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Treatment of Acute Pain in Adults With Sickle Cell Disease in an Infusion Center Versus the Emergency Department

A Multicenter Prospective Cohort Study

Sophie Lanzkron, MD, MHS; Jane Little, MD; Hang Wang, PhD; Joshua J. Field, MD; J. Ryan Shows, MD; Carlton Haywood Jr., PhD, MA; Mustapha Saheed, MD; Marc Proudford; Derek Robertson, MBA, JD; Adrienne Kincaid; Lorri Burgess, BS†; Charles Green; Rebecca Seufert, BS; Jasmine Brooks, BA; Allie Piehet, BS; Brandi Griffin, BSN, RN; Nicole Arnold; Steven Frymark; Marcus Wallace, MD; Nebras Abu Al Hamayel, MBBS, MPH; Chiung-Yu Huang, PhD; Jodi B. Segal, MD, MPH; and Ravi Varadhan, PhD, PhD

Background: Patients with sickle cell disease (SCD) have vaso-occlusive crises (VOCs). Infusion centers (ICs) are alternatives to emergency department (ED) care and may improve patient outcomes.

Objective: To assess whether care in ICs or EDs leads to better outcomes for the treatment of uncomplicated VOCs.

Design: Prospective cohort. (ClinicalTrials.gov: NCT02411396)

Setting: 4 U.S. sites, with recruitment between April 2015 and December 2016.

Participants: Adults with SCD living within 60 miles of a study site.

Measurements: Participants were followed for 18 months after enrollment. Outcomes of interest were time to first dose of parenteral pain medication, whether pain reassessment was completed within 30 minutes after the first dose, and patient disposition on discharge from the acute care visit. Treatment effects for ICs versus EDs were estimated using a time-varying propensity score adjustment.

Results: Researchers enrolled 483 participants; the 269 who had acute care visits on weekdays are included in this report. With inverse probability of treatment-weighted adjustment, the mean time to first dose was 62 minutes in ICs and 132 minutes in EDs; the difference was 70 minutes (95% CI, 54 to 98 minutes; E-value, 2.8). The probability of pain reassessment within 30 minutes of the first dose of parenteral pain medication was 3.8 times greater (CI, 2.63 to 5.64 times greater; E-value, 4.7) in the IC than the ED. The probability that a participant's visit would end in admission to the hospital was smaller by a factor of 4 (0.25 [CI, 0.18 to 0.33]) with treatment in an IC versus an ED.

Limitation: The study was restricted to participants with uncomplicated VOCs.

Conclusion: In adults with SCD having a VOC, treatment in an IC is associated with substantially better outcomes than treatment in an ED.

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† Deceased.

Sickle cell disease (SCD) affects approximately 100 000 persons in the United States (1). This population has historically been underserved by the medical community, and gains in clinical care have been slow to reach patients (2). The most prevalent complication of SCD is the vaso-occlusive crisis (VOC). These acute, excruciatingly painful events are the leading cause of hospital and emergency department (ED) use in SCD (3), and the ED has been the standard location where patients seek care for them. Although SCD is considered a rare disease in the United States, the burden of ED care and subsequent hospitalization is high (4). Patients and health care providers are dissatisfied with the quality of SCD pain management in the ED, as summarized in a systematic review (5). Patients with SCD often face both structural and interpersonal racism, presenting to EDs with severe pain only to be met with racist attitudes expressed by those in health care and receiving inadequate care (6). In a recent article, Power-Hays and McGann wrote, "There may be no population of patients whose health care and outcomes are more affected by racism than those with . . . SCD" (6). Ballas and colleagues (7) have suggested that more aggressive treatment of a VOC at onset can result in shorter duration and fewer complications. The National Heart, Lung, and Blood Institute made recommendations for the management of acute pain in its 2014 guidelines, including rapid initiation of analgesic therapy within 30 minutes of triage or within 60 minutes of registration and reassessment of pain every 15 to 30 minutes until controlled (8).

A growing literature supports the role of the subspecialty infusion center (IC) or day hospital as an alternative to the ED in delivering individualized care to people with acute pain and meeting the recommendations of the National Heart, Lung, and Blood Institute. Benjamin and colleagues (9) first reported that the establishment of a dedicated SCD day hospital, which consisted of a triage room and 3 beds for treatment of VOCs, led to a 40% reduction in inpatient admissions relative to ED management. Since this seminal work, many additional, single-center studies have suggested that rapid assessment of VOCs, close monitoring, and individualized care improve

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outcomes in IC settings (10–13). A single-center IC model in Boston, Massachusetts, consisted of a 2-bed monitored unit and operated during weekdays with a nurse practitioner who independently managed patients; 5% of its patients required hospital admission, compared with 58% of patients seen in the institution's ED. The mean hospital cost from patients seen in the IC versus the ED for a VOC was $1609 versus $2689 (12). In Baltimore, Maryland, an IC model consisting of 5 treatment beds resulted in 85% of patients with a VOC being treated and discharged home, compared with 64% of patients seen in the ED of the same facility (14).

No direct, prospective comparison has been made between ICs and the ED for pain management in SCD. Patients seeking care in an ED may have more severe disease and therefore may be more likely to be admitted than those seeking care in an IC. Although a randomized trial comparing IC with ED would provide unbiased evidence, it is exceptionally difficult and even ethically problematic to randomly assign patients during a VOC episode. Hence, a prospective observational study is the best pragmatic option for a direct comparison of IC versus ED, with careful attention to differences in patient characteristics. We did a multisite study comparing patient-centered outcomes between IC-based care and ED-based care of VOCs.

METHODS

The ESCAPED (Examining Sickle Cell Acute Pain in the Emergency Versus Day Hospital) study was a prospective observational study done in 4 U.S. cities (Baltimore, Maryland; Cleveland, Ohio; Milwaukee, Wisconsin; and Baton Rouge, Louisiana) (ClinicalTrials.gov: NCT02411396). Two of these sites have ICs that are solely for the care of adults with SCD (Baltimore and Milwaukee), whereas the other 2 share infusion space with other hematology-oncology patients (Cleveland and Baton Rouge). All 4 sites are located in hospitals that also have EDs. The ED at the Baltimore site has a "fast-track" system where patients with SCD are given priority over all other patients to be placed in a bed in the ED-run, 15-bed observation unit.

Adults (aged ≥18 years) with any SCD genotype living within 60 miles of the study site's IC were eligible for this study. Patients may have received their comprehensive care at one of the centers, but if they lived far from the center they were likely to receive care for acute pain at an ED closer to their home. Between April 2015 and December 2016, participants were enrolled and asked for consent during regular outpatient clinic visits. To avoid enrolling persons who were unlikely to have acute care visits during the study period, we excluded those whose disease was well controlled with long-term transfusion therapy and who also had no acute care visits in the prior 2 years. We also excluded pregnant women because they were likely to receive care for acute pain in the labor and delivery ward.

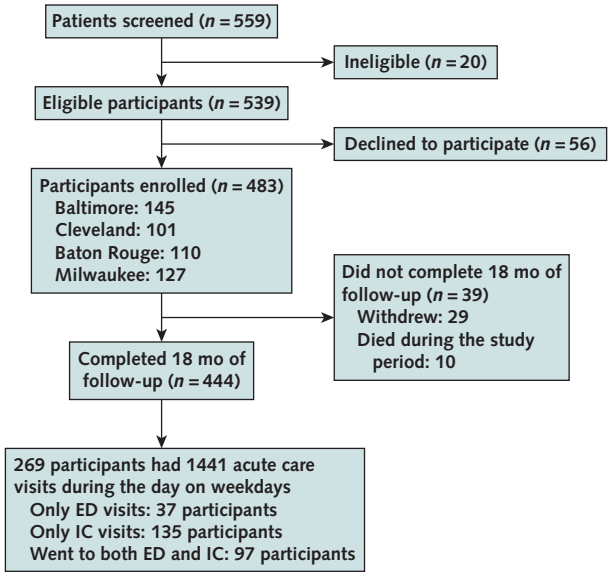
After giving informed consent, participants filled out a survey about demographic characteristics, baseline medical history, and presence or absence of chronic pain. Medical records were reviewed to confirm existing disease complications.

Each participant was followed for 18 months with the expectation that each would have at least 1 or 2 acute care visits per year, based on data from the CSSCD (Cooperative Study of Sickle Cell Disease) (3). We collected both subjective and objective data at the time of a visit for an acute uncomplicated VOC, which was defined as an acute episode of pain with no other known cause that required parenteral therapy for pain relief. Data were not collected for visits that met criteria for a complicated VOC (such as acute chest syndrome, priapism, or stroke), which was reviewed and confirmed by the site principal investigator.

Infusion centers were not open 24 hours per day or on weekends, so patients presenting in pain when the IC was closed necessarily sought another site for care. We reduced patient survey burden by not collecting surveys from every acute care visit. If a participant went to 2 different EDs in the same month, we collected all data from each of those ED visits. If, however, a patient had more than 1 visit to the same ED or IC in a calendar month, we collected data from only the first visit and simply tracked the other visits (Appendix Figure 1, available at Annals.org). For this analysis, we present only IC and ED visits that occurred during the day on weekdays when the ICs at each site were open.

The following outcome data were collected at each eligible visit: time to first dose of parenteral pain medication, time to reassessment of pain after the initial dose of pain medication, patient disposition after acute pain treatment (that is, hospitalized vs. discharged home), changes to medical history, and patient-reported experience of care. Patients were surveyed about their satisfaction with pain management, and these results will be published separately (15).

Figure. Study flow diagram.



ED = emergency department; IC = infusion center.

The primary outcome was time to first dose of parenteral pain medication. All participants were contacted monthly (by telephone, by e-mail, or in person) to obtain information on acute care visits. We also reviewed statewide health information exchanges, where available, to ensure that we had captured all such visits. The institutional review boards at all participating sites approved this study.

Statistical Analysis

To account for possible differences in characteristics of patients seeking care in ICs versus EDs, we used propensity score methodology to balance patient characteristics in the 2 treatment groups. The unit for the propensity score model was each individual patient visit. Therefore, each participant has as many propensity score estimates as their number of visits.

We generated time-varying propensity scores by fitting a logistic regression model, with a patient-specific random intercept (16) (random slope for visit time was considered but did not improve the model fitness), to estimate the probability of visiting an IC (vs. visiting an ED), accounting for both fixed (baseline) and time-varying covariates corresponding to each acute care visit. Covariate balance was assessed using an inverse probability of treatment–weighted (IPTW) regression for each covariate, where the covariate was the outcome and the treatment indicator, IC or ED, was the predictor (the "survey" package in R was used [17]). If the balance was inadequate, we refitted the model by adding quadratic terms or interactions of the offending covariates until balance was adequate.

The IPTW method (18) was used to estimate the average treatment effect (ATE). We did not require a response model because the treatment effect was estimated as a direct contrast between ED and IC participant visits. For example, to compute the ATE of time to first dose, under the assumption of no residual confounding, we calculated the weighted mean of time to first dose for all of the ED visits using the weights $1 / (1 - e_i)$, and for all of the IC visits using weights $1 / e_i$, and taking the difference (e_i is the propensity score of the *i*th participant). The ATE was calculated similarly for the binary end points of pain reassessment within 30 minutes and hospital readmission. The time of the visit was considered only in the estimation of the propensity score but not in the response model for treatment effect estimation because the timing of VOC events was assumed to be noninformative for the potential outcomes (for example, time to first dose in IC or ED) given the observed covariates. Because individuals may have multiple propensity scores, a cluster bootstrap approach (19), with the individual as the bootstrap resampling unit, was used to estimate unbiased SEs for the treatment effects. We resampled 1000 times with replacement, estimated the propensity score and IPTW ATE for each bootstrap, and computed the CIs. In calculating the CIs for city-specific estimates of relative risk, we added 0.5 to the numerator and 1.0 to the denominator to stabilize the estimates. This is equivalent to imposing a uniform prior on the relative risk, which is a Beta (0.5, 0.5) distribution.

To assess the potential vulnerability of our treatment effect to residual confounding, we computed the E-values for the 3 primary outcomes (20, 21). We report the E-values corresponding to the lower 95% confidence limit, which is closest to the null value of the treatment effect.

Missing data, such as patient medical characteristics, were imputed for acute care visits as described in the **Appendix** (available at Annals.org). There were few changes in medical history for visits where full data were collected (3.3% of visits). We did not impute outcome data. Fewer than 6% of visits were missing outcome data; hence, complete-case analysis was used. For further details on the time-varying propensity score estimation and missing data, see the **Appendix**.

We used R, version 3.6.2 (R Foundation), for all primary analyses.

Role of the Funding Source

This study was funded by the Patient-Centered Outcomes Research Institute, which had no role in the design, conduct, or analysis or decision to publish the study results.

RESULTS

The **Figure** shows the patient flow diagram. A total of 483 participants with SCD enrolled in the cohort; of these, 444 (92%) completed 18 months of follow-up. One hundred fourteen patients (24%) had no acute care visits and did not contribute to the study. The entire cohort had 3027 eligible acute care visits; 1558 were in an ED and 1469 in an IC. Complete data for analysis were available from 269 participants who had visits on a weekday. **Table 1** shows participant characteristics for all 483 enrolled patients and the 269 included in this analysis. The number of visits per participant is in **Appendix Figure 2** (available at Annals.org).

We excluded 175 patients whose 1586 visits occurred on nights and weekends to ensure valid comparison with

Table 1. Baseline Patient Characteristics

Characteristic	Analytic Sample (*n* = 269)*	Entire Sample (*n* = 483)†
Female sex, %	61.0	60.7
Genotype: sickle cell anemia, %	71.0	69.2
Mean age (SD), *y*	33.6 (10.8)	34.4 (11.5)
Graduated high school, %	80.7	80.7
Employed, %	36.1	39.3
Insured by Medicaid, %	58.4	53.8
Married or with significant other, %	20.4	21.5
Living alone, %	27.1	28.3
Low annual income, <$20 000, %	52.5	49.9
Disability, %	73.2	61.7
Kidney disease, %	16.0	14.3
Leg ulcer, %	4.8	4.8
Stroke, %	16.4	12.8
Retinopathy, %	23.0	19.0
Avascular necrosis, %	34.9	32.5
Receiving long-term transfusion therapy, %	11.5	10.8
Chronic pain, %	73.6	66.9
Receiving hydroxyurea (sickle cell anemia only), %	63.4	63.1

* Includes participants who had acute care visits during the day on weekdays and whose visits were used for the analysis presented in this manuscript.
† Includes all participants enrolled in the study.

Table 2. Time to First Dose*

Population	Mean Time to First Dose (95% CI), min		Mean Difference (95% CI), min
	IC	ED	
Analytic sample	62 (60–65)	132 (116–161)	70 (54–98)†‡
Baltimore site	73 (70–76)	128 (100–176)	55 (27–103)†
Cleveland site	49 (44–55)	140 (99–198)	91 (51–151)†
Baton Rouge site	71 (68–76)	115 (84–159)	44 (13–90)†
Milwaukee site	46 (42–50)	160 (91–284)	114 (44–238)†

ED = emergency department; IC = infusion center.
* Estimates based on inverse propensity–weighted adjustment (from Appendix Table).
† $P < 0.001$.
‡ E-value for the lower confidence limit = 2.8 (see interpretation in the main text).

ICs, which operated only on weekdays. For the 269 patients with at least 1 acute care visit on a weekday, we recorded 1441 such visits for uncomplicated VOCs. Of the 1441 eligible visits, 241 occurred in an ED and 1200 in an IC. The mean number of visits per patient was 5.4 (SD, 5.2); the median number was 3 (interquartile range, 1 to 8). Baltimore had 454 eligible acute care visits, Cleveland had 283, Baton Rouge had 385, and Milwaukee had 319. **Appendix Figures 3** and **4** (available at Annals.org) show participant and visit data by institution.

The **Appendix Table** (available at Annals.org) lists the fixed and time-varying patient characteristics used for our propensity score modeling for the weekday cohort. Before propensity score adjustment, several confounders had large imbalances. There were no covariate imbalances of concern after the IPTW adjustment.

In the IPTW analyses, the mean time to first dose of parenteral pain medication was 62 minutes in ICs and 132 minutes in EDs. Thus, the mean difference between time to first dose was 70 minutes (95% CI, 54 to 98 minutes; $P < 0.001$; E-value, 2.8) in favor of ICs (**Table 2**). The E-value represents the robustness of our findings to the threat of unmeasured confounding, with larger values indicating greater robustness. Here, the value of 2.8 indicates that an unmeasured confounder must be 2.8 times more prevalent in the IC than the ED, and its (standardized) effect on time to first dose must be 2.8, for it to nullify the estimated treatment effect, but weaker associations cannot nullify the treatment effect. The probability that a participant would have their pain reassessed 30 minutes after their first dose of parenteral pain medication was 3.8 times greater (CI, 2.63 to 5.64 times greater; $P < 0.001$; E-value, 4.7) in the IC than the ED (**Table 3**). The probability that a participant's visit for an uncomplicated VOC would end with a hospital admission was smaller by a factor of 0.25 (CI, 0.18 to 0.33; $P < 0.001$; E-value, 5.4) in the IC compared with the ED (**Table 4**). In other words, there was a 75% relative risk reduction for admission for those seen in the IC.

Tables 3 and **4** show site-specific data. Some of these estimates are highly variable because the number of visits was too small. Results for the primary outcome were similar at all sites. Despite the presence of a fast-track system in the Baltimore ED, patients seen in the IC received their first dose of parenteral pain medication 55 minutes faster on average than in the ED. Of note, among EDs, risk for hospitalization was lower in Baltimore than at any other site and time to first dose was the second fastest; this suggests that a fast-track system may be better than standard ED care.

DISCUSSION

The ESCAPED trial rigorously compared outcomes between EDs and ICs in the management of uncomplicated VOCs in adults with SCD. We found that patients treated in an IC received parenteral pain medication substantially faster than those seen in the ED. Patients seen in the IC were more likely to have their pain reassessed 30 minutes after their initial dose of parenteral medication and substantially less likely to be hospitalized than those who received care in an ED. These results suggest that ICs are more likely to provide guideline-based care than EDs and that care can improve overall outcomes. These results are consistent with prior, single-center studies showing the benefits of ICs in decreasing the need for hospitalization (12, 22).

Several possible explanations exist for the better outcomes seen in our study for patients treated in an IC than those seen in the ED. Structural problems, such as overcrowding, and ED providers' limited knowledge about individual patients can contribute to the limitations of care provided in this setting. Adequacy of pain management in the ED has also been a well-recognized problem despite guidelines to assist with management. In contrast, ICs are staffed by clinicians and staff with experience caring for people with SCD. Whether the essential elements of care provided in the IC can be provided in the ED is unclear. Tanabe and colleagues (23) have looked at several methods to improve outcomes in the ED (24), and a study examining whether the use of patient-specific treatment plans can be implemented in the ED setting and whether this results in improved outcomes for patients is currently under way. In addition, others have reported that "fast-tracking" patients in the ED into an observation unit can decrease ED use and may be an alternative to an IC model (25). However, our data show that at the Baltimore site, where a fast-track system exists, the outcomes in the IC were still substantially better than those in the ED.

ESCAPED was done in 4 U.S. cities. These sites used varying models for their individual ICs, including shared

Table 3. Probability of Pain Reassessment Within 30 Minutes of First Dose of Parenteral Pain Medication*

Population	Probability (95% CI)		Risk Ratio (IC vs. ED) (95% CI)†	Risk Difference (IC – ED) (95% CI)
	IC	ED		
Analytic sample	0.38 (0.35–0.41)	0.1 (0.07–0.15)	3.8 (2.63–5.64)‡§	0.28 (0.23–0.32)‡
Baltimore site	0.28 (0.24–0.32)	0.054 (0.013–0.093)	5.06 (3–22)‡	0.22 (0.12–0.39)‡
Cleveland site	0.46 (0.42–0.51)	0.013 (0–0.04)	34.66 (11.54–240.1)‡	0.44 (0.39–0.49)‡
Baton Rouge site	0.42 (0.37–0.46)	0.19 (0.1–0.31)	2.22 (1.32–4.26)‡	0.23 (0.1–0.34)‡
Milwaukee site	0.37 (0.3–0.43)	0.15 (0.05–0.26)	2.43 (1.43–6.7)†	0.22 (0.11–0.32)‡

ED = emergency department; IC = infusion center.
* Estimates based on inverse propensity-weighted adjustment (from Appendix Table).
† Because of rounding to 2 significant digits, the reported risk ratio may not be exactly equal to the ratio of the risks.
‡ $P < 0.001$.
§ E-value for the lower confidence limit = 4.7 (see interpretation in text).

infusion models and both academic and community-based hospitals, and no important differences were seen in the primary outcomes between sites of care. This suggests that a dedicated center might not be necessary to provide guideline-based care and that shared space with dedicated personnel might be just as effective as single-focus ICs in improving patient outcomes. Use of multiple sites across the United States and imposition of very few exclusion criteria for participant enrollment support the conclusion that our results are generalizable to populations with SCD across the country. We restricted this study to evaluating outcomes for participants with uncomplicated VOCs; therefore, we cannot extrapolate our findings for patients who might present with other complications of SCD.

Our study has several design strengths. First, to increase the representativeness of our sample, we recruited participants from 4 diverse geographic regions and clinical settings in the United States. Second, this study used a prospective cohort to examine acute care use (3) and describes acute care use in the modern era after the approval of hydroxyurea to treat SCD. Finally, throughout the study period from design to the discussion of results, the input of stakeholders, including people living with SCD, their families, and community-based organizations, ensured that the research was focused on the aspects of the study that were important to those the disease affects.

Our study also has limitations. Unmeasured confounding may explain some of the treatment effects. Randomly assigning people with SCD and a VOC to sites of care is not possible because patients are reluctant to be assigned to ED-only care. There is also the ethical and pragmatic challenge of randomizing during an acute VOC event. The best way to minimize the threat of residual confounding is to measure a comprehensive set of covariates. We identified and assessed many variables that can affect the severity of the disease. These were all included in the propensity score analysis, and good balance was achieved for all of them. Furthermore, because the magnitude of the treatment effects estimated in our study is large and we have captured most of the important potential confounders, an unmeasured confounder that can nullify the treatment effect is unlikely to exist. We examined the threat to validity due to unmeasured confounding using the concept of E-values, which were sufficiently large to alleviate any major concerns. We chose to look only at acute care visits for uncomplicated VOCs that occurred during the weekday when both the ED and IC were open, and we still saw substantial differences in outcomes between sites of care. We cannot extend our results to nights and weekends because ICs were not available during those times, so further study is needed to assess the potential benefits of extending IC hours, which would entail increased staffing. Finally, we limited our data collection to the first visit to each site of care each month. Because there was no reason to suspect differences between the first visit of the month and subsequent visits to the same site of care, the risk for selection bias is minimal.

Table 4. Probability of Admission to the Hospital Versus Discharge Home*

Population	Probability (95% CI)		Risk Ratio (IC vs. ED) (95% CI)†	Risk Difference (IC – ED) (95% CI)
	IC	ED		
Analytic sample	0.093 (0.075–0.11)	0.37 (0.29–0.48)	0.25 (0.18 to 0.33)‡§	−0.25 (−0.38 to −0.20)‡
Baltimore site	0.021 (0.004–0.034)	0.27 (0.14–0.41)	0.076 (0.020 to 0.16)‡	−0.25 (−0.39 to −0.12)‡
Cleveland site	0.2 (0.16–0.26)	0.52 (0.32–0.76)	0.39 (0.25 to 0.69)‖	−0.31 (−0.55 to −0.1)‖
Baton Rouge site	0.089 (0.07–0.12)	0.36 (0.17–0.63)	0.25 (0.14 to 0.53)¶	−0.27 (−0.53 to −0.09)¶
Milwaukee site	0.064 (0.03–0.11)	0.354 (0.19–0.06)	0.18 (0.077 to 0.40)‡	−0.29 (−0.53 to −0.12)¶

ED = emergency department; IC = infusion center.
* Estimates based on inverse propensity-weighted adjustment (from Appendix Table).
† Because of rounding to 2 significant digits, the reported risk ratio may not be exactly equal to the ratio of the risks.
‡ $P < 0.001$.
§ E-value for the lower confidence limit = 5.4 (see interpretation in text).
‖ $P = 0.004$.
¶ $P = 0.002$.

The ED is currently the most common site of care for patients with an uncomplicated VOC but is marked by long delays, lack of efficacy, and conflict. Patients with SCD report that they do not have enough involvement in decisions about their own care and that providers do not show respect, trust, and compassion. Evensen and colleagues (26) surveyed participants with SCD and found that 81% chose to suffer with their pain at home rather than seek care in an ED because of negative ED experiences. We have shown that the IC model can lead to improved outcomes for this patient population. Although the ICs in this study were open only during the day, Grady Hospital in Atlanta, Georgia, has a dedicated clinic that is open 24 hours per day. Given the limitations of ED care, this may provide the best option for treatment of SCD in regions where large populations live with the disease. Decreased hospital admissions should decrease costs for payers and may motivate insurers to assist hospitals in developing IC models. Future studies should evaluate the cost-effectiveness of IC versus ED care and assess the size of the local population that would justify the expense of investing in a dedicated center versus a shared model. Studies of alternative methods of delivering timely, high-quality VOC care in EDs are also essential to meet the needs of communities, especailly those in rural areas where the populations of people living with SCD may not be large enough to support an IC model. Cost notwithstanding, the most important goal that ICs can achieve is to address structural racism in health care by alleviating suffering that affects this historically underserved population.

From Johns Hopkins University School of Medicine, Baltimore, Maryland (S.L., H.W., M.S., R.S., J.B., J.S.); Case Western Reserve University School of Medicine and University Hospitals, Cleveland, Ohio (J.L., B.G., N.A.); Blood Center of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin (J.J.F., S.F.); Our Lady of the Lake Hospital, Baton Rouge, Louisiana (J.R.S., A.P.); The Johns Hopkins Berman Institute of Bioethics, Johns Hopkins University, Baltimore, Maryland (C.H.J.); William E. Proudford Foundation, Baltimore, Maryland (M.P.); Maryland Sickle Cell Disease Association, Columbia, Maryland (D.R.); Kincaid's Kindred Spirits, Euclid, Ohio (A.K.); Baton Rouge Sickle Cell Disease Association, Baton Rouge, Louisiana (L.B.); Community Partner, Milwaukee, Wisconsin (C.G.); Louisiana Health Care Connection, Baton Rouge, Louisiana (M.W.); Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (N.A.A.); University of California, San Francisco, San Francisco, California (C.H.); and Oncology Biostatistics and Bioinformatics, Johns Hopkins University, Baltimore, Maryland (R.V.).

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Corresponding Author: Sophie Lanzkron, MD, 1830 East Monument Street, Suite 7300, Baltimore, MD 21205; e-mail, slanzkr@jhmi.edu.

Correction: This article was corrected on 3 August 2021 to report risk ratios and risk differences for admission to the hospital by treatment site in the abstract, the text, and Table 4.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Lanzkron: 1830 East Monument Street, Suite 7300, Baltimore, MD 21205.
Dr. Little: 3140 Physician's Office Building, Houpt Building, 170 Manning Drive, or Campus Box 7305, Chapel Hill, NC 27599-7235.
Dr. Wang: 2024 East Monument Street, Suite 2-700, Baltimore, MD 21205.
Dr. Field: 9000 West Wisconsin Avenue, Milwaukee, WI 53226.
Dr. Shows: 4950 Essen Lane, Suite 300, Baton Rouge, LA 70809.
Dr. Haywood: 2024 East Monument Street, Suite 2-600, Baltimore, MD 21205.
Dr. Saheed: 1800 Orleans Street, Zayed G1080, Baltimore, MD 21287.
Mr. Proudford: PO Box 42411, Baltimore, MD 21284-2411.
Mr. Robertson: 8775 Centre Park Drive #701, Columbia, MD 21045.
Ms. Kincaid: 784 East 266th Street, Euclid, OH 44132.
Mr. Green: 11405 West Grange Avenue, Hales Corners, WI 53130.
Ms. Seufert: 15 Lauriann Court, Parkton, MD 21120.
Ms. Brooks: 3218 Ravenwood Avenue, Baltimore, MD 21213.
Ms. Piehet: 4985 Lower Roswell Road, Building 100, Marietta, GA 30068.
Ms. Griffin: 11100 Euclid Avenue, Cleveland, OH 44106.
Ms. Arnold: 1000 Liberty Avenue, Pittsburgh, PA 15222.
Mr. Frymark: 7315 County Road South, Sobieski, WI 54171.
Dr. Wallace: 285 LeCirque, Madisonville, LA 70447.
Dr. Abu Al Hamayel: 624 North Broadway, Room 610, Baltimore, MD 21205.
Dr. Huang: 550 16th Street 2535, San Francisco, CA 94158.
Dr. Segal: 624 North Broadway, Room 644, Baltimore, MD 21287.
Dr. Varadhan: 550 North Broadway, Room 1111, Baltimore, MD 21287.

Author Contributions: Conception and design: S. Lanzkron, H. Wang, J.J. Field, C. Haywood, M. Saheed, L. Burgess, N. Abu Al Hamayel, J. Segal, R. Varadhan.
Analysis and interpretation of the data: S. Lanzkron, J. Little, H. Wang, M. Proudford, D. Robertson, L. Burgess, M. Wallace, N. Abu Al Hamayel, C.Y. Huang, J. Segal, R. Varadhan.
Drafting of the article: S. Lanzkron, J.J. Field, D. Robertson, C.Y. Huang, R. Varadhan.
Critical revision of the article for important intellectual content: S. Lanzkron, J. Little, H. Wang, J.J. Field, D. Robertson, A. Kincaid, M. Wallace, N. Abu Al Hamayel, J. Segal, R. Varadhan.
Final approval of the article: S. Lanzkron, J. Little, H. Wang, J.J. Field, J.R. Shows, C. Haywood, M. Saheed, M. Proudford, D. Robertson, A. Kincaid, L. Burgess, C. Green, R. Seufert, J. Brooks, A. Piehet, B. Griffin, N. Arnold, S. Frymark, M. Wallace, N. Abu Al Hamayel, C.Y. Huang, J. Segal, R. Varadhan.
Provision of study materials or patients: S. Lanzkron, J.R. Shows, M. Saheed.
Statistical expertise: H. Wang, C. Haywood, M. Wallace, C.Y. Huang, J. Segal, R. Varadhan.
Obtaining of funding: S. Lanzkron, J. Segal, R. Varadhan.
Administrative, technical, or logistic support: M. Saheed, C. Green, R. Seufert, A. Piehet.
Collection and assembly of data: S. Lanzkron, J. Little, H. Wang, J.J. Field, R. Seufert, J. Brooks, A. Piehet, B. Griffin, N. Arnold, S. Frymark.

Appendix: Supplementary Information on Methods

Time-Varying Propensity Score

We generated time-varying propensity scores by fitting a logistic regression model, with a patient-specific random intercept (16) (random slope for visit time was considered but did not improve the model fitness), to estimate the probability of visiting an IC (vs. visiting an ED), accounting for both fixed (baseline) and time-varying covariates corresponding to each acute care visit. We used the "glmer" function in the "lme4" package in R and fitted a binomial model for treatment site using a logit link function. We used the maximum likelihood criterion and employed the Laplace approximation for integrating out the random effects. The best predicted response (the conditional mode, which is the maximum likelihood estimate of the random effects) from the model provided the probability (propensity) of visiting the IC for each participant at each visit. Thus, each individual has a unique propensity score for each visit. Covariate balance was assessed using IPTW regression for each covariate using the "survey" package in R, where the covariate was used as the response variable and the treatment site (IC vs. ED) was the predictor variable.

Handling of Missing Data

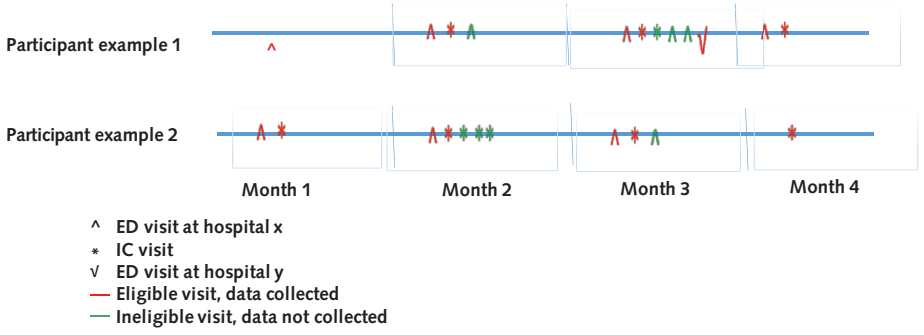
Missing data, such as patient medical characteristics, were imputed for acute care visits using the following approach. Suppose a participant had 3 visits. We had collected full information on clinical covariates at visits 1 and 3 but not at visit 2. We filled in covariate status at visit 2 with information from visit 3. We could collect missing information from the medical history at the time of visit 3 because we checked for any changes that occurred after visit 1 from the electronic health record and then included any of those additional medical problems as covariates for the missing visits as appropriate. For example, the coordinator would ask at visit 3, "Since the patient's last eligible visit (visit 1), where all of the acute care visit forms were completed, has the patient been diagnosed with avascular necrosis?"

Appendix Table. Inverse Probability of Treatment Weighting Balancing Table

Covariate	Before Balancing					After Balancing				
	IC Mean	ED Mean	Standard Effect Size	KS Statistic*	*P* Value†	IC Mean	ED Mean	Standard Effect Size	KS Statistic*	*P* Value†
Probability of going to IC before current visit‡	0.58	0.39	0.56	8.09	<**0.001**	0.55	0.55	0.00	0.04	**0.97**
Probability of being hospitalized before current visit‡	0.17	0.23	−0.23	−2.86	**0.004**	0.18	0.17	0.05	0.56	**0.57**
Mean ED visits in the past 12 mo before enrollment into the study, *n*‡	5.19	7.61	−0.34	−3.08	**0.002**	5.44	5.91	−0.07	−0.96	**0.34**
Mean IC visits in the past 12 mo before enrollment into the study, *n*‡	10.43	8.06	0.23	3.18	**0.002**	10.03	10.11	−0.01	−0.08	**0.94**
Mean admissions in the past 12 mo before enrollment into the study, *n*‡	3.52	3.45	0.02	0.29	0.77	3.48	3.32	0.05	0.53	0.60
Pain level on arrival‡	8.41	8.77	−0.30	−4.21	<**0.001**	8.47	8.38	0.07	0.72	**0.47**
Avascular necrosis	0.38	0.32	0.13	3.57	0.059	0.37	0.36	0.02	0.03	0.87
Stroke	0.17	0.15	0.05	0.57	0.45	0.17	0.18	−0.01	0.01	0.91
Retinopathy	0.31	0.24	0.16	4.93	**0.027**	0.30	0.30	0.00	0.00	**0.97**
Gallbladder disease	0.58	0.63	−0.09	1.59	0.21	0.59	0.62	−0.07	0.61	0.43
Pulmonary hypertension	0.13	0.11	0.08	1.41	0.23	0.13	0.16	−0.08	0.49	0.49
Kidney disease	0.19	0.15	0.11	2.27	0.13	0.19	0.19	−0.01	0.01	0.91
Male with priapism	0.18	0.19	−0.02	−0.24	0.81	0.18	0.21	−0.08	−0.62	0.53
Male	0.36	0.40	−0.09	1.49	0.22	0.36	0.39	−0.06	0.31	0.58
Receiving long-term transfusion therapy	0.15	0.11	0.12	2.91	0.088	0.14	0.17	−0.07	0.28	0.60
Graduated high school	0.83	0.71	0.28	15.63	<**0.001**	0.81	0.79	0.05	0.40	**0.53**
Married	0.21	0.13	0.21	8.33	**0.004**	0.20	0.16	0.09	0.58	**0.45**
Age, *y*‡	32.99	31.02	0.21	3.10	**0.002**	32.66	32.12	0.06	0.57	**0.57**
Receiving disability benefits	0.80	0.81	−0.03	0.14	0.71	0.80	0.77	0.08	0.51	0.47
Has a primary care physician	0.65	0.63	0.05	0.42	0.52	0.65	0.59	0.11	1.22	0.27
Has a hematologist	0.93	0.93	0.02	0.12	0.73	0.93	0.95	−0.06	0.61	0.43
Has daily chronic pain	0.76	0.73	0.07	0.92	0.34	0.75	0.74	0.04	0.18	0.68
Insured by Medicaid	0.61	0.76	−0.31	18.65	<**0.001**	0.63	0.61	0.04	0.17	**0.68**
Lives with others	0.73	0.69	0.09	1.57	0.21	0.72	0.69	0.08	0.63	0.43
Sickle cell anemia	0.69	0.73	−0.10	1.95	0.16	0.70	0.78	−0.17	3.87	0.049
Receiving hydroxyurea (sickle cell anemia only)	0.46	0.48	−0.02	0.12	0.73	0.47	0.50	−0.05	0.30	0.59
Not employed	0.68	0.74	−0.12	2.91	0.088	0.69	0.65	0.10	0.92	0.34
Follow-up, *mo*‡	8.72	9.44	−0.13	−1.79	0.073	8.80	8.91	−0.02	−0.20	0.84
Study site	–	–	–	0.25§	0.86§	–	–	–	0.34§	0.79§
Baltimore	0.30	0.28	0.04	–	–	0.29	0.32	−0.07	–	–
Cleveland	0.24	0.23	0.02	NA	NA	0.24	0.23	0.03	–	–
Baton Rouge	0.29	0.30	−0.03	NA	NA	0.29	0.30	−0.02	–	–
Milwaukee	0.17	0.19	−0.05	NA	NA	0.18	0.15	0.07	–	–

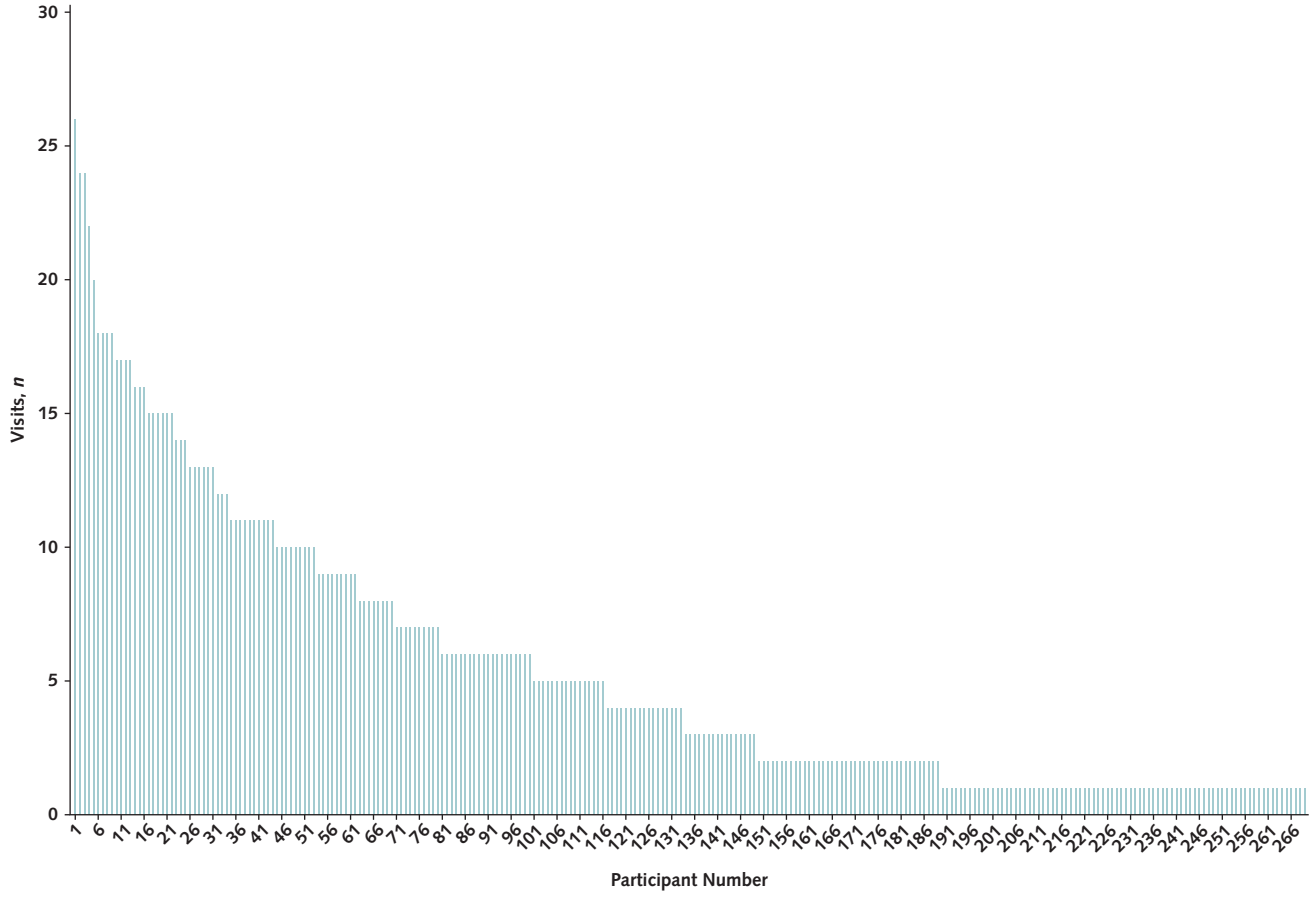
ED = emergency department; IC = infusion center; KS = Kolmogorov–Smirnov; NA = not applicable.
* For testing the difference in covariate distribution between IC and ED.
† Bolded values indicate that the covariate was unbalanced between the 2 treatment sites. However, after propensity score balancing, the imbalance was eliminated.
‡ Denotes continuous variables; all others are binary or categorical.
§ The balance test statistic for the study site is a global statistic testing whether the proportion of IC visits was the same across all study sites.

Appendix Figure 1. Representation of participant visit and data collection.

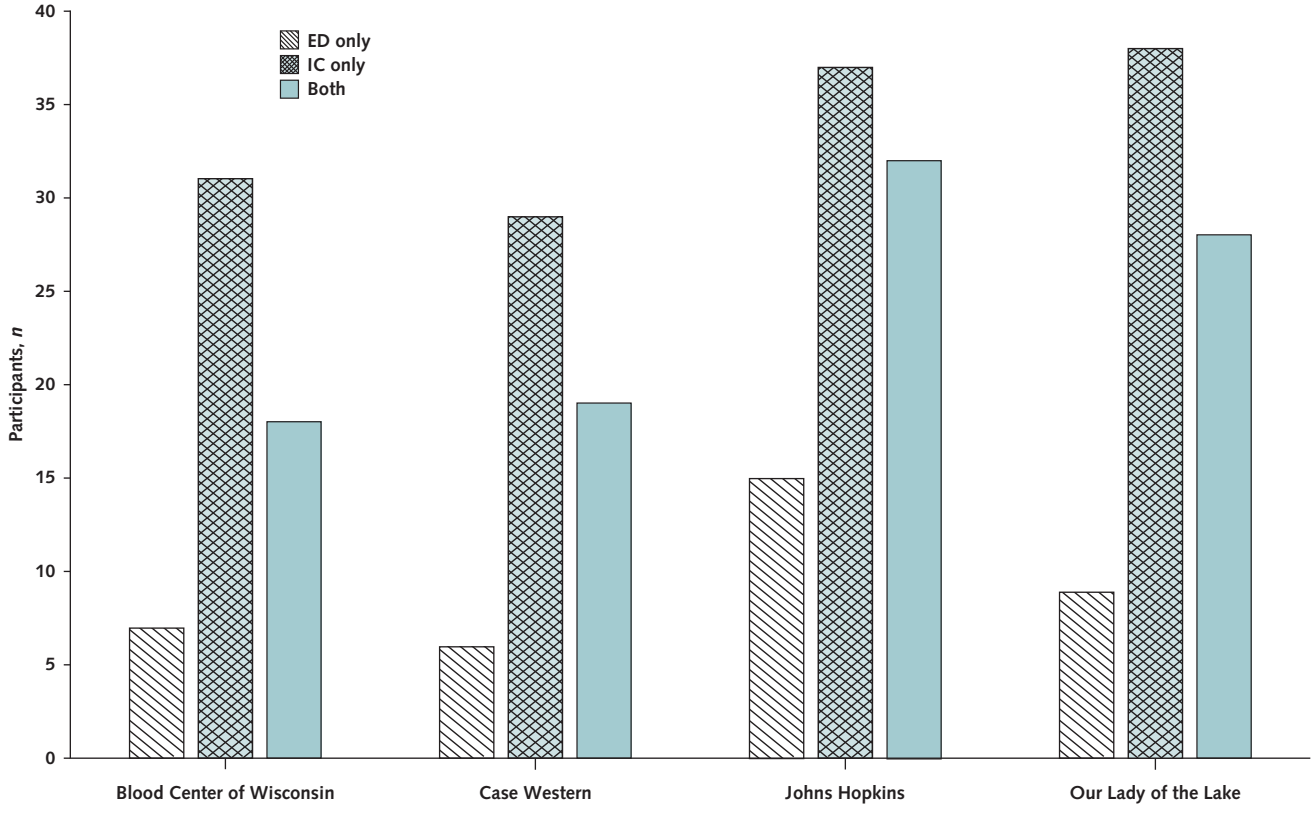


Visit data were collected from the first visit each month to each site of care. This includes IC visits and ED visits, and if the participant went to a second ED at a different facility, data were also collected from that visit. If, however, a participant had a second visit to the same ED or IC in a single month, only the first visit data were collected. ED = emergency department; IC = infusion center.

Appendix Figure 2. Number of visits per participant.

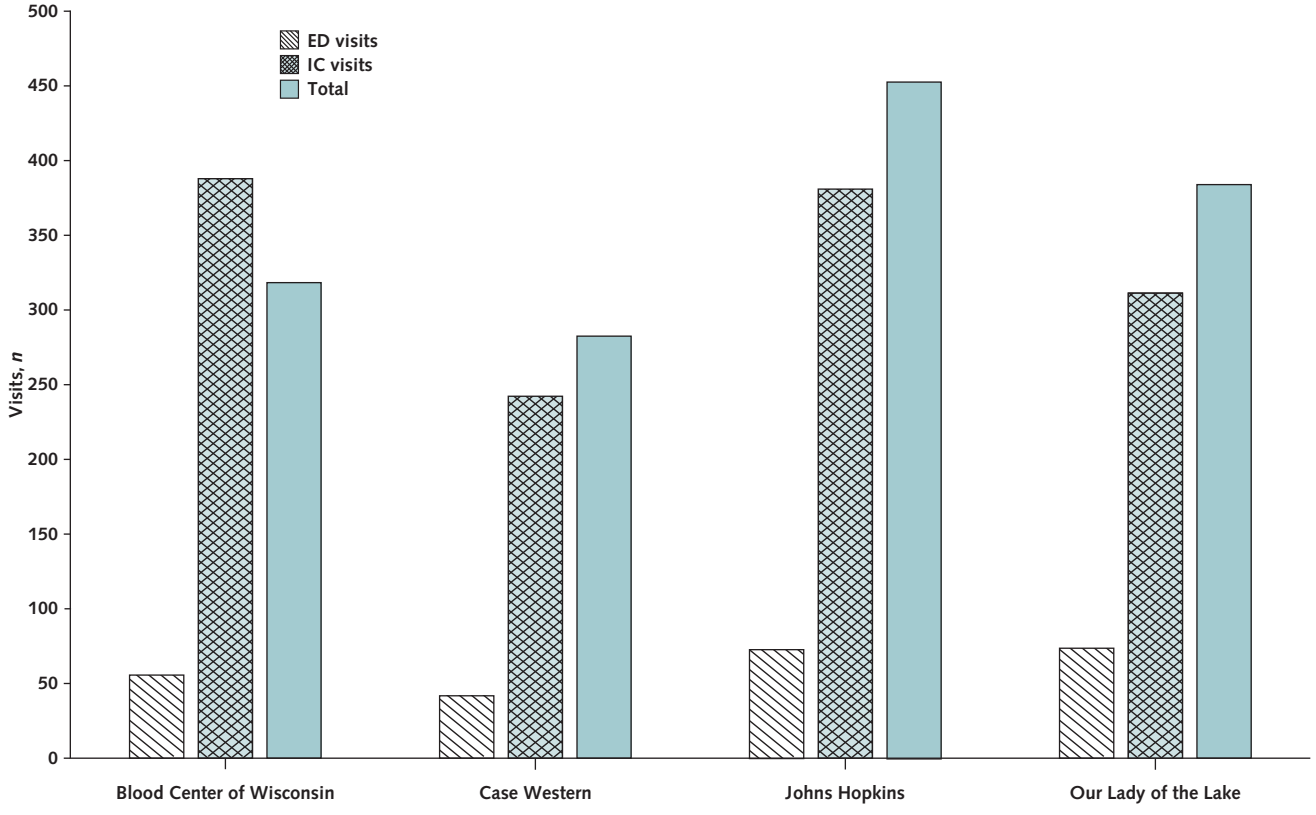


Appendix Figure 3. Number of participants who visited each site of care, by institution.



ED = emergency department; IC = infusion center.

Appendix Figure 4. Number of ED and IC visits, by institution.



ED = emergency department; IC = infusion center.