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National Trends in Hospitalizations for Sickle Cell Disease in the United States following the FDA Approval of Hydroxyurea, 1998 to 2008

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Abstract

Background—Patients with sickle cell disease (SCD) can suffer frequent hospital admissions for painful vaso-occlusive crises. Hydroxyurea was approved by the FDA in 1998 to decrease the morbidity of SCD, but nationwide hospitalizations for SCD in the United States (US) since 1998 have not been evaluated. We hypothesized that the availability of hydroxyurea for SCD would be associated with a decrease in hospitalizations for SCD over time.

Objective—To assess trends in hospitalization and length-of-stay in hospital for SCD in the US, 1998 through 2008.

Research Design—Retrospective cohort study of SCD-related hospital discharges in the Nationwide Inpatient Sample of US hospital discharges.

Subjects—All discharges in the Nationwide Inpatient Sample associated with a principal diagnosis of SCD in Blacks, 1998 through 2008.

Measures—Trends in hospitalization rates and average length-of-stay in hospital for SCD.

Results—We found 216 (95% confidence interval (CI), 173.3–258.7) SCD-related hospitalizations per 100,000 US Blacks in 1998 and 178.4 (95% CI 144.2–212.5) in 2008, but no consistent yearly decrease, 1998 through 2008 ($p=0.30$). Conversely, the length-of-stay in hospital in 1998 was 5.38 days and in 2008 was 5.18 days, an absolute change of 0.2 days and a downward trend that was statistically significant.

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Conclusion—Between 1998 and 2008, there was not a steady decrease in hospitalization rates for the population of SCD in the US. On the contrary, there was a decline in length-of-stay in hospital over this time. Hydroxyurea underuse is well documented. Efforts to increase hydroxyurea use may help to reduce hospitalization rates.

Keywords

sickle cell disease; hospitalizations; Nationwide Inpatient Sample; length-of-stay

Introduction

Sickle cell disease (SCD) is the most common inherited disease in Blacks in the United States. Nearly 100,000 people in the United States (US) have SCD (1), the vast majority are Black and an estimated 3% are Hispanic (2). The average life expectancy of homozygous SCD in the US is 42 years for males and 48 for females (3). The manifold complications of SCD include severe anemia, fatigue, renal failure, strokes and excruciating episodes of pain. The hallmark clinical manifestation of SCD is the vaso-occlusive crisis, which represents the most common cause of morbidity and leads to frequent hospital admissions. Hospitalization rates in patients with SCD in the Tennessee Medicaid program, for example, were 7–30 times greater than hospitalization rates of Blacks without SCD in this program (4). The aim of this study was to evaluate the improvement in hospitalizations for SCD in the US over a decade, 1998 through 2008.

SCD is a genetic hematologic disorder in which a single amino acid substitution at the sixth position of the beta-globin chain of hemoglobin (β glu \rightarrow val) produces an abnormal sickle hemoglobin (Hb S). Under conditions of deoxygenation, Hb S polymerizes into rigid fibers (5) that deform the shape of erythrocytes to a ‘sickle’-shaped cell. Sickle cells cause occlusion of microvasculature and ischemia and infarction of distal tissues and organs. The vast majority of hospitalizations in SCD patients are for vaso-occlusive crises. Cellular events such as endothelial cell activation (6, 7), platelet activation (8) and heightened leukocyte adhesion (9, 10) contribute to *in vivo* vaso-occlusion in SCD, but polymerization of sickle hemoglobin (Hb S) is the principal event in the molecular pathogenesis of SCD. Fetal hemoglobin (Hb F) inhibits the polymerization of Hb S and ameliorates the effects of SCD (11–17). Hydroxyurea is an anti-metabolite that causes a dramatic increase in Hb F levels in phlebotomized non-human primates (18), and in children and adults with SCD (19, 20). Published in 1995, the Multicenter Study of Hydroxyurea (MSH) enrolled 299 adults (aged 18 years and older) with clinically severe SCD in the US over 21 months, with 152 patients randomized to hydroxyurea. Participants receiving hydroxyurea had a 46% decrease in pain crises per year and a 60% decrease in hospitalization rates (21). A subsequent evaluation of average length of stay (LOS) in hospitalized patients on the MSH trial showed responders to hydroxyurea spent an average of 2 fewer days in hospital over the 21-month study period than patients on placebo (22). Based on the results of the MSH trial, in February 1998 hydroxyurea was approved by the US Food and Drug Administration (FDA) for the treatment of SCD in adults. The 1998 approval of hydroxyurea for SCD is arguably the single most significant advancement made in the management of SCD. Hydroxyurea lessens the frequency of pain crises, acute chest syndrome, need for blood transfusions and

hospitalizations. The impact of this on the US population of SCD patients has not been previously explored. We hypothesized that the availability of hydroxyurea for the treatment of SCD would be associated with a significant decrease in hospitalizations for SCD in the US.

The primary objectives of this study were to evaluate the changes in national hospitalization rates and LOS in hospital for SCD in the US. We examined in-patient hospitalizations for a primary diagnosis of SCD, 1998 through 2008.

Methods

Data Sources

Nationwide Inpatient Sample—Hospital discharge abstracts from 1998 to 2008 were obtained from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost Utilization Project (HCUP) maintained by the federal Agency for Healthcare Research and Quality (AHRQ). These data cover the period since the initial FDA approval of hydroxyurea in 1998. The NIS is a stratified probability sample of hospitals selected by region, size and teaching status. The NIS is the largest all-payer inpatient database in the US with data from approximately 8 million hospital discharges from 1,056 hospital located in 42 states during 2008 (23). The large sample of discharges in NIS enables analyses of rare conditions such as SCD. The hospitals included in the NIS can vary from year to year and race data is incomplete in some years. Because the NIS database includes publicly available de-identified data, our study was deemed exempt from review by the institutional review board of the Partners Healthcare System.

US Census Bureau—To correct for population growth in the US over the years of the study, we examined hospitalization rates each year. The reference population was based on annual population estimates of the US Black population provided by the US Census Bureau.

Hospitalization Rates for a Principal Diagnosis of SCD in 'Year X' = $\frac{\text{Absolute no. of Hospitalizations for a Principal I}}{\text{US Census Bureau Population Est}}$

The estimates for 1998 and 1999 were extracted from files of the Monthly Postcensal Resident Population, by single year of age, sex, race, and Hispanic origin July 1998 and July 1999. Equivalent information for years 2000 through 2008 was extracted from files of Annual Estimates of the Black or African American Alone Resident Population by Sex and Age for the US: April 1, 2000 to July 1, 2009.

Study Cohort

The study population included discharges with a principal diagnosis of SCD and patients' race coded as Black in the NIS database from 1998 to 2008. Discharges were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of SCD (282.41, 282.42, 282.6, 282.60 – 282.64, 282.68 and 282.69), as has been used previously (24). We limited our analyses to Blacks in the NIS to facilitate the calculation of hospitalization rates using population estimates as the

denominator, recognizing that over 95% of discharges for SCD in the NIS were among Blacks (3% were among Hispanics and 2% among others). Because the US Census Bureau collection of data on 'Hispanics' was inconsistent between Census 1990 and Census 2000 (25), we did not include hospitalizations of Hispanic patients in this study. Discharges associated with sickle cell trait (282.5) or thalassemia (282.49) were excluded from this study.

Outcome Measures

The primary outcomes of the study were the hospitalization rates associated with a principal diagnosis of SCD from 1998 to 2008. The secondary outcome was LOS for patients with a principal diagnosis of SCD over the same time period.

Statistical Analysis

The patient population included Black patients with SCD. Weighted least squares regression was used to model hospitalization rates as a function of time (26), within subgroups of age. Poisson regression was used to model hospital trends in LOS over time, adjusting for age, gender, household income and insurance status.

Our analysis was restricted to Blacks, but 11 of 42 states in the NIS did not report race. Blacks comprise approximately 96% of SCD patients, but we could not determine the proportion of patients in these 11 states who were Black. Thus, in order to include patients from these 11 states in the analyses, we multiply imputed patients' race. We fitted a logistic regression model to data from the states with race observed whose outcome was race (Black, non-Black) and whose predictors were variables available in all states, including the 11 states where race was missing, including patient characteristics (e.g., age, gender, median household income by zip code, hospital length of stay, etc.), hospital characteristics (e.g., region, number of beds, etc.), and the logit of the fraction of Blacks in the state. We imputed missing race 10 times. After imputing race, analyses of each imputed dataset were restricted to Blacks. The 10 imputation results were combined to get a single estimate and 95% confidence interval (CI). Analyses excluding the 11 states with incomplete race data yielded similar results (see supplemental digital content material). SAS (Proc Logistic and Proc MIanalyze) version 9.2 (SAS Institute Inc., Cary, NC) was used for multiple imputations.

Hospitalization rates and LOS analyses were performed using SAS-callable SUDAAN version 10.0.1 (Research Triangle Institute, Research Triangle Park, NC) to account for the complex design of the NIS including clustering by hospital. To ensure that changes in state inclusion in the NIS did not significantly affect the percentage of Blacks represented each year in the NIS, we confirmed that the Black population in the NIS database each year of the study changed by less than 2 percentage points (13%–14.6%). We report two-sided p-values, 95% confidence intervals and significance tests at the 0.05 level.

Results

In 1998 there were 14,030 unweighted discharges associated with a principal diagnosis of SCD in Blacks in the NIS database, representing 74,344 weighted (actual) discharges in the US. In 2008, there were 14,384 unweighted discharges corresponding to a nationally

weighted estimate of 69,845 hospital discharges. All results below, including tables and figures, are weighted (actual) values. The characteristics of the patients in 1998 and 2008 are shown in Table 1.

Hospitalization Rates

The hospitalization rate for all Black patients with a principal diagnosis of SCD in the US in 1998 was 216.0 (95% CI, 173.3 – 258.7) per 100,000 Blacks in the US population, and in 2008 this rate was 178.4 (95% CI 144.2 – 212.5) but with no statistically significant trend from 1998 to 2008 ($p=0.30$), see figure 1. The hospitalization rate in adults (≥ 18 years) in 1998 was 230.5 (95% CI 187.8, 273.2) and in 2008 was 197.5 (95% CI 163.5, 231.6) again with no statistical trend through this period ($p=0.30$). In children (<18 years) the hospitalization rate was 184.2 (95% CI 119.9, 248.5) in 1998 and 131.0 (95% CI 80.1, 181.8) in 2008 ($p=0.34$). Though these rates seem strikingly different, there was no consistent downward trend from 1998 through 2008 (Figure 2). Within previously defined age ranges of patients with SCD (24), hospitalization rates varied minimally through the years of study with no statistically significant trends from 1998 to 2008 (See details in Table 2).

Average Length of Stay in Hospital (LOS)

The LOS of patients with a principal diagnosis of SCD in 1998 and 2008 were 5.38 days (95% CI 5.07–5.70) and 5.18 days (95% CI 5.0–5.41) respectively, an absolute difference of 0.20 days that was statistically significant ($p<0.001$). Adjusting for age, gender, median household income and insurance status by Poisson regression, the LOS in all children as a group (age <18 years), and adults aged 45–64 years old showed a decreasing linear trend from 1998 to 2008 ($p=0.01$ and $p<0.01$ respectively). See Figure 3; details in Table 2.

Discussion

Our nationally representative study found inconsistent changes in hospitalization rates for patients with a primary diagnosis of SCD in the US from 1998 to 2008. Though the hospitalization rates in 1998 (216.0) were higher than in 2008 (178.4), there was no steady decline in hospitalization rates through the intervening years. The same was true of hospitalization rates in adults and children examined separately. Conversely, there was a significant decrease in LOS over time. LOS in all patients with SCD decreased by 0.2 days in 2008 compared to 1998, and in children there was a significant decreasing trend through the years, from 4.1 days in 1998 to 3.8 days in 2008.

Since the MSH trial (described above), hospitalizations and LOS have been assessed in other clinical trials in SCD (27–30). They have all shown a decrease in hospitalizations and/or LOS for patients on hydroxyurea, establishing the efficacy of hydroxyurea in closely monitored clinical studies. Also, children on hydroxyurea routinely managed in a tertiary SCD center had decreased hospitalizations compared to patients not on hydroxyurea (31). In contrast, our study of hospitalizations of SCD patients in the US showed no consistent reduction in hospitalization rates over 11 years. Likewise, an earlier retrospective study of hospitalization rates associated with SCD in Maryland between 1995 and 2003 documented

an increase in hospitalizations during this time period (32) and a study in Tennessee, showed no trend in hospitalizations for SCD from 1995 to 2002 (4). Thus, in the era of hydroxyurea use in SCD, there has been a reduction in LOS but not a consistent decline in hospitalization rates over time, when viewed at the population level.

Recent studies have identified barriers at the patient, provider and systems levels that have adversely impacted hydroxyurea use in SCD. Patients with SCD in the US tend to be of low socioeconomic status and have problems with continuity of health insurance (33), causing difficulty in keeping clinic appointments and obtaining prescribed medications (34). Patient compliance with hydroxyurea can be excellent in controlled SCD studies (30). However, in retrospective observational studies, patient adherence to hydroxyurea was only 35–49% (35). Similarly, 70% of patients with SCD at a university hospital who were appropriate candidates for hydroxyurea were not on the medication (32). This would imply that the full benefit of hydroxyurea use is not being gained by all SCD patients.

Community-based hematologist/oncologists have expressed anxiety about hydroxyurea's carcinogenic potential, doubts about its effectiveness, perceptions of patient reservations about its adverse effects, and concern about lack of concurrent contraceptive use (36). These concerns about hydroxyurea are in contrast to evidence in studies (21, 29, 37, 38). Classification of hydroxyurea as a chemotherapeutic agent and the need for diligent laboratory monitoring may also make physicians reluctant to administer the drug. Furthermore, physicians who are not well-informed and highly motivated may not escalate patients to the maximum tolerated dose of hydroxyurea, as recommended to induce HbF. Physicians may therefore prematurely conclude that hydroxyurea offered no benefit to a particular patient and discontinue its use.

Hydroxyurea was proven in 1995 to be beneficial in SCD. It is perhaps the most significant advancement in the care of individuals with SCD. No change in hospitalization rates in 1998 through 2008 does not equate to no change from a pre-hydroxyurea time. It is possible that there was a decline in hospitalizations from 1995 to 1998 due to hydroxyurea use, though a previous smaller study does not suggest this (32). With the evidence of current hydroxyurea underuse (34, 36), greater impact on hospitalization rates is likely with improved hydroxyurea use.

Increases in hydroxyurea therapy in SCD could reduce hospitalizations and other metrics of morbidity in SCD patients in the US, at the population level. Reduced hospitalizations should also result in decreased healthcare costs. With targeted intervention, significant improvements in medication use are possible (39). Efforts should focus on improving knowledge and awareness of patients and families regarding the evidence-based benefits of hydroxyurea use in SCD, and on educating physicians and other providers in the use of hydroxyurea to manage SCD. Clear guidelines on the indications, dosing, contra-indications and complications of hydroxyurea for specific age groups should also be disseminated to providers. Potential differences in the adoption of effective therapies according to level of specialist involvement seen in other disease states (40, 41), are likely also at play in SCD and can be improved by enhanced collaboration and communication between SCD

specialists and primary care providers. This would offset the effects of the limited supply of hematologists in practice (42).

New agents such as histone deacetylase inhibitors, thalidomide derivatives, adenosine receptor agonists and P-selectin inhibitors are currently in Phase I and II trials of SCD. These new agents will benefit from efforts aimed at tackling the current barriers to broader use of hydroxyurea in SCD. Since 2009, the NIH has led an effort to develop a set of evidence-based guidelines for the management of SCD (43). The NIH is also aimed at identifying areas where additional research is needed to guide practice.

Our study had limitations. The NIS database is the largest all-payer inpatient database in the US, but variation in sampled hospitals from year to year contributed to wide confidence intervals around the hospitalization rates. Because race information was incomplete in some states and years, imputations of missing race data were performed and could introduce some statistical imprecision in our results. We analyzed data on Blacks with SCD (>95% of SCD hospitalizations) and may not be able to extrapolate our findings to Hispanic SCD patients in the US. In the absence of a comparison group, it is not possible to attribute the decrease in LOS specifically to the availability of hydroxyurea. Increased use of home health services, changes in hospital and physician reimbursement methods may have favorably influenced LOS for all diseases over the time of the study. Due to the expansion of universal newborn screening and implementation of penicillin prophylaxis, there was an age migration in SCD from pediatrics to adults from 1979 to 2006 (2). However by 1999 and in later years the age migration was minor (2) and was not likely to have affected the population at risk for hospitalizations in the time span of this study. This was a retrospective database study, and the accuracy of diagnosis coding in NIS is unknown, therefore we evaluated SCD hospitalizations making no distinction between hospitalizations for pain crises from other complications of SCD. However only principal diagnoses of SCD were included in this study and SCD patients admitted for unrelated ailments were not included. Finally, we chose to study an 11 year timeframe. Evaluating a longer period of time could reveal more subtle trends that were not detected over our 11 years of evaluation. Despite these limitations, it is unlikely that a substantial reduction in SCD hospitalizations 1998 through 2008 was missed by our analyses.

Conclusion

Our results reflect hospitalizations for a decade after hydroxyurea became standard care. There was a consistent decreasing trend in LOS but no consistent decrease in hospitalization rates. Undoubtedly hydroxyurea was used to varying degrees before 1998, therefore we do not conclude that hydroxyurea has had no impact on hospitalization rates. We however show no steady decrease from 1998 to 2008 and more widespread hydroxyurea use is likely to decrease these hospitalization rates. Studies are needed to evaluate and improve the implementation of hydroxyurea and other evidence-based management approaches in SCD. Specifically, we need to identify ways of broadening access to care that includes access to the appropriate use of hydroxyurea in patients with SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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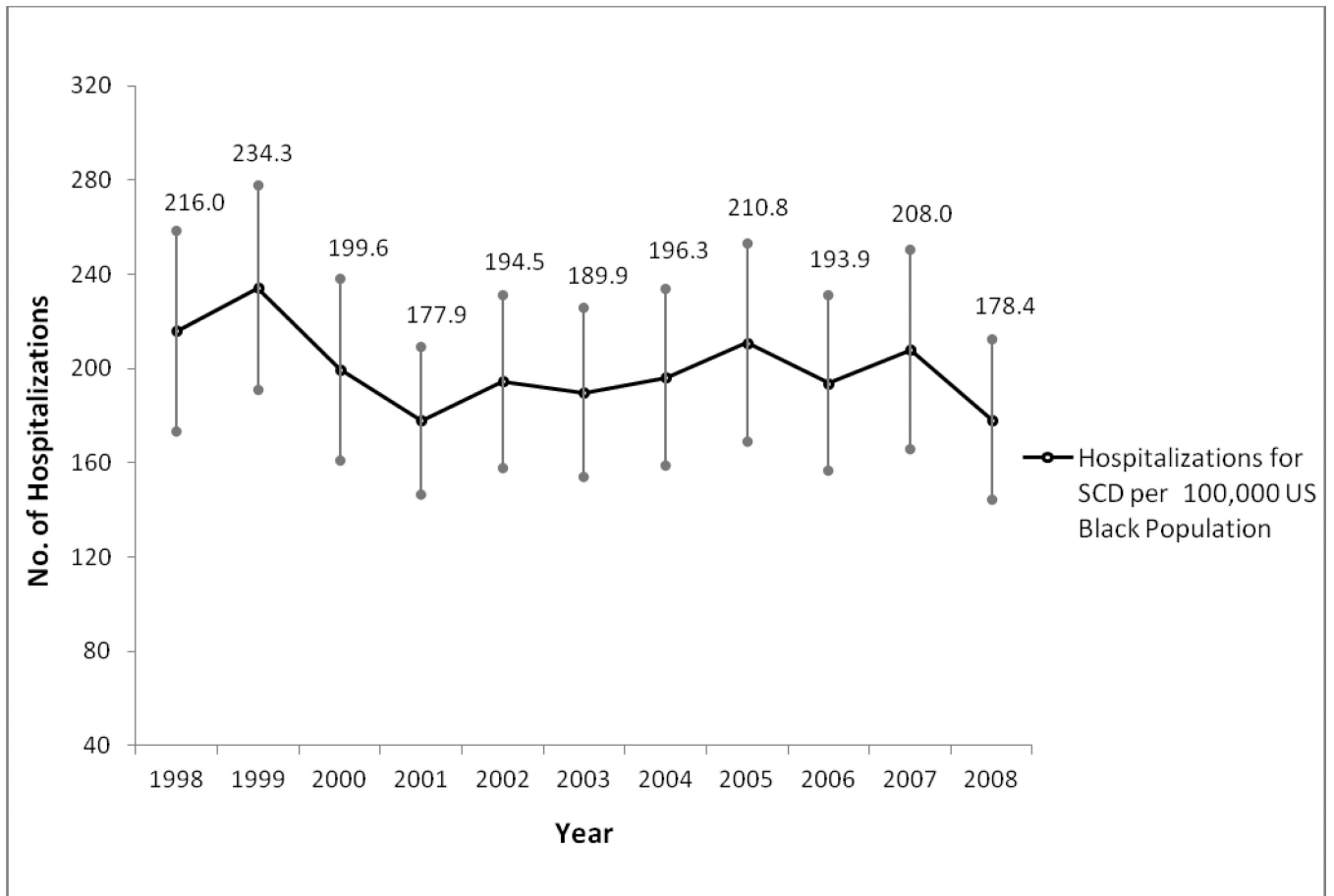


Figure 1. Trends in Hospitalization Rates for Sickle Cell Disease per 100,000 Black Population in the United States, 1998 to 2008. (Trend, $p = 0.30$)

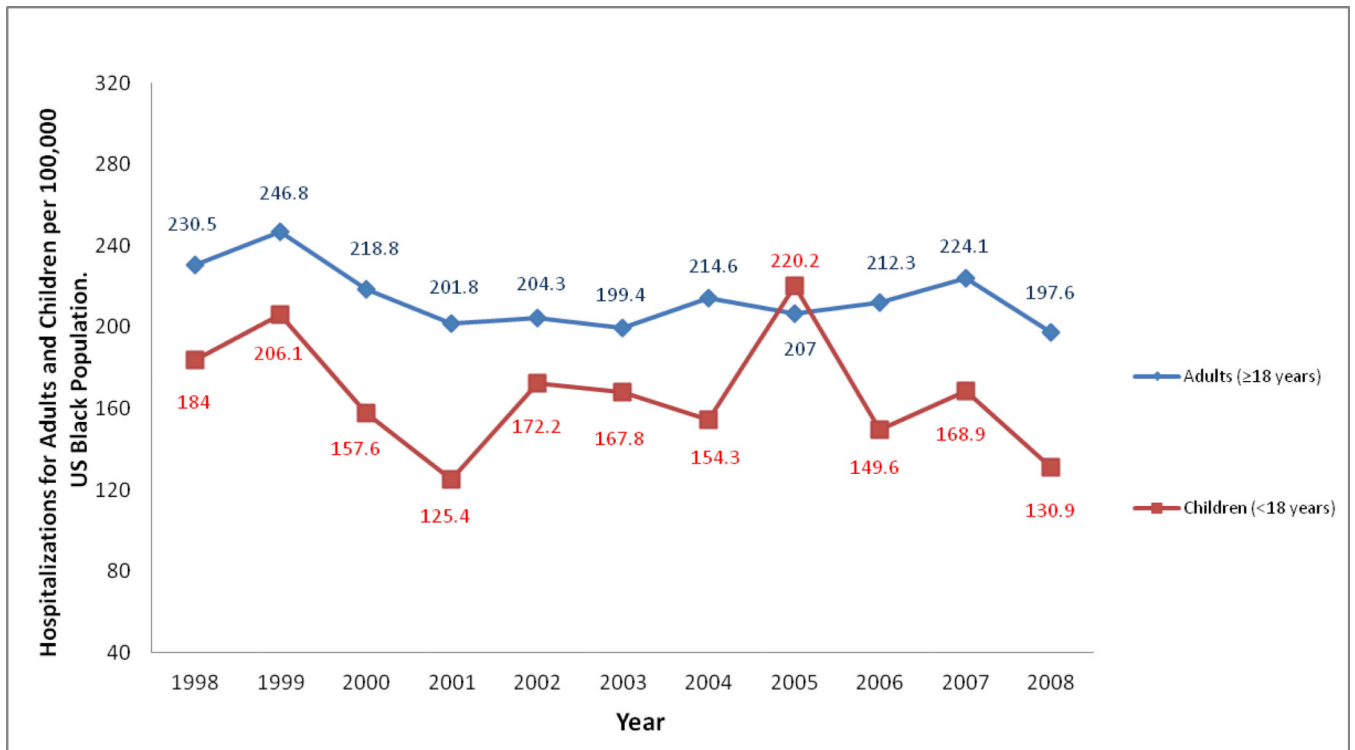


Figure 2. Trends in Hospitalization Rates for Sickle Cell Disease in Adults and Children per 100,000 Black Population in the United States, 1998 to 2008. (trend in adults, $p = 0.30$; trend in children, $p = 0.34$)

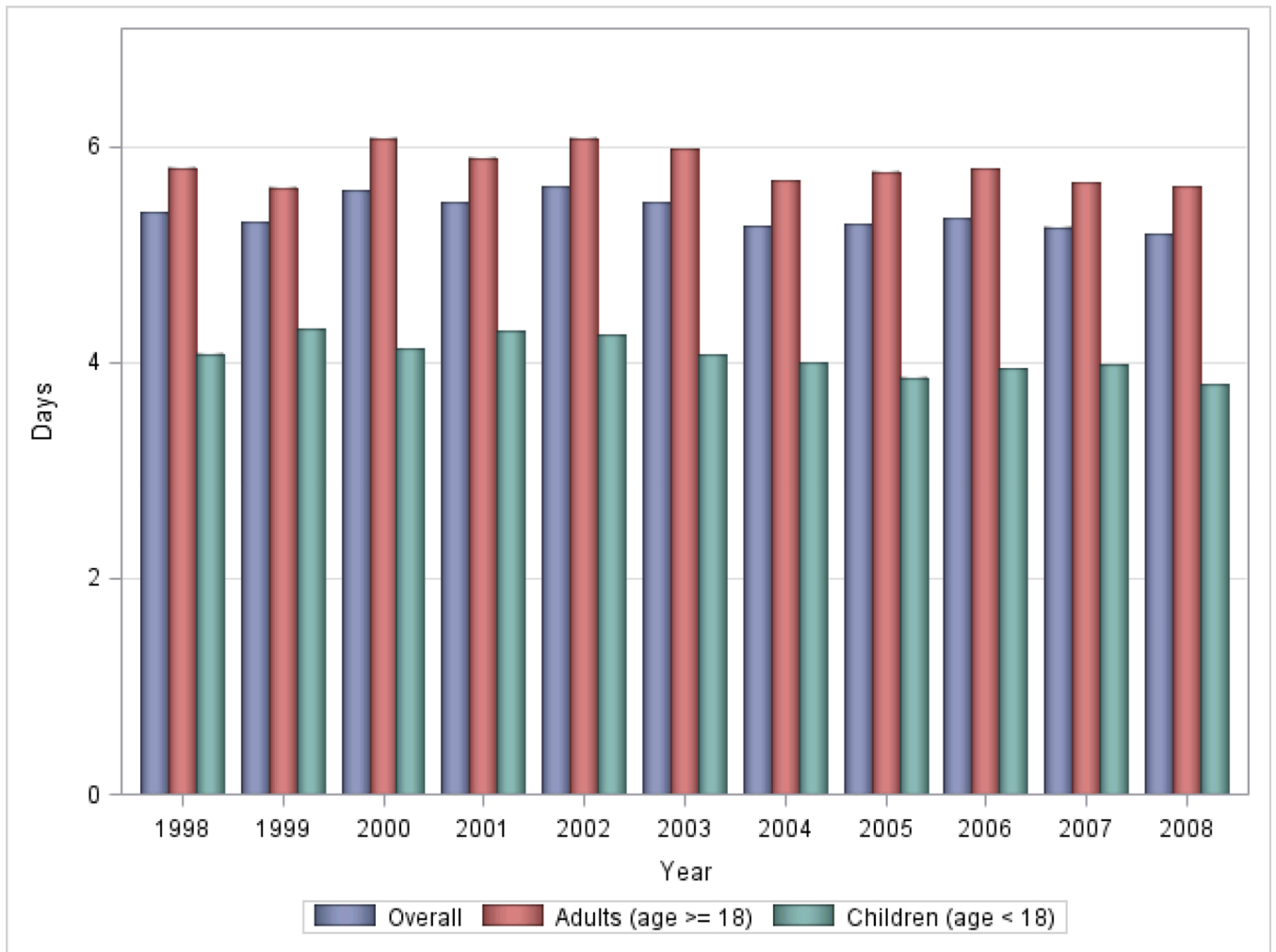


Figure 3. Trends in Hospital Length of Stay (LOS) for Sickle Cell Disease in the United States, 1998 to 2008.

Table 1

Black Patients Hospitalized with a Principal Diagnosis of Sickle Cell Disease in the United States, 1998 and 2008.

	1998		2008		p values
	Number	Percent	Number	Percent	
Patients, total No.	74,344		69,845		
Gender					0.66
Male	35,267	47	33,547	48	
Female	39,077	53	36,298	52	
Age, y					
Adults (18yrs)	54,490	73	55,042	79	0.11
Children (<18yrs)	19,850	27	14,803	21	
< 5	4,760	6	3,493	5	<0.001
5 – 13	9,537	13	6,418	9	
14 – 17	5,553	8	4,891	7	
18 – 29	26,620	36	27,586	40	
30 – 44	22,527	30	19,567	28	
44 – 64	5,203	7	7,631	11	
65 +	139	0	259	0	
Primary expected payer					0.05
Medicare	14,506	20	16,757	24	
Medicaid	38,649	52	35,790	51	
Private/HMO	16,366	22	12,578	18	
Self-pay	2,824	4	2,954	4	
No charge/other	1,974	3	1,644	2	
Hospital Region					0.55
Northeast	12,956	17	15,079	22	
Midwest	14,374	19	10,333	15	
South	41,941	56	37,855	54	
West	5,074	7	6,584	9	
Hospital teaching status					0.55

	1998		2008		p values
	Number	Percent	Number	Percent	
Patients, total No.	74,344		69,845		
	21,875	30	22,641	32	
Non-Teaching					
Teaching	52,391	71	47,209	68	

Table 2
Rates of Hospitalization and Average Length of Stay (LOS) for Black Patients with Sickle Cell Disease in the United States, 1998 through 2008.

Age, y	Hospitalization Rates per 100,000 US Black population											Average Length of Stay (LOS)				
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	P value for Trend in Hospital Rates	LOS, 1998 (days)	LOS, 2008 (days)	Absolute change (days)	P value for Trend in LOS
Total	216	234.3	199.7	177.9	194.5	189.9	196.3	210.8	193.9	208	178.4	0.3	5.4	5.2	-0.2	<0.001
<18	184.2	206.3	157.5	125.4	172.5	168	199.5	220.1	149.9	168.9	131	0.34	4.1	3.8	-0.3	0.01
18	230.5	247	219	201.7	204.3	199.5	154.3	206.9	212.4	224.2	197.5	0.3	5.8	5.6	-0.2	0.29
<5	168.4	177.6	123.9	88.6	133.5	128.1	126.5	171	108.3	141.7	110	0.43	3.4	3	-0.4	<0.001
5-13	171	194	155.2	120.2	170.1	155.2	137.6	210.3	143.1	153.7	118.8	0.17	4.1	3.8	-0.3	0.007
14-17	234	268.5	203.3	181.8	223.7	242.4	221	294	208.6	229	179.4	0.6	4.7	4.4	-0.3	0.07
18-29	411	433.1	370.8	346.4	352.6	344.1	379.6	387.1	390.9	411.4	362	0.77	5.8	5.6	-0.2	0.3
30-44	271.6	309.7	288	255.5	257.5	256.2	271.3	246.2	258.2	273.8	240.1	0.21	5.8	5.7	-0.1	0.97
45-64	86.4	79.8	72.7	77.8	83.1	80.9	84.6	82.6	87.5	96.5	86.8	0.21	5.9	5.5	-0.4	0.008
65+	4.9	6.9	6.1	7.7	7.6	5.5	9	9.1	9.2	4.9	7.8	0.39	5.3	5.3	0	0.83