Systemic Corticosteroids in the Treatment of Acute Vaso-occlusive Episodes in Sickle Cell Disease

By
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A thesis submitted to Johns Hopkins University in conformity with the requirements for the degree of Master of Science

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ABSTRACT

Background: Vaso-occlusive episodes (VOEs) such as pain and acute chest syndrome (ACS) are the leading cause of hospitalization in patients with sickle cell disease (SCD) and a leading cause of morbidity. Moreover, ACS is a leading cause of death. Since these events are at least partially inflammatory in nature, systemic corticosteroids have been proposed as an adjunct to therapy, though use has been hampered by reports of rebound complications, especially pain. The objective of this study was to determine the role of corticosteroids in the treatment of patients with SCD hospitalized for a VOE. Methods: A systematic review with pre-defined eligibility criteria was performed. Studies were eligible for inclusion if they were randomized controlled trials in which patients with SCD hospitalized for a VOE received intravenous or oral corticosteroids or placebo. Planned analyses included the duration of hospitalization, duration of opioid therapy, percentage of patients readmitted with pain, and other adverse events.

Results: Sixty-four citations were identified, of which three double-blind, randomized controlled trials were included. This represented a total of 110 VOEs (107 episodes in children, 3 in adults), of which 53 received corticosteroids and 57 received placebo. Meta-analysis showed a reduction in the length of hospitalization for ACS (mean difference 26.9 hours, 95% CI 12.2-41.6), a trend towards a shorter duration of opioid therapy, and fewer transfusions (RR 0.15, 95% CI 0.04-0.62) in patients receiving corticosteroids compared to those receiving placebo. However, a pooled analysis also showed a combined relative risk of 9.68 (95% CI 1.27-73.8) for readmission to the hospital for pain in the corticosteroid group compared to the placebo group.

Conclusions: While potentially efficacious, corticosteroids should be used with caution in patients with SCD until further research is done.

Thesis Readers: Kay Dickersin, PhD, and James Casella, MD
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BACKGROUND

Sickle cell disease (SCD) is the most common genetic disorder in the United States, affecting approximately 100,000 individuals.\textsuperscript{1-2} Pain is the leading cause of hospitalization and morbidity in this patient population with a lifetime prevalence of greater than 95%.\textsuperscript{3} There is a general consensus that an underlying inflammatory state contributes to the pain of SCD and to the complex phenomenon called sickle cell vasculopathy, which also consists of many other pathophysiologic components.\textsuperscript{4} Pro-inflammatory red cells and cytokines are believed to activate the vascular endothelium, compromise vascular integrity, and promote both erythrocyte and leukocyte adhesion in vascular beds. Multiple studies have demonstrated patients with SCD have chronically elevated levels of multiple inflammatory mediators\textsuperscript{5-6}, suggesting the utility of systemic corticosteroids as a treatment for vaso-occlusive events such as pain and acute chest syndrome (ACS), also a leading cause of hospitalization and death.\textsuperscript{7-8} However, the exact relationship of measures of pain to those of vaso-occlusion and sickle cell vasculopathy are still under study. Furthermore, recent retrospective data suggests a correlation between the use of corticosteroids for ACS and complications such as rebound pain and stroke\textsuperscript{9-11}, raising the question of both safety and efficacy of corticosteroids in this patient population. The phenomenon of rebound pain is especially intriguing as steroids are sometimes used as a treatment in other chronic pain states, especially those in which inflammation is implicated in the underlying pathophysiology.\textsuperscript{12-13} In order to determine the potential role of systemic corticosteroids in the management of acute vaso-occlusive episodes (VOEs) in SCD, this review consisted of a comprehensive, computerized literature search for randomized, double-blind, placebo-controlled trials in which patients with SCD were treated with intravenous (IV) or oral corticosteroids for pain or ACS.
Objectives

The objective of this review is to determine the efficacy and safety of systemic corticosteroids in the treatment of acute VOEs requiring hospitalization in children and adults with SCD. Specific outcomes include duration of hospitalization, duration of opioid therapy, re-hospitalization for rebound pain, and other adverse events.

METHODS

Eligibility criteria for study inclusion

This review included only randomized controlled trials (RCTs) or quasi-RCTs published in English in peer-reviewed journals. Observational studies were excluded. Studies of adults and children with SCD of any genotype were included if participants were randomized to receive IV or oral corticosteroids vs. placebo for the treatment of an acute VOE (defined as acute vaso-occlusive crisis (VOC) pain or ACS) requiring hospitalization, as defined by the study investigators. There were no restrictions with respect to gender, co-morbidities, or race. Studies of outpatient or emergency department pain management were not included as this would likely represent a clinically heterogeneous group of participants. Studies of synthetic mineralocorticoids and inhaled corticosteroids were also excluded. Since VOE may require additional treatments such as oxygen and blood transfusions, data for co-interventions was recorded.

Types of outcome measures

The primary outcome measure was the duration of hospitalization for VOEs in the experimental vs. control arms. Planned a priori secondary outcome analyses included 1) the difference in duration of opioid therapy required for pain control in the experimental and control
arms, 2) the difference in hospitalizations for rebound pain between the two arms, and 3) differences in other reported adverse events.

**Search Strategy**

Medline was searched combining the Medical Subject Heading (MeSH) term “Anemia, Sickle Cell” (no restrictions, 17,469 hits) with the keyword glucocorticoids (in order to exclude studies in which patients received synthetic mineralocorticoids). Ongoing studies were identified through a search of clinicaltrials.gov utilizing the search terms “sickle cell” AND “steroids”. The same terms were used to search the Cochrane Central Register of Controlled Trials (CENTRAL). The bibliographies of included articles were scanned for relevant citations, and the principal investigators of ongoing clinical trials were contacted via email for preliminary results.

**Data collection and analysis**

The titles and abstracts of the articles retrieved by the search strategy were placed into an Excel spreadsheet via Refworks software and then reviewed for relevance and eligibility criteria. All potentially eligible articles were then retrieved in full text and reviewed to be sure they met eligibility criteria prior to abstraction. Reasons for exclusion were documented. Review was not blinded to author or journal.

Included trials were evaluated for bias according to guidelines outlined in Section 8 of the *Cochrane Handbook for Systematic Reviews of Interventions*. Methodological quality of allocation was scored as Grade A: adequate concealment, Grade B: uncertain, or Grade C: clearly inadequate concealment. In addition, each study was assessed using a 0-5 scale and summarized as follows: 1) Was the study described as randomized (1=yes; 0=no), 2) Was the study described as double-blind (1=yes; 0=no), 3) Was there a description of withdrawals and
dropout (1=yes; 0=no), 4) Was the method of randomization well-described and appropriate (1=yes; 0=no), and 5) Was the method of double-blinding well-described and appropriate (1=yes; 0=no)\footnote{Conclusions were based on an evidence-based grading scheme recommended by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group\cite{16} and modified in the Evidence-Based Practice Center manual.\cite{17}}

All trials were combined and statistical analyses performed using the Review Manager (Revman 5.0). Outcomes from prospectively collected data were reported as relative risk ratios (RR) and corresponding 95% confidence intervals (95% CI) using a random-effect model as it was felt effect size would likely vary between studies. For continuous outcomes, individual and pooled statistics were calculated as weighted mean differences with 95% CIs. A priori subgroup analyses were planned for adults vs. children, VOC vs. ACS, and differences in efficacy based on sickle genotype (hemoglobin (Hb) SS and Sβ⁰ thalassemia vs. Hb SC and Sβ⁺ thalassemia).

**RESULTS**

Results of the search

As shown in figure 1, the search strategy yielded 64 citations for review. Excluded were 21 case-reports, seven editorials, six reviews, three retrospective studies, and one meta-analysis. Additional exclusions included one article that was not available in English, one title that was not retrievable as an abstract or manuscript, eleven studies in which participants were not administered IV or oral corticosteroids, and seven reports that were not specific to participants with SCD. Five full-length manuscripts were left for review, two of which were excluded since one was a case-series\footnote{As a result, three studies met the eligibility criteria for additional analysis.\cite{20-22}} and one an in-vitro study.\footnote{One ongoing trial was identified, but no preliminary results were available for analysis. This review is considered updated through February of 2014.} One ongoing trial was identified, but no preliminary results were available for analysis. This review is considered updated through February of 2014.
Description of included studies

Two of the three remaining manuscripts\textsuperscript{20-21} were single-center studies originating from the same institution conducted between 1990 and 1995. They represented 74 patients between the ages of 1.4 and 19 years (mean age approximately 6.7 years; table 1). The 74 patients represented 99 episodes of either acute pain or ACS, of which 48 episodes were randomized to receive steroids, and 51 episodes were randomized to receive placebo. Supportive care and pain management procedures followed structured protocols.

One study\textsuperscript{20} randomized patients admitted with pain to either methylprednisolone 15 mg/kg/dose up to 1,000 mg IV for 2 doses or placebo and reported a shorter duration of opioid therapy in the experimental arm (41.3 vs. 71.3 hours, p=0.03). Duration of hospitalization was not specifically quantified, but it was suggested patients were discharged following completion of opioid therapy and that the mean duration of hospitalization in the control arm was 4.14 days. Seven patients in the placebo group required intensification of therapy in that intermittent morphine sulfate doses were transitioned to a continuous infusion. This was only required in three patients in the experimental group, though results were not statistically significant (p=0.10). Four participants in the steroid group required readmission for pain between one and six days following discharge. One participant in the placebo group was readmitted for pain eight days after discharge. No other additional complications were noted.

The second study\textsuperscript{21} randomized patients admitted with “mild to moderately severe” ACS (based on standardized study criteria) to either dexamethasone 0.3 mg/kg/dose IV for 4 doses or placebo and reported a shorter mean duration of hospitalization in the experimental arm (47 vs. 80 hours, p=0.005). Participants in the dexamethasone group received a mean of 2.46 opioid doses over a 19 hour period (range 1-5 doses over 2-37 hours) compared to 20.2 opioid doses
over a 76 hour period (range 2-53 doses over 37-123 hours) in the placebo group (p<0.001 for both number of opioid doses and duration of opioid therapy). Patients receiving placebo seemed more likely to require modifications (i.e. changing the route of opioid administration from oral to IV or from intermittent dosing to continuous infusion and/or increasing the dose) of analgesic therapy (five events vs. one, p=0.08). The authors also reported statistically significant differences in duration of oxygen therapy (30 vs. 60 hours, p=0.004), persistence of fevers (4.5% vs. 67% of participants, p<0.001), and rates of clinical deterioration (0 vs. 38% patients, p<0.001) in favor of the experimental arm. Two patients (9%) treated with dexamethasone and 10 patients (47%) treated with placebo required transfusion (p=0.013). Overall, seven patients were readmitted within 72 hours of discharge. Four patients in the dexamethasone arm were readmitted with rebound pain compared to none in the placebo arm. Two other patients in the dexamethasone arm were readmitted for stroke and recurrent ACS, respectively. Only one patient who received placebo was readmitted, and this was for an aplastic crisis.

The remaining study’s stated goal was to determine if a tapered regimen of oral dexamethasone could decrease the duration of ACS (defined as a new lobar or segmental pulmonary infiltrate on a chest radiograph in combination with fever, tachypnea, dyspnea, increased work of breathing, chest wall pain, or a peripheral oxygen saturation <90% on room air) while minimizing rebound pain. The trial intended to enroll 56 patients per arm but was terminated early due to slow accrual and closure of the Comprehensive Sickle Cell Centers network, through which the trial was being conducted. Twelve participants with Hb SS (nine children, three adults; mean age 17.3 years, range 5-45) from five centers were enrolled, but one did not receive study drug due to a pharmacy error. Of the eleven remaining patients, five were randomized to oral dexamethasone (0.3 mg/kg up to 12 mg every 12 hours x 2 days, then tapered
by 0.1 mg/kg/day over 6 days with a total duration of therapy not to exceed 8 days) and six to placebo. The authors reported a reduction in duration of hospitalization by 20.8 hours in patients receiving dexamethasone compared to those receiving placebo (41.5 hours vs. 62.3 hours, p=0.024). There was no statistical difference in total opioid usage in milligrams (mg) of morphine equivalents (54.4 in the dexamethasone arms vs. 68 in the placebo arm, p=0.8852). Three patients in the placebo group received a blood transfusion compared to none in the dexamethasone group. There were no statistical differences between the groups in durations of hypoxemia or supplemental oxygen administration. Three patients in the dexamethasone arm reported a rebound painful event within two weeks of discharge (one requiring re-hospitalization) compared to one in the placebo group (zero re-hospitalizations; p=0.24). No other adverse events were reported.

**Outcome assessments**

This review represented 110 total VOEs, of which 53 received corticosteroids and 57 received placebo. Fifty-six of these episodes were attributed to VOC pain and 54 were attributed to ACS. Participants included 61 patients with Hb SS disease, one patient with Hb Sβ⁰ thalassemia, two patients with Hb Sβ⁺ thalassemia, and ten patients with Hb SC disease. Duration of hospitalization for ACS was shorter by 26.9 hours in the corticosteroid group (44.3 hrs vs. 71.2 hrs; 95% CI 12.2-41.6, p=0.0012). Duration of opioid therapy was difficult to assess as one study did not provide standard deviations and another study reported opioid use only in total mg of morphine equivalents. However, based on the results provided, there did appear to be a trend towards less opioid use in patients receiving corticosteroids. The mean duration of opioid therapy from two of the studies was approximately 30 hours in the corticosteroid group vs. 73.7 hours in the control group. The third study reported less total opioid use in the
experimental arm as well [mean in mg (SD) 54.4 (70.3) vs. 68 (78.4), p=0.8852]. A pooled analysis showed a combined relative risk of 0.15 (95% CI 0.04-0.62, p=0.008) for the need for a blood transfusion in patients admitted with ACS receiving corticosteroids compared to those receiving placebo, suggesting a protective effect of steroids. However, the combined relative risk for readmission to the hospital for rebound pain was 9.68 (95% CI 1.27-73.8, p=0.03) in the corticosteroid arm compared to the placebo arm. There did not appear to be any other statistical differences in the rate of adverse events, though one participant in the corticosteroid group was readmitted with an overt stroke 36 hours after being discharged for the treatment of ACS.\textsuperscript{21}

*A priori* subgroup analyses were planned for the effects of corticosteroids on adults vs. children, VOC pain vs. ACS, and differences in safety or efficacy between genotypes. Only three of the total 110 episodes occurred in adults, so these results are likely more applicable to children less than 19 years of age. There was not enough data to make direct comparisons between patients admitted for pain and those admitted for ACS, though there is some suggestion corticosteroids were potentially efficacious in both. Not surprisingly, the majority of episodes occurred in participants with Hb SS disease (82%). Moreover, none of the three studies addressed differences between genotypes, so no direct conclusions can be made.

**Methodological quality and risk of bias**

Overall, the methodological quality of the included studies was rated as high. All three studies were double-blind, placebo-controlled trials and demonstrated an appreciation of the need for allocation concealment. Concealment was scored as “adequate” in all three trials. Using the Jadad method\textsuperscript{15}, these studies were rated as “strong”. Two\textsuperscript{20,22} of the three studies received a rating of 5/5, and the remaining study\textsuperscript{21} received a rating of 4/5. In this study, it was noted at least two of the participants randomized to receive dexamethasone did not receive all of the
prescribed four doses. No reason for this was given. In addition, 52 patients were initially deemed eligible but subsequently excluded since three withdrew consent and six were deemed ineligible based on a retrospective review of their eligibility criteria. Also of note, 76% of participants randomized in this study were male. In another study, one of the randomized participants did not receive study drug due to a pharmacy error.

**DISCUSSION**

The objective of this study was to evaluate the efficacy and safety of systemic corticosteroids as an adjunct to the management of VOEs such as VOC pain and ACS requiring hospitalization in patients with SCD. Treatment with systemic corticosteroids appeared to reduce the duration of hospitalization by approximately one day in patients admitted with ACS. There was also a trend towards less aggressive opioid management and a shorter duration of opioid therapy in patients who received corticosteroids, at least in children. However, it is unknown whether this equates to a shorter duration of pain. Patients with ACS who received corticosteroids also tended to require less aggressive supportive measures, including a statistically and clinically significant reduction in the number of blood transfusions. However any potential benefit in the use of steroids must be weighed against its risk as the use of corticosteroids does appear to increase the risk of rebound pain and subsequent readmission to the hospital. The underlying mechanism of rebound pain following the use of corticosteroids is unknown, though proposed hypotheses include rebound inflammation and retrograde embolization of marrow fat.

This review does have several limitations. Considering the prevalence of SCD, analyses are based on relatively few participants, the majority of which are children. There also appears to be slightly more males than females represented, based primarily on a skewed distribution in
one trial. Thus it is unclear how generalizable these results are to adults and females, especially since a growing body of literature suggests differences in pain perceptions among both children and adults and between genders. Also of concern to generalizability, the majority of participants originated from the same institution as two of the three studies were from the same center and authors in the third study had affiliations with that group. Two of the three studies allowed participants to be enrolled more than once. The marked variability in pain reports and frequency of hospitalization for pain has been well-described, so it is certainly possible participants enrolled more than once skewed some of the results, though this was reported to be unlikely by the study authors. A final concern is loss to follow-up. While this was not a major issue since only hospitalized participants were reviewed, at least two participants in one study did not receive the total prescribed amount of study drug for reasons that were unclear.

VOEs such as VOC and ACS are the most common reason for hospitalization in SCD and a leading cause of both morbidity and mortality. Treatment is generally empirical and supportive. More effective, evidence-based treatments are needed. While this review suggests the potential for some benefit in the use of systemic corticosteroids in SCD, there was a high rate of rebound pain requiring hospitalization. The overall effectiveness of steroids in this patient population needs to be further explored. Efforts to decrease corticosteroid rebound toxicity have included co-treatment with transfusion and the use of prednisone instead of dexamethasone in lower relative doses. However, this analysis does suggest reduced transfusion burden may be one of the benefits of corticosteroid use.

Important questions that should be addressed with subsequent studies include the use of a steroid wean, impact of duration of steroid therapy, effects of varying steroid doses and
preparations, and the role of co-treatment with transfusion and other disease-specific therapies such as hydroxyurea. The role of steroids in children with both SCD and asthma needs to be further studied. Corticosteroids are standard in children experiencing an asthma exacerbation who do not have SCD\textsuperscript{35-36}, and it is known children with both SCD and asthma experience more sickle-related complications\textsuperscript{37-38}, so it is feasible recommendations regarding corticosteroid use might be different in this subset of patients. Additional trials will also be required to evaluate potential mediators such as genotype and age. Before steroids are used routinely, the potential association with stroke should also be further explored as should the underlying mechanisms of rebound pain.

Investigators in one of the included trials\textsuperscript{22} attempted to study the impact of a steroid wean on rebound pain, but this study was closed early. Based on their experience, the authors estimated it would take as many as 25 clinical sites and five years of accrual to answer this research question. This stresses the importance of multi-center collaborations in improving the standard of care for children and adults with SCD.

**CONCLUSIONS**

Using the GRADE criteria\textsuperscript{16,39}, the strength of recommendation for the use of systemic corticosteroids in patients admitted for acute VOC pain or ACS of SCD is 2B. This recommendation is based on three relatively sound clinical trials in small numbers of mostly children which yielded both benefits and possible harms of therapy. While the potential for efficacy exists, systemic corticosteroids should be used with caution in patients with SCD. Further research into the phenomenon of rebound pain following the use of corticosteroids may help to further elucidate the underlying pathophysiology of varying pain phenotypes in SCD and improved treatments.
Disclosures
Conflict-of-interest disclosures: LVB declares no competing financial interests

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References


23) ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT00263562, Steroid Treatment for Sickle Cell Pain Crises (PI: Charles Macias, MD, MPH);
Available from (last accessed June 28, 2010):
http://clinicaltrials.gov/ct2/show/NCT00263562?term=sickle+cell+and+steroids&rank=1


Figure 1: Flow chart showing summary of literature search, review process, and selection of trials.

Potentially relevant studies identified (64)
- Medline (62)
- CENTRAL (1)
- Clinicaltrials.gov (1)

Duplicates (0)

Titles and abstracts screened (64)

Excluded (59)
- Case reports (21)
- Editorials (7)
- Reviews (6)
- Retrospective analyses (3)
- Meta-analysis (1)
- Not available in English (1)
- Not administered corticosteroids (11)
- Not specific to SCD (7)
- No results available (1)
- Abstract/manuscript not available (1)

Full texts retrieved and screened

Excluded (2)
- Case series (1)
- In vitro study (1)

Randomized controlled trials included in final analysis
**TABLE I. Effects of Corticosteroids on Opioid Dosing and Pain in SCD**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients (Episodes*)</th>
<th>Duration of Opioid Therapy (hours) **</th>
<th>Readmissions for Pain (no. of patients) **</th>
<th>Mean time to Readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffin 1994</td>
<td>36 (56)</td>
<td>41.3 vs. 71.3</td>
<td>4 vs. 1</td>
<td>60 hours</td>
</tr>
<tr>
<td>Bernini 1998</td>
<td>38 (43)</td>
<td>19 vs. 76</td>
<td>4 vs. 0</td>
<td>39 hours</td>
</tr>
<tr>
<td>Quinn 2011</td>
<td>11 (11)</td>
<td>NE</td>
<td>1 vs. 0</td>
<td>NE</td>
</tr>
</tbody>
</table>

* Episodes of either pain or ACS; ** Comparing steroid group to placebo group; NE not evaluated
Curriculum Vitae

Name
Lucien Vandy Black, M.D., FAAP (Vandy)

Current Position
Staff Physician
St. Jude Affiliate
OLOL Children’s Hospital
Baton Rouge, Louisiana

Citizenship
USA

Date of Birth
August 6, 1976

Place of Birth
Tuscaloosa, Alabama

Martial Status
Married

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7777 Hennessy Blvd
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Education
2009-Present
Johns Hopkins University School of Public Health
Graduate Training Program in Clinical Investigation
Master’s Degree in Clinical Investigation
Baltimore, Maryland

1999-2003
University of Alabama School of Medicine
Medical Doctorate
Birmingham, Alabama
1995-1999  University of Alabama
Bachelor of Science, *magna cum laude*
Tuscaloosa, Alabama
Major: Biology
Minor: Psychology
   Honors: Phi Beta Kappa, Phi Kappa Phi

1991-1995  Tuscaloosa County High School
Northport, Alabama
Advanced Diploma

**Postdoctoral Training**

2006-2009  Pediatric Hematology and Oncology Fellowship
The University of Alabama at Birmingham
Birmingham, Alabama

2004-2006  Pediatric Resident
The University of Alabama at Birmingham
Birmingham, Alabama

2003-2004  Pediatric Intern
The University of Alabama at Birmingham
Birmingham, Alabama

**Licensure**

2004-Present  State of Alabama Medical License #26220
2009-Present  State of Maryland Medical License #D0068909
2012-Present  State of Louisiana Medical License #MD.205621

**Certifications**

2011  ABP Pediatric Hematology-Oncology
2006  ABP General Pediatrics

**Current and Past Appointments**

2012-Present  Staff Physician, Pediatric Hematology-Oncology
               St. Jude Affiliate, OLOL Children’s Hospital

2013-Present  Adjunct Clinical Faculty Member
               St. Jude Children’s Research Hospital
               Memphis, Tennessee

2014-Present  Clinical Assistant Professor of Pediatrics
Louisiana State University Health Sciences Center
School of Medicine
New Orleans, Louisiana

2011-2012  Assistant Professor, Pediatric Hematology
            Johns Hopkins University

2009-2011  Instructor, Pediatric Hematology
            Johns Hopkins University

2009-2012  Sickle Cell/BTRP Scholar
            Johns Hopkins University

2007-2009  Associate Member, UAB Comprehensive Neuroscience Center

2006-2009  Fellow, UAB Pediatric Hematology-Oncology

2003-2006  Resident, UAB Department of Pediatrics

**Professional Organizations**

2007-Present  American Society of Pediatric Hematology and Oncology
2007-Present  American Society of Hematology
2003-Present  American Academy of Pediatrics (Fellow, July 2010-Present)
2003-Present  American Medical Association
2008-2013    International Association for the Study of Pain
2008-2013    American Pain Society
2007-2013    American Society of Clinical Oncology
2008-2010    Society for Neuroscience

**Committees**

**National**
2010-Present  ASPHO Professional Development Committee
2013-Present  EPIC trial enrollment committee

**Local**
2014-Present  OLOL Blood Utilization Review committee
2013-Present  OLOL Children’s Hospital Pharmacy and Therapeutics committee
2007-2009    Children’s Hospital of Alabama Medical Ethics Committee
2007-2009  Children’s Hospital of Alabama Pediatric Palliative Care Initiative
2003-2005  UAB Department of Pediatrics Housestaff Council
2002-2003  UAB Medical Education committee
2002-2003  UAB Medical Student Education and Programs Committee – Tuscaloosa Campus
2000-2001  UAB Medical Student Orientation committee
1999-2003  UAB Pediatric Interest Group, President 2000-2001

**Awards**
2010  International Association of Pediatricians *Top Pediatrician* in Baltimore, MD.

2009  Cambridge Who’s Who
2008  UAB Institutional Nominee, Burroughs Wellcome Fund 2009 Career Award for Medical Scientists
2008  Dixon Fellowship Training Program Award
2008-2010  America’s Top Pediatricians, SLD Industries, Simi Valley, CA.
2003-2006  Letters of Commendation in Neonatology, Newborn Nursery, Pulmonology, Wards, Neurology, Hospitalist, and Hematology-Oncology

2003  Pediatric Recognition Award – Awarded to the senior medical student from the Tuscaloosa branch campus of UAB with the best overall performance in the Pediatrics clerkship
2000  Letter of Commendation for Introduction to Clinical Medicine course

1995-1999  University of Alabama President’s List
1995-1999  University of Alabama Dean’s List

**Educational Activities**
2012-Present  OLOL Children’s Hospital Core Faculty
Pediatric Hematology-Oncology Attending
2011-2012  Director, Pediatric Hematology Outpatient Rotation, JHU-NIH Pediatric Hematology-Oncology Fellowship Program

2009-2012  Pediatric Hematology Attending, 4th year medical students, pediatric residents, and pediatric hematology-oncology fellows, 2-3 months/year (JHU)

2009-2012  Pediatric Hematology Clinic Attending, 4th year medical students, pediatric residents, and pediatric hematology-oncology fellows, ½ day/week (JHU)

2009-2012  Pediatric Bone Marrow Aspirate and CSF Interpretations, 2-3 months/year (JHU)

2009-2012  Pediatric Hematology Multidisciplinary Weekly Clinic Conference CME accredited, participant (JHU)

2009-2012  “Evaluating a child with anemia” lecture to 3rd and 4th year medical students – once/year (JHU)

2007-2009  Introduction to Clinical Medicine Preceptor for first and second year medical students (UAB)

2007-2009  Lecturer for UAB Surgical Physician Assistant Program
- Pediatric Hematology and Oncology (2007-2008)
- Pediatric Pain Management (2008)

2006-2009  UAB Fellow teaching residents and medical students (Letter of Commendation, January 2009)

2003-2006  UAB Resident teaching interns and medical students

**Volunteer Activities**

2012-Present  Board of Directors, Cancer Services of Greater Baton Rouge


**Special Training**

2014  Stanford Faculty Development Program for Medical Teachers Preceptor: Chad Miller, MD

2009  American Society of Hematology Clinical Research Training Institute (1 of 20 selected participants through a competitive application process)
**Research/Academic Interests**
1. Characterizing the genetic, hormonal, and developmental determinants of pain perceptions in children
2. Pain management in sickle cell disease
3. Symptom management in Pediatric Oncology
4. Clinical trials in sickle cell disease
5. Management of children with neutropenia and bone marrow failure syndromes

**Collaborative Research Projects/Clinical Protocols**
1. A prospective, multicenter, double-blind, randomized, placebo-controlled study of nitric oxide for inhalation in the acute treatment of sickle cell pain crises
   - Sponsor: INO Therapeutics
   - Role: UAB Institutional Co-Investigator
2. Intranasal oxytocin for the treatment of pain associated with interstitial cystitis
   - Sponsor: UAB Department of Anesthesiology
   - PI: Meredith Robbins, PhD
   - Role: Co-Investigator
3. Evaluating the prevalence of fatigue in childhood cancer patients with a poor prognosis
   - Sponsor: Children’s Oncology Group Palliative Care Subcommittee
4. Evaluation and treatment of stroke in adults with sickle cell disease
   - PI: John J. Strouse, MD, PhD
   - Role: JHU Co-investigator
5. Interpersonal quality of care for patients with painful crises due to sickle cell disease
   - Sponsor: NIH/NHLBI
   - PI: Mary Catherine Beach, MD, MPH
   - Role: JHU Co-Investigator
6. Psychometric Evaluation of the Inpatient Pediatric Physical Activity Questionnaire (IPPAQ) in pediatric patients with sickle cell disease hospitalized with vaso-occlusive pain
   - Sponsor: NIH/NHLBI
   - PI: William Zempsky, MD
   - Role: JHU Institutional co-investigator
7. Pain in sickle cell disease
   - Sponsor: NIH/NHLBI
PI: Jennifer Haythornthwaite, PhD
Role: JHU Co-investigator

8. Validation of the Sickle Cell Disease Pain Burden Interview
PI: William Zempsky, MD
Role: JHU Institutional co-investigator

**Grants and Contracts**

**Current**
Role: OLOL institutional PI
Sponsor: Mast Therapeutics
Project period: June 2013-Present
Amount: $200,895

EPIC tissue oxygenation sub-study: A study of the effects of MST-188 on tissue oxygen saturations in sickle cell subjects experiencing a vaso-occlusive crisis
Role: Institutional PI
Sponsor: Mast Therapeutics
Project period: April 2014-Present
Amount: $5,875

A phase II, Multicenter, Randomized, Placebo-controlled, Double-blind Study to Assess Safety and Efficacy of SelG1 in Sickle Cell Disease Patients with Sickle Cell-Related Pain Crises (SUSTAIN)
Role: Institutional PI
Sponsor: Selexys Pharmaceuticals Corporation
Project period: March 2014-Present
Amount: $112,180

**Past**
Comprehensive Sickle Cell Center at JHU and UAB
Sickle Cell Scholar Component
NIH 5U54HL090515
PI: James Casella, MD
Role: Provided salary support plus $30,000/year for research
Period: July 2009-February 2012

The Dixon Fellowship Training Program Award
PI: Vandy Black, M.D.
Project Period: July 2008-July 2009
Amount: $5,000 Discretionary Funds plus Salary Support

UAB Center for Palliative Care Intramural Research Grant Program
PI: Vandy Black, M.D.
Title: Exploring the Role of Genetic Polymorphisms in the OPRM1 and COMT Genes on the Treatment of Painful Vaso-Oclusive Crises in Sickle Cell Disease
Project Period: May 2008-May 2009
Amount: $6,500

Manuscripts


Abstracts


Book Chapters


Multimedia and Educational Materials

Local Research or Educational Presentations

2. Isolated CNS Relapse of Acute Lymphocytic Leukemia. Pediatric Tumor Board Presentation, August 2006.


**Invited Visiting Lectures**


2. Exploring the Role of Genetic Polymorphisms in the OPRM1 and COMT Genes on Pain Perceptions and the Treatment of Painful Vaso-Occlusive Crises in Sickle Cell Disease. SIT Trial annual meeting, St. Louis, MO, November 2008.

Ad-Hoc Reviewer Positions

National Organization for Rare Disorders
Pediatrics
Journal of Pediatrics
Pediatric Blood & Cancer