content, relaxed</td>
<td>Reassured by occasional touching/hugs or being talked to.</td>
<td>Difficult to console or comfort</td>
</tr>
</tbody>
</table>

3. Each of the 5 categories (F, L, A, C, C) is scored from 0-2 and these scores are then added together to give a total FLACC score.

4. FLACC Behavioural Pain Assessment Tool
Wong & Baker  SUGGESTED AGE GROUP: 4 years and over  Self-report

Point to each face using the words to describe the pain intensity. Ask the child to choose a face that best describes their own pain and record the appropriate number overleaf.

(adapted from Wong & Baker, 1988)

0  No hurt
2  Hurts little bit
4  Hurts little more
6  Hurts even more
8  Hurts whole lot
10 Hurts worst

VAS

0  1  2  3  4  5  6  7  8  9  10  Self-report
Individualized pain management plan

**PAIN CRISIS**

- **A & E**
  - A. 0-3 — Oral Paracetamol and Ibuprofen and PRN Dihydrocodeine
  - B. 4-6 — oral Paracetamol and Ibuprofen and stat dose of immediate release Morphine Sulphate
  - C. 7-10 intranasal morphine single dose stat dose of immediate release morphine sulphate

- **Ward**
  - >7 — oral oxycodone, if >7 after more than four hours of oxycodone give clonidine
  - If not controlled, start NCA iv Morphine
Acute Pain Management

1. **Baseline pain score 0-3:** If admitted prescribe analgesia as above + PRN oral morphine.

2. **Baseline pain score 4-6:** Prescribe regular oral paracetamol and diclofenac and (after stat dose oral morphine) regular oral morphine 4hrly (review after 24hours).

3. **Baseline pain score 7-10:** Give both intranasal diamorphine and oral morphine as stat doses. Prescribe regular oral morphine 4hrly + paracetamol and diclofenac.

4. **After 30min:**

5. **If pain score is 6-10 (and not on regular opioids i.e. opioid naive):** Request Paediatric Nurse Practitioner (bleep 0699) or Paediatric Anaesthetic registrar (bleep 0254) to set up NCA/PCA and prescribe:

   Appropriate (for weight) standard PCA/NCA on drug chart (using sticker) and complete appropriate standard PCA/NCA chart prior to transfer to ward.

   * DO NOT give ANY oral opioids whilst NCA/PCA opioids in progress and ensure any previous prescription for regular oral opioids is crossed off drug chart.
Morphine PCA/NCA

- **Morphine PCA (For weight ≥25kg):** increase background infusion from 4mcg/kg/hr to 10mcg/kg/hr and continue with standard prescribed PCA bolus doses (10mcg/kg). For patient ≥40kg, maximum PCA bolus is 1mg with 6min lockout and maximum background infusion can be increased to 20mcg/kg/hr (Maximum 1mg/hr for patients > 40kg).

- **Morphine NCA:** increase background infusion from 20mcg/kg/hr to 30mcg/kg/hr. For persistent severe pain consider increasing NCA background further, if clinically indicated, to 40mcg/kg/hr (maximum 2mg/hr for patient weight ≥40kg). Continue with standard boluses (10mcg/kg).
Fentanyl PCA/NCA:

1. Fentanyl PCA/NCA may be considered as an alternative to morphine in patients who respond poorly / exhibit tolerance to morphine or in cases of morphine-allergy. (Refer to appendix for standard fentanyl NCA/PCA protocols)

2. Fentanyl PCA (For weight ≥25kg): increase background infusion from 0.2mcg/kg/hr to 0.4mcg/kg/hr for patient ≥40kg and continue with standard prescribed PCA bolus doses (0.4mcg/kg), and bolus dose can be increased to 0.6mcg/kg if needed. For

3. Fentanyl NCA: increase background infusion from 0.4mcg/kg/hr to 0.6mcg/kg/hr for patient ≥40kg and continue with standard NCA bolus doses (0.4mcg/kg). For patient weight ≥20 - <40kg, increase bolus dose to 0.6mcg/kg/hr and continue with standard background infusion (0.2mcg/kg/hr).

❖ patient weight ≥20 - <40kg, increase bolus dose to 0.6mcg/kg/hr and continue with standard background infusion (0.2mcg/kg/hr).

❖ Only consider using ‘out of protocol’ fentanyl regimes for those patients meeting the criteria for use described above.
Step 2: Further management
Consider increasing clonidine dosage up to a maximum of 5mcg/kg TDS

1. For patients on morphine NCA / PCA in whom pain remains resistant to step 1 of ‘out of protocol’ regime described above (i.e. pain scores remain > 6/10 for more than 4 hours), consider increasing bolus morphine doses by 50%, e.g. from 10mcg/kg/to 15mcg/kg and/or commencing a ketamine NCA / PCA in addition to morphine NCA / PCA.

2. Patients receiving ketamine NCA / PCA must be nursed in HDU

3. Ketamine NCA / PCA is made up manually by adding weight-banded dose of ketamine to make up a total volume of 50mL with sodium chloride 0.9%.

4. For NCA in patients weighing 4–19.9kg add 10mg ketamine.

5. For NCA in patients > 20kg and for PCA in patients > 25kg add 50mg ketamine.

   (PCA method is not currently used in patients < 25kg)
Further management

- 2. Regular oral clonidine 3 micrograms/kg 8 hourly when NCA/PCA commenced (or if adolescent give a maximum of 100 micrograms tds). Monitor BP closely while on Clonidine!
- 3. Naloxone, chlorphenamine and ondansetron as PRN
- 4. Regular IV/PO paracetamol and PO ibuprofen OR diclofenac and PRN lactulose
Supportive care - Acute Pain Management

• Regular re-assessment
• Incentive spirometer

• Fluids
• Oxygen
• Adjuvants
  • NSAIDs (RCT of ketoprofen showed no benefit)
  • Laxatives
  • Anti-pruritics
  • Anti-emetics

• Discharge planning
  • Weaning plan for analgesics

Bartolucci et al 2009
Acute treatment of sickle pain

• Acutely
  • Target different pathways
  • Anti-adhesives: Rivipansel Phase 2 trial: 83% reduction cumulative opiate dosing
    • Not replicated in phase 3 trials
  • Anti-inflammatory agents

• Role of transfusion
  • ‘Transfusion is not recommended in uncomplicated painful crisis’
  • Pilot data shows no benefit
  • Admissions date shows decrease in mortality and re-admission rate

<table>
<thead>
<tr>
<th></th>
<th>Mean hospital stay (days)</th>
<th>Total opiate use (mg/kg)</th>
<th>Mean decrease daily pain score</th>
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<tbody>
<tr>
<td>Transfused</td>
<td>4.2</td>
<td>1.6</td>
<td>51%</td>
</tr>
<tr>
<td>Non transfused</td>
<td>5.8</td>
<td>4.2</td>
<td>17%</td>
</tr>
<tr>
<td>p =</td>
<td>0.44</td>
<td>0.33</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Kelly et al 2015
Nouraie and Gordeuk 2015
Weaning analgesic medication:

**Clonidine:** Clonidine works synergistically with opioids and may reduce the dose of opioid required and also facilitate opioid withdrawal. Wean opioids first, then gradually decrease clonidine to avoid any potential rebound hypertension (see clonidine monograph in paediatric formulary). If duration of clonidine therapy is < 2 weeks it may be stopped without a weaning programme. If duration of clonidine therapy > 14 days then reduce daily over 5 days.

**Morphine:** Where opioids have been used continuously for > 1 week, their withdrawal should be gradual. Weaning may involve giving oral morphine, initially at an equivalent dose to the intravenous dose, for 24 hours and then reducing.

1. A typical 5 day opioid weaning plan could be as follows:

**Opioids used for >1 week:**

1. Wean background NCA / PCA gradually until bolus only. Then consider halving bolus or alternatively convert to oral morphine. For continuous IV infusions consider reducing by 1 micrograms/kg/12 hours  **OR:**

2. Convert to oral Morphine when IV rate 10 micrograms/kg/hr (240 micrograms/kg/24 hours): The equivalent oral dose would be 80 micrograms/kg PO 4 hourly (480 micrograms/kg in 24 hours). Wean over 5 days: 80–60–40–20 micrograms/kg PO 4 hourly).
New ways of treating sickle cell pain

• Acutely
  • Target different pathways
  • Anti-adhesives
  • Anti-inflammatory agents

• Prevention
  • Increase HbF
  • Anti-sickling drugs
  • Anti-adhesives
  • Anti-platelet agents
  • Transfusion

• Role of blood transfusion
Prevention of recurrent acute pain crises

- Increase HbF
  - Hydroxycarbamide
- L-glutamine
- Anti-sickling drugs
  - Voxelotor (GBT 440)
- Anti-adhesives
  - Crizalizumab
- Anti-platelet agents
  - Prasugrel

Ataga et al 2017, Nihara 2018
Summary and conclusions

• Pain is common in sickle cell disease
• Pain phenotypes may vary based on underlying etiology/mechanisms
• One or more mechanisms may be active at a given time in a patient (acute on chronic pain)
• Pain management should be individualized
• Include comprehensive pain management plan when possible including integrative approaches
• Future research is needed for improved understanding of pain mechanisms, effective pain management of SCD pain
Geographic pattern of pain – a flavour
Geographic Differences in Phenotype and Treatment of Children with Sickle Cell Anaemia from the Multinational DOVE Study

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1Evelina Children’s Hospital, and Guy’s and St. Thomas’ Hospital, London, UK; 2Clinic of Pediatric Hematology-Oncology, Azienda Ospedaliera-University of Padua, Padua, Italy; 3King’s College Hospital, Denmark Hill, London, UK; 4Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston, Massachusetts, USA; 5UCSF Benioff Children’s Hospital Oakland, Oakland, CA, USA; 6U.S. Army Medical Research Unit-Kenya, Centre for Clinical Research, Kenya Medical Research Institute, Kisumu, Kenya; 7Pediatric Department and Clinical Research Center, Faculty of Medicine, Alexandria University, Alexandria, Egypt; 8Eli Lilly and Company, Indianapolis, IN, USA; 9Department of Pediatrics and Adolescent Medicine, American University of Beirut, Beirut, Lebanon

Sponsored by Daiichi Sankyo Company, Ltd. and Eli Lilly and Company
Phase 3 double-blind, randomised, placebo-controlled, parallel-group, multinational study

Conducted at 51 sites in 13 countries across 4 continents

n=number of subjects in the specified category; OLE=open-label extension

## Demographics

<table>
<thead>
<tr>
<th>Parameter Assessed [n (%)]</th>
<th>SSA (N=148)</th>
<th>Americas (N=57)</th>
<th>North Africa/Middle East (N=110)</th>
<th>Europe (N=26)</th>
<th>Total (N=341)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 to &lt;6 years</td>
<td>32 (21.6)</td>
<td>9 (15.8)</td>
<td>17 (15.5)</td>
<td>9 (34.6)</td>
<td>67 (19.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 to &lt;12 years</td>
<td>72 (48.6)</td>
<td>22 (38.6)</td>
<td>29 (26.4)</td>
<td>9 (34.6)</td>
<td>132 (38.7)</td>
<td></td>
</tr>
<tr>
<td>12 to &lt;18 years</td>
<td>44 (29.7)</td>
<td>26 (45.6)</td>
<td>64 (58.2)</td>
<td>8 (30.8)</td>
<td>142 (41.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>75 (50.7)</td>
<td>32 (56.1)</td>
<td>52 (47.3)</td>
<td>14 (53.8)</td>
<td>173 (50.7)</td>
<td>0.733</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0 (0.0)</td>
<td>1 (1.8)</td>
<td>110 (100.0)</td>
<td>5 (19.2)</td>
<td>116 (34.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black or African American</td>
<td>148 (100.0)</td>
<td>54 (96.4)</td>
<td>0 (0.0)</td>
<td>20 (76.9)</td>
<td>222 (65.3)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>0 (0.0)</td>
<td>1 (1.8)</td>
<td>0 (0.0)</td>
<td>1 (3.8)</td>
<td>2 (0.6)</td>
<td></td>
</tr>
</tbody>
</table>

n=number of subjects in the specified category; N=number of randomised subjects; race=self-reported race; SSA=sub-Saharan Africa

SSA=Ghana and Kenya; Americas=Brazil, United States, and Canada; North Africa/Middle East=Saudi Arabia, Oman, Egypt, Lebanon, and Turkey; Europe=Belgium, Italy, and the United Kingdom
VOC and Hospitalization during DOVE

- The overall rate of VOCs (events per patient-year) was 3.2 in Europe, 3.0 in the Americas, 2.6 in SSA, and 2.0 in North Africa/Middle East.
- VOCs leading to hospitalisation were more likely to occur in Europe.

However, mean hospital stay per VOC was similar across regions (5.3-6.2 days).
Management of VOCs during DOVE

- In SSA, the majority of VOCs were managed as outpatient visits
- Regardless of region, almost all VOCs were treated with analgesics; approximately half were treated with intravenous fluids
- The proportion of VOC-related transfusions was greatest in Europe and North Africa/Middle East

<table>
<thead>
<tr>
<th>Parameter Assessed</th>
<th>SSA (N=148)</th>
<th>Americas (N=57)</th>
<th>North Africa/ Middle East (N=110)</th>
<th>Europe (N=26)</th>
<th>Total (N=341)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of VOCs</td>
<td>296</td>
<td>200</td>
<td>226</td>
<td>96</td>
<td>818</td>
</tr>
<tr>
<td>VOCs managed by outpatient hospital visit</td>
<td>201 (67.9)</td>
<td>10 (5.0)</td>
<td>44 (19.5)</td>
<td>6 (6.3)</td>
<td>261 (31.9)</td>
</tr>
<tr>
<td>VOCs managed by inpatient hospital visit</td>
<td>71 (24.0)</td>
<td>89 (44.5)</td>
<td>75 (33.2)</td>
<td>53 (55.2)</td>
<td>288 (35.2)</td>
</tr>
<tr>
<td>VOCs requiring analgesics</td>
<td>295 (99.7)</td>
<td>199 (99.5)</td>
<td>224 (99.1)</td>
<td>96 (100.0)</td>
<td>814 (99.5)</td>
</tr>
<tr>
<td>VOCs requiring IV fluids</td>
<td>136 (45.9)</td>
<td>113 (56.5)</td>
<td>150 (66.4)</td>
<td>46 (47.9)</td>
<td>445 (54.4)</td>
</tr>
<tr>
<td>VOCs requiring transfusion</td>
<td>19 (6.4)</td>
<td>20 (10.0)</td>
<td>42 (18.6)</td>
<td>18 (18.8)</td>
<td>99 (12.1)</td>
</tr>
</tbody>
</table>

IV=intravenous; n=number of subjects in the specified category; N=number of randomised subjects; VOCs=vaso-occlusive crises; SSA=Sub-Saharan Africa.
Conclusions

• Overall rate of VOCs during DOVE was highest in Europe > Americas > SSA > North Africa/Middle East; VOCs leading to hospitalization were more likely to occur in Europe

• Proportion of VOC-related transfusions was greatest in Europe and North Africa/Middle East

• Regional differences in VOC-related hospitalizations and transfusions may reflect differences in culture, utilization of resources, disease severity, or a combination of factors