**Title:** Intravenous Fluid Therapy and Hospital Outcomes for Vaso-Occlusive Episodes in Children, Adolescents, and Young Adults with Sickle Cell Disease[[1]](#footnote-1)

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**Abbreviation Key:**

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| Abbreviation | Full Term |
| ACS | Acute Chest Syndrome |
| HLOS | Hospital Length of Stay |
| ICU | Intensive Care Unit |
| IVF | Intravenous Fluid |
| mIVF | Maintenance Intravenous Fluid |
| PICU | Pediatric Intensive Care Unit |
| SCD | Sickle Cell Disease |
| VOE | Vaso-Occlusive Episodes |

**Abstract**

**Background:** While intravenous fluid (IVF) therapy in patients with sickle cell disease (SCD) admitted for a vaso-occlusive episodes (VOE) can help reduce red blood cell sickling, clinical practice varies across institutions. We examined the relationship between IVF therapy and hospital length of stay (HLOS), as well as adverse events, such as acute chest syndrome (ACS), pediatric intensive care unit (PICU) transfer and 28-day readmission.

**Methods:** This is a single-center retrospective analysis of SCD VOE hospitalizations between January 2015 and April 2020. Patients with SCD, age 0-30, with consecutive hospitalizations for VOE were included. For the first 3 days of each admission, an “IVF ratio” was calculated by dividing actual IVF rate administered by weight-based maintenance IVF (mIVF) rate.

**Results:** A total of 617 hospitalizations for 161 patients were included. Mean HLOS was 5.7 days, (SD 3.9), and mean IVF volume over the first 3 days of admission was 139.6 ml/kg/day (SD 57.8). Multivariate analysis showed that for each additional 0.5 times the mIVF rate, HLOS increased by 0.53 days (P<0.001; 95% CI: 0.609–0.989), but there was no significant association between IVF therapy and adverse events. History of chronic pain was associated with increased odds of readmission (OR, 6.4; 95% CI: 3.93 – 10.52).

**Conclusions:** Despite the theoretical potential for IVF therapy to slow down the sickling process, our findings suggest that increased IVF therapy was associated with prolonged HLOS, which places a burden on patients, families, and the health system.

**Introduction**

Vaso-occlusive episodes (VOE) represent a major complication of sickle cell disease (SCD). VOEs occur when sickled red blood cells block the flow of blood and oxygen to tissues, causing severe pain and inflammation.1 The pathophysiology of VOEs is complex and is due to abnormal hemoglobin within sickle-shaped red blood cells, which accumulate in blood vessels and lead to endothelial dysfunction, activation of the coagulation cascade, inflammation and the release of various pro-inflammatory cytokines and chemokines.1 In addition, other factors such as infection, dehydration, cold exposure and stress exacerbate VOEs by further promoting the adhesion of red blood cells to the endothelium, inducing the release of vasoactive mediators.1

VOEs can last for several hours to days and, over time, can lead to chronic pain and disability,2 leading to a significant economic burden across a patient’s lifespan.3 Factors such as disease severity and non-adherence to disease-modifying therapies, such as hydroxyurea, contribute to the frequency of VOEs.4-7 VOEs are the leading cause of emergency department (ED) visits and hospitalizations, and greatly impact the quality of life for individuals with SCD.8,9 The main strategies for managing a VOE are supportive care with intravenous fluid (IVF) therapy and analgesics coupled with non-pharmacological approaches.10

The goal of IVF therapy is to increase intravascular volume, thereby improving blood flow to reduce the risk of further blood vessel occlusion, hence reducing pain.10,11 IVF also replaces fluid loss due to hyposthenuria, a common issue in SCD patients secondary to chronic microvascular kidney injury.12-14 However, excess IVF during a VOE can lead to complications, including volume overload, acute chest syndrome (ACS) and electrolyte imbalance, all of which may lead to prolonged hospital admissions.15-17 Currently, there is limited data regarding the safety and effectiveness of different IVF therapy approaches in pediatric and adult patients with SCD, which is reflected in the heterogeneity in clinical practices across providers and institutions.11,18

In this retrospective analysis, we examined the relationship between IVF therapy in children, adolescents, and young adults with SCD admitted for a VOE and key clinical outcomes, including hospital length of stay (HLOS), development of ACS, transfer to the pediatric intensive care unit (PICU) and readmission within 28 days. We hypothesized that excess IVF therapy would prolong HLOS and lead to adverse events, including ACS, PICU transfer and 28-day readmission.

**Methods**

*Study Design*

This is a single-center retrospective analysis of VOE hospitalizations in patients with SCD between January 2015 to April 2020. This study was approved by the institutional review board (IRB # 2020-3497). No informed consent was required since the study used de-identified data.

*Population*

Electronic medical records of patients between the ages of 0 and 30 years with SCD (HbSS, HbSC, HbSβ0-thalassemia and HbS-β⁺ thalassemia) hospitalized for VOEs were included in this study. Repeat admissions for the same patient were included as unique encounters in the study. Patients with SCD who were admitted for other complications, such as splenic or hepatic sequestration, fever or bacteremia were excluded. To assess the relationship between IVF therapy with the development of ACS, patients with ACS on presentation or admission were also excluded.

*Demographics and Clinical Variables*

Demographic data, including age, gender, SCD genotype was collected. Other clinical variables including HLOS, incidence of ACS, transfer to the PICU, readmission within 28 days, new oxygen requirement, blood transfusion requirement, history of chronic pain, and use of disease-modifying medications, such as hydroxyurea, voxelotor and crizanlizumab were also recorded. Chronic pain was defined as pain present on most days for at least 6 consecutive months and/or treated with a selective serotonin reuptake inhibitor (SSRI) or long-acting opioid.19

The average hourly IVF rate received by each patient was compared to their estimated weight-based maintenance IVF (mIVF) rate, calculated using the Holliday-Segar method (“4-2-1 rule”),20 over the first 3 days of admission. The “IVF ratio” was calculated by dividing actual IVF rate administered by the estimated weight-based mIVF rate for the first 3 days of each admission. The IVF ratio is a useful measure of the amount of IVF therapy administered compared to estimated weight-based mIVF over the first 3 days of hospitalization.21 This metric was used to assess the appropriateness of IVF therapy in patients with SCD during VOEs and to predict clinical outcomes such as HLOS, incidence of ACS, transfer to the PICU, readmission within 28 days, new oxygen requirement, and blood transfusion requirement. The first 3 days of admission were selected to assess IVF in our analysis because this period aligns with the resuscitation and stabilization phase of care.21 New oxygen requirement was defined as documented supplemental oxygen above baseline requirement. ACS was identified using established criteria of pulmonary infiltrate on chest X-ray along with fever or respiratory symptoms.22

*Outcomes*

The primary outcome was association of IVF ratio with HLOS. The secondary outcome analyzed was association between IVF ratio and adverse events, including development of ACS, transfer to the PICU and readmission within 28 days in patients with SCD admitted for VOEs.

*Statistical Analysis*

Descriptive statistics, including frequency and distribution, were conducted to analyze demographics, clinical data, and hospitalization characteristics. Non-normally distributed continuous variables were log-transformed. Bivariate analyses between the dependent variables and the potential covariates were conducted: correlation coefficients between two continuous variables, t-tests between categorical and continuous variables and chi-square tests between two categorical variables. All variables with unadjusted p values < 0.05 by the bivariate analysis were added into the model of multivariate analysis. Multivariable linear regression analysis was conducted for the HLOS outcome. Multivariable logistic regression analysis was conducted for the ACS, PICU transfer and readmission outcomes. All analyses were conducted in SAS 9.4 (Cary, NC) and significance level was set at p < 0.05.

**Results**

*Patient and Hospitalization Characteristics*

A total of 617 individual patient encounters who were hospitalized due to a VOE were identified from 161 patients with SCD. The mean age of the patient cohort upon hospital admission was 13.5 years (range 0.36 – 25.01, standard deviation (SD) 5.2). There was a higher proportion of male patients (328/617, 51%) and those with hemoglobin SS disease genotype (488/617, 79.1%), and nearly half of patients were taking hydroxyurea (288/617, 46.7%). The mean HLOS was 5.7 days (SD 3.9). The mean IVF volume during the total admission and over the first 3 days of admission was 49.9 ml/kg/day (SD 20.3) and 139.6 ml/kg/day (SD 57.8), respectively. Blood transfusions were given to patients in 106 encounters (17.2%); of these, three needed exchange transfusion during their hospitalizations. Table 1 summaries study population.

*Clinical Outcomes*

During the 5-year study period, ACS occurred in 141 admissions (22.9%), new oxygen requirement occurred in 131 admissions (21.2%), PICU transfer occurred in 15 admissions (2.4%), and readmission occurred within 28 days following 121 discharges (19.7%) (Table 1).

Linear regression analysis was performed to examine the association between HLOS and IVF ratio, as well as other clinical variables including new oxygen requirement, history of chronic pain, hydroxyurea use, blood transfusion, 28-day readmission, and PICU transfer. Multivariable analysis of the mean IVF ratio showed that during the first 3 days of admission, HLOS increased by 0.53 days for each additional 0.5 times the mIVF rate (P<0.001; 95% CI: 0.609–0.989) (Figure 1). Other factors that were significantly associated with prolonged HLOS included PICU transfer (p < 0.001; estimate: 0.4836, 95% CI: 0.106–0.692), 28-day readmission (p = 0.035; estimate: 0.1126, 95% CI: 0.008 – 0.217), history of chronic pain (< 0.001; estimate: 0.3346, 95% CI: 0.231 – 0.438), hydroxyurea use (p < 0.001; estimate: 0.1906, 95% CI: 0.088 – 0.293) and blood transfusion during admission (p < 0.001; estimate: 0.5116, 95% CI: 0.393 – 0.630) (Table 2). There was no significant association between new oxygen requirement and prolonged HLOS. In the univariate analysis, patient gender, age at admission and fluid bolus in the ED were not associated with prolonged HLOS and thus were excluded from the multivariate models.

Logistic regression analysis was performed to examine the association of IVF ratio and other controlling factors, including new oxygen requirement, history of chronic pain, hydroxyurea use, requirement of blood transfusion, readmission, and transfer to the PICU with adverse events. Multivariable analysis of the mean IVF ratio during the first 3 days of admission was not associated with increased odds of developing ACS (OR, 0.90; 95% CI: 0.32 – 2.54). New oxygen requirement and blood transfusion were both, independently, associated with significantly increased adjusted odds of developing ACS (OR, 12; 95% CI: 5.79 – 24.88 and OR 4.6, 95% CI: 2.15 – 9.85, respectively). After adjusting for confounders, multivariable analysis of the mean IVF ratio over the first 3 days of admission showed no significant increase in the odds of PICU transfer (OR, 0.98, 95% CI: 0.14 – 7.10) or readmission (OR, 1.51, 95% CI: 0.75 – 3.10). Nevertheless, history of chronic pain was associated with an increased adjusted odds of readmission (OR, 6.4; 95% CI: 3.93 – 10.52) (Table 3).

**Discussion**

In our study, we evaluated the relationship between IVF therapy to HLOS and other adverse events during a VOE admission in a large cohort of children, adolescent, and young adults with SCD. Previous studies on IVF therapy for SCD patients mainly focused on adults, and those that included pediatric populations were limited by small sample size. IVF therapy is crucial for treating patients with SCD during VOEs. Low fluid intake during a VOE and persistent hypovolemia from hyposthenuria decreases plasma volume and raises blood viscosity, worsening the sickling process.23 Administration of IVF therapy aims to restore euvolemia and provide maintenance fluids if oral intake is insufficient to reduce the sickling process and achieve volume repletion.10,24,25 Despite widespread use of fluids in management of VOEs, the best approach for therapy, including the rate, amount, type and duration, remains uncertain.

In our study, we examined IVF volume, using IVF ratio, and found that the HLOS increased by half a day for every 0.5 increase in mIVF rate. Our approach allowed for a more comprehensive and accurate understanding of the relationship between IVF therapy and clinical outcomes. By focusing on the specific incremental changes in IVF volume relative to the estimated mIVF rate, we found an association between fluid administration and HLOS. The IVF ratio is particularly useful in assessing fluid administered in pediatric patients, as mIVF rates vary significantly based on weight. Without a standardized metric, it is difficult to compare IVF rates in clinical practice.

Similar to our study, Gaut et al. recently reported the association between fluid therapy volume during VOE treatment and adverse events like ACS, oxygen use and intensive care unit (ICU) transfer.15 The study found a correlation between high fluid volumes and adverse events during hospitalization, highlighting the potential risks of aggressive IVF therapy. Similarly, Gaartman et al. found that fluid overload was a frequent complication of IVF therapy in patients with SCD, and a positive history of fluid overload was independently associated with fluid overload occurrence.16 Moreover, the study also noted that hospitalizations that resulted in fluid overload were associated with a significantly prolonged duration of hospital stay when compared to individuals who did not develop fluid overload. Furthermore, Carden et al. assessed the association between normal saline bolus (NSB) in the ED and change in pain score in children with SCD presenting with VOEs and found that use of NSB was significantly associated with worse final pain scores and worse change in pain scores.26

In addition to the amount of IVF, the type and tonicity of fluids may have an impact on outcomes in VOEs. In our study, the majority of patients received normal saline with 5% dextrose as their maintenance fluid. However, previous research has indicated that reducing serum osmolality with hypotonic fluids can decrease the occurrence of sickling, whereas hypertonic solutions may impair red blood cell deformability and increase the likelihood of vascular occlusion.27-29 As a result, half-normal saline is often recommended as an appropriate choice for maintenance fluid. Although this particular aspect of fluid resuscitation was not evaluated in our study, it represents an important area for investigation in future studies.

Other factors associated with prolonged hospital stay were PICU transfer, 28-day readmission, history of chronic pain, use of hydroxyurea and red blood cell transfusion during admission. Patients requiring transfer to the ICU, or a blood transfusion are more likely to have a severe SCD phenotype, leading to a longer hospital stay. Those with a history of chronic pain, disease-modifying therapy use, and frequent readmissions also likely have a severe form of SCD disease and can therefore result in longer hospital stay. While Panepinto et al. observed that older children experiencing a VOE had a prolonged HLOS when compared to younger children (under 10 years old),30 our study did not find a significant association between age and HLOS.

Families of children with chronic conditions, like SCD, experience numerous challenges, including but not limited to financial challenges, time constraints, concerns about the child's health, anxiety about long-term care, societal stigma, and uncertain future prospects, such as time away from work for parents and missed school days.31 These factors can result in stress, maladjustment, and psychosocial difficulties for both the patient and the family. An extended hospital stay can add to the already heightened stress and strain on both patients and their families, as well as the healthcare system. For example, further disruption of daily routines can amplify the stress and anxiety levels for both patients and their families.32 Additionally, the financial burden of a lengthy hospitalization, coupled with the potential loss of income due to parents' absence from work, can exacerbate the existing financial challenges faced by these families.33

Our study's strengths lie in the large sample size and the comprehensive analysis of patient and hospitalization characteristics as well as clinical outcomes. Furthermore, the study introduced a novel metric, the IVF ratio, which measures the appropriateness of IVF therapy compared to the estimated weight-based maintenance IVF rate and allows for a more precise evaluation of the impact of IVF therapy on clinical outcomes. Our study also has several limitations worth mentioning. First, the retrospective nature of the study limited the ability to draw causal inferences, and the study's focus on a single academic center may limit the generalizability of the results. Second, our analysis of fluid replacement therapy only considered IVF intake and not oral fluid intake, for which charting is often unreliable, thus we may have underestimated the total fluid volume during admissions. Moreover, the estimated IVF is greatly influenced by the accuracy of documentation by nursing staff. We also did not account for fluid losses, such as urine output, emesis, or other unmeasurable losses, which also depend on meticulous, accurate charting, nor did we assess the overall fluid balance recorded. Thus, with our dataset, we were unable to analyze patients’ overall volume status. We also considered accounting for acute kidney injury or nephropathy on presentation to the ED, but most patients did not have a documented creatinine measurement. Additionally, our study did not examine the potential benefits of IVF administration in SCD patients during hospitalization for VOEs, such as reducing pain intensity, due to inconsistent documentation of pain scores. Finally, a potential bias exists in the data processing as it assumes each patient encounter as an independent event, however the same patient may have a predisposition to adverse events across different hospitalizations. To address this potential bias, it is possible to mitigate it by conducting analyses specifically on a subset comprising the first hospitalization of each patient during the study period.

**Conclusion**

Despite the potential benefit of fluid administration in reducing red blood cell sickling, our study findings suggest that excessive fluid administration during a VOE in SCD patients may be associated with a prolonged hospital stay, which can be burdensome for patients, their families, and the healthcare system. The results of this study may be helpful to inform and standardized clinical practice as well as contribute to the ongoing effort to improve outcomes for patients with SCD. Prospective studies to further investigate the relationship of IVF therapy, including rate and type, key clinical outcomes during VOEs in patients with SCD with the goal of reducing symptoms, while preventing complications, and limiting the use of resources that may be unnecessary or even harmful are needed.

**Conflict of Interest**

None of the authors have financial disclosures related to the submitted work.

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