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BRIEF REPORT

# Characterizing complication risk from multisite, intermittent transfusions for the treatment of sickle cell disease

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## Abstract

Blood transfusions are indicated for some acute complications of sickle cell disease (SCD). To characterize the SCD population at increased risk of transfusion-associated complications, Georgia hospital discharge data were used to estimate the frequency of intermittent transfusions and the proportion of patients receiving them at multiple institutions. Ten years of data (2007-2016) showed almost 19% of patients with SCD (1585/8529) received transfusions at more than one hospital. The likelihood of multisite transfusions increased from ages 18 through 40 and with the number of transfusions received. The results support the need to track and share transfusion histories in order to reduce complication risks.

**KEYWORDS**
blood transfusions, interoperability, patient safety, sickle cell disease

## 1 | INTRODUCTION

Many individuals with sickle cell disease (SCD) will develop acute complications that require urgent transfusions, such as acute stroke, acute chest syndrome, splenic or hepatic sequestration, aplastic crisis, or multisystem organ failure. Chronic transfusions are used for primary and secondary stroke prophylaxis, prevention of recurrent splenic sequestration, and frequent pain episodes.[1] Chronic transfusions are typically administered in an outpatient setting at a single center. Urgent transfusions may occur at multiple different sites over time.[2]

Even with appropriate pretransfusion testing and iron chelation, red blood cell (RBC) transfusions still carry risks of complications, such as alloimmunization and iron overload. RBC alloimmunization is particularly problematic in SCD because it limits subsequent transfusion options and can cause potentially fatal delayed hemolytic transfusion reactions (DHTRs). The risk of DHTRs is more common in intermittently transfused versus chronically transfused patients, and increases when patients receive multiple transfusions.[2–5] This could be related to having incomplete transfusion histories available to transfusing providers. Past studies show that a significant percentage of individuals with serologically undetectable antibody titer due to evanescence are transfused at multiple health centers and at risk for DHTRs, hyperhemolysis, and further alloimmunization.[2,6]

Georgia is home to one of the largest SCD populations in the United States—an estimated 7000-8500 of the 90 000-120 000 individuals in the country with SCD.[7,8] To characterize the SCD population at increased risk of transfusion-associated complications, the Registry and Education for Hemovigilance in Hemoglobinopathy Transfusion Therapy (REdHHoTT) project in Georgia used hospital discharge data to estimate the frequency of intermittent transfusions and the proportion of patients receiving them at multiple institutions.

Abbreviations: DHTR, delayed hemolytic transfusion reaction; ED, emergency department; REdHHoTT, Registry and Education for Hemovigilance in Hemoglobinopathy Transfusion Therapy; SCD, sickle cell disease.

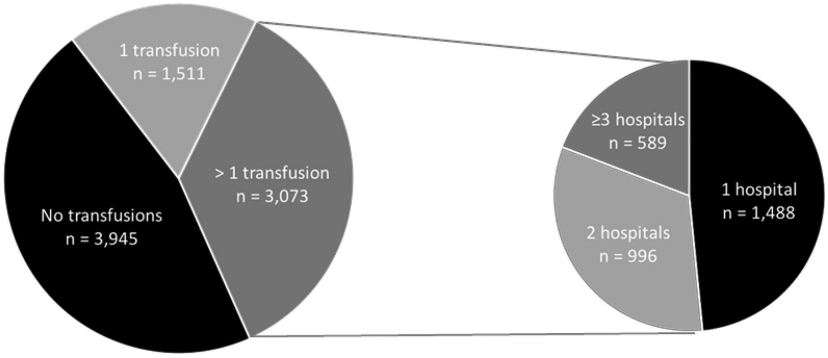


**FIGURE 1** Patients with sickle cell disease (n = 8529) identified in hospital discharge data in Georgia, 2007-2016, by the number of intermittent transfusions and hospitals where >1 intermittent transfusions were received

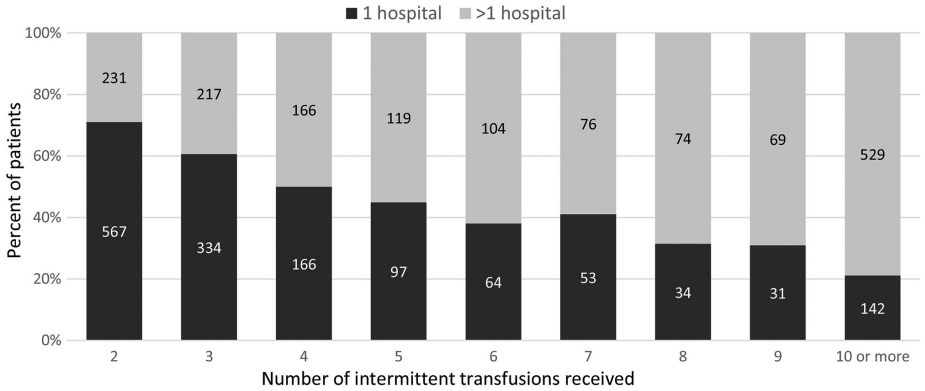


**FIGURE 2** Multiply transfused patients with sickle cell disease (n = 3073) with single-site versus multisite intermittent transfusions, by number of cumulative transfusions, 2007-2016

## 2 | RESULTS

Using longitudinal data from Georgia's Sickle Cell Data Collection Program, we characterized the use of intermittent transfusions for treatment of SCD in emergency departments (EDs) and inpatient settings in Georgia from 2007 to 2016. Patients receiving outpatient transfusions are not captured in this dataset as this analysis used hospital discharge data (ED and inpatient data only). A transfusion was defined as a single transfusion episode, regardless of the blood volume given. Individuals with SCD were defined as those who had three or more encounters with an SCD diagnosis code during the study period.[9,10] Patient age was defined as of the date the first transfusion was received during the study period. Based on a previous, unpublished analysis of Georgia Medicaid claims data, inpatient and ED transfusions represent about one-third of all SCD-related transfusions in the state.

A total of 8529 unique patients with SCD were identified in Georgia. Of these, 4584 (53.7%) had at least one ED or inpatient transfusion, and more than two-thirds of these patients (n = 3073) received multiple transfusions (Figure 1).

Fewer than half of patients with SCD who had multiple transfusions received them all at the same hospital (1488/3073); nearly one in five (589/3073) received transfusions at three or more sites (Figure 1). The likelihood of multisite transfusions increased with the total number of transfusions received (Figure 2); the Cochran-Armitage trend test was significant, at $P < .0001$. While roughly one-third of the 798 patients who had exactly two intermittent transfusions over the 10 years received them at different hospitals, a vast majority of patients (529/671, or 80%) who had 10 or more transfusions received them at multiple sites. There was no significant difference in sex distribution between patients who were multiply transfused at a single site (53% female, 46.7% male) versus those who received multisite transfusions (56.6% female, 43.4% male).

Out of the 1585 patients who had multisite transfusions, 175 patients (11%) were <10 years of age, 207 (13.1%) were 11-17, 471 (29.7%) were 18-25, 488 (30.8%) were 26-40, and 244 (15.4%) were >40.

## 3 | DISCUSSION

These findings show that almost one-fifth of patients within Georgia receive intermittent transfusions at multiple hospital sites. Given the lack of a statewide system to share patient transfusion histories across hospitals, this likely leads to increased risks of transfusion complications such as RBC alloimmunization and DHTRs. Prior case reports from Georgia have demonstrated the potentially fatal consequences of patients receiving transfusions without their alloantibody history being known.[6] Additionally, most hospitals providing intermittent transfusions to patients with SCD do so infrequently. Though a few Georgia hospitals are high-volume intermittent transfusion providers for patients with SCD, many others average fewer than one SCD transfusion per year. With limited experience, provider knowledge and practice may not be current with the latest evidence-based recommendations for transfusion in SCD.

While 30% of patients who received multisite transfusions were between 18 and 25 and presumably transitioning from pediatric to adult facilities, the rate was similar in those who were 26-40, suggesting age-related transition from pediatric to adult care was important but not solely responsible for these findings. These results also highlight the need to address alloantibody history during transition planning.

Additionally, there was no significant difference in sex distribution between patients who were multiply transfused at a single institution versus those receiving multisite transfusions, suggesting that pregnancy did not increase the risk of receiving multisite transfusions. Some Georgia residents may also be intermittently receiving transfusions outside of Georgia and out-of-state residents may be receiving treatment within Georgia, so our results may actually underestimate the extent of multisite transfusions.

We are unable to accurately determine the impact of transfusions at multiple centers on alloimmunization rates and frequency of DHTRs due to retrospective use of administrative datasets. Future prospective studies should be considered to accurately characterize this risk.

The National Heart, Lung, and Blood Institute's 2014 expert panel report, *Evidence-Based Management of Sickle Cell Disease*, recommends that patients with sickle cell receive blood with extended phenotypic matching, including matching for C, E, and Kell antigens.[11] The guidance further advises that providers obtain an accurate transfusion history. British guidelines from 2017 state "a transfusion history should be obtained in all patients with SCD requiring transfusion, whether elective or emergency. Close communication is essential between clinical and laboratory teams so that appropriate blood is given."[12] Failure to follow these recommendations can result in formation of new alloantibodies or reactivation of a previous one—even ones that may no longer be serologically detectable—resulting in a potentially lethal DHTR.[2–4]

Previous studies show that a centralized regional or statewide transfusion database can enhance transfusion safety, but privacy issues have limited the establishment of a national database.[2,3] The REdHHoTT project is assessing the feasibility of implementing a transfusion data registry using software applications designed to interface with hospital blood bank data systems, retrieve select patient data, and store them in a provider-accessible database. Antibody cards are known to prevent potential DHTRs, but they are not standard practice at all hospitals.[13] REdHHoTT is also developing a campaign to inform patients about the need to carry transfusion history information. This is being proposed using personalized approaches such as physical cards, smartphone health data apps, or photographs of blood bags and medical charts, and other technologies. Prospective studies that include the cost and benefit analysis of preventive approaches are required to determine the impact on DHTR and alloimmunization.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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