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Impact of a Clinical Pharmacy Service on the Management of Patients in a Sickle Cell Disease Outpatient Center

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Abstract

Background—Ambulatory care clinical pharmacy services have expanded beyond primary care settings, but literature supporting the benefits of clinical pharmacy involvement with patients who have rare diseases such as sickle cell disease (SCD) is lacking. Hydroxyurea is the only agent approved by the United States Food and Drug Administration for the treatment of SCD; full benefit in controlling pain episodes and other complications is achieved through monitored escalation to a maximum tolerated dose. The primary objective of this analysis was to evaluate the impact of a newly implemented clinical pharmacy service on the management of patients with SCD.

Methods—We performed a retrospective, cross-sectional analysis of 385 adults with SCD who received care between January 1, 2014, and December 31, 2014, at a single sickle cell disease outpatient center that implemented a clinical pharmacy service in August 2013. Data were collected on hydroxyurea dose escalation, immunization completion rates, and health maintenance metrics (screening for nephropathy with microalbuminuria testing, retinopathy with annual retinal examinations, and pulmonary hypertension with echocardiography). The impact of the clinical pharmacy service on quality measurements was evaluated by using univariate and multivariate analyses.

Results—The number of pharmacist encounters, defined as a clinic visit when a clinical pharmacist interacted with a patient as documented in the medical records, was associated with improved hydroxyurea dose escalation rate (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.07–2.05, $p=0.02$). Immunization rates for the 23-valent pneumococcal polysaccharide vaccine, the 13-valent pneumococcal conjugate vaccine, and influenza vaccine were 66%, 47%, and 62% respectively. The number of pharmacist encounters was associated with the improved immunization completion rates (OR 1.38, 95% CI 1.17–1.62, $p<0.001$). Improved screening for microalbuminuria (OR 2.14, 95% CI 1.60–2.86, $p<0.001$) and sickle cell retinopathy (OR 1.16, 95% CI 1.00–1.35, $p=0.05$) were also associated with the number of pharmacist encounters.

Conclusion—A new clinical pharmacy service implemented in managing a rare disease, SCD, was associated with improved hydroxyurea dose escalation rate, immunization completion rates, and health maintenance metrics.

Keywords

sickle cell disease; clinical pharmacy service; rare disease; hydroxyurea; immunization; clinical pharmacist

Sickle cell disease (SCD) is a rare hematologic disorder caused by homozygosity for a mutation in the beta-hemoglobin gene (1). An estimated 100,000 people are affected by SCD in the United States (2). SCD is associated with high utilization of health care resources (3), and an estimated \$2.4 billion is spent on emergency department visits and hospitalizations due to SCD in the United States every year (4).

Hydroxyurea is the only medication approved by the United States Food and Drug Administration for treating SCD (5). It substantially reduces the frequency of pain crises and acute chest syndrome, decreases the need for red blood cell transfusions and hospitalization, and improves long-term survival (5, 6). Eligible patients with SCD should be offered hydroxyurea at the starting dose of 15 mg/kg/day, and the dose should be escalated to 35 mg/kg/day or until mild myelosuppression is observed, at which point further titration is prohibited (7). Additionally, the 13-valent pneumococcal conjugate vaccine (PCV13), the 23-valent pneumococcal polysaccharide vaccine (PPSV23) immunizations, and an annual influenza vaccination are recommended in patients with SCD because they are at higher risk of invasive pneumococcal disease due to functional or anatomic asplenia (7, 8). It is also important to perform routine screening for various complications because SCD affects multiple organ systems during the lifespan of these patients. This includes screening for nephropathy with microalbuminuria testing (9, 10), retinopathy with annual retinal examinations (10, 11), and pulmonary hypertension with echocardiography every 1–3 years. (12, 13). As a disease with chronic complications, SCD is best managed by a multidisciplinary team providing comprehensive care (14). With a good understanding of clinical pharmacology and the medication-dispensing process, clinical pharmacists are distinctively positioned to address the medication-related issues in this patient population.

With the provision of health care in the United States gradually shifting from the inpatient to outpatient setting (15), the role of the ambulatory care pharmacy service has significantly expanded over the past decade (16), and the scope has extended to various areas (17–21). According to an American Society of Health-System Pharmacists survey, the most common specialty area where ambulatory care clinical pharmacists practiced was oncology, followed by psychiatry, heart failure, asthma, and nephrology (22). However, literature supporting the benefits of clinical pharmacy involvement in rare diseases such as SCD is lacking. The escalation of hydroxyurea treatment requires frequent monitoring, and quality measurements, such as immunization and health maintenance, also demand additional help. To meet these needs, the clinical pharmacy service was implemented in the Sickle Cell Outpatient Center at University of Illinois at Chicago (UIC; Chicago, IL) in August 2013. The primary objective of this report was to evaluate the impact of the clinical pharmacy

service on the management of patients with SCD by measuring hydroxyurea dose escalation rate, immunization completion rates, and health maintenance metrics (screening for nephropathy, retinopathy, and pulmonary hypertension).

Methods

Implementation of Clinical Pharmacy Service in the Sickle Cell Outpatient Center

The development of this new pharmacy service can be summarized by a four-step implementation framework (Figure 1) (23). In the exploration stage, the increasing needs for pharmaceutical care were identified by the pharmacy department and sickle cell outpatient center. After communicating among the stakeholders, including the physicians and the pharmacy leadership, the pharmacy department provided funding to support a clinical pharmacist and installed a pharmacy service in the sickle cell outpatient center. During the initial implementation phase, the clinical pharmacist underwent additional training on SCD and delineated the clinical responsibilities. During patient visits, the nursing staff collected vital signs and phlebotomy for laboratories while the physicians examined the patients, ordered laboratory or other clinical tests, and prescribed medications. The clinical pharmacist had a face-to-face patient interaction before or simultaneously with the physicians. The encounter lasted approximately 20 minutes, and activities included drug therapy monitoring (especially hydroxyurea monitoring that included review of the dosage and laboratory test results to evaluate for myelotoxicity), patient education, and health maintenance counseling that included vaccinations and screening for nephropathy, retinopathy, and pulmonary hypertension. The use of opioids was also evaluated to improve pain management and to decrease adverse effects or abuse potential. The clinical pharmacist also had privilege to refill prescriptions for noncontrolled substances and order vaccines under a written protocol. The clinical pharmacist documented the encounter and interventions in a clinical note, and the interventions were also provided to the physicians via face-to-face communication. The pharmacist also conducted follow-up phone calls with patients if any medication change was needed after reviewing laboratory test results. After the pharmacy service was fully implemented, the pharmacy department and the sickle cell outpatient center maintained their support and started to assess the impact on quality metrics.

Patient Population and Pharmacist Encounters

A retrospective, cross-sectional chart review of the outpatient prescription records was performed. Patients were included if they were adults (age ≥ 18 years) with SCD (hemoglobin [Hb] SS, Sβ⁰-thalassemia, SC, or Sβ⁺-thalassemia) who were prescribed at least one medication at the Sickle Cell Outpatient Center at UIC from January 1–December 31, 2014.

A pharmacist encounter was defined as a patient visit when a clinical pharmacist interacted with a patient and documented the interaction in the medical records. Due to multiple patients being scheduled simultaneously and other scheduling conflicts, a pharmacist encounter occurred in 49% of the patient visits in 2014, and 83% of patients had at least one face-to-face encounter with the pharmacist during 2014. One hundred clinical notes

documenting pharmacist encounters were randomly selected from 2014 and reviewed to delineate the types of pharmacist interventions. This activity was approved by the UIC Institutional Review Board.

Data Collection and Measured Outcomes

The data collection was performed by an investigator independent of the clinical pharmacist working in the sickle cell outpatient center. Patients' demographic and clinical data, including age, sex, SCD genotype, number of clinic visits and pharmacy encounters, immunization and health screening records, and hydroxyurea dose escalation history, were extracted from the electronic medical records system.

The primary outcome was to evaluate if the pharmacist encounters had any association with hydroxyurea dose escalation in the patients who met the following criteria: hemoglobin SS or S β^0 -thalassemia genotype, current hydroxyurea dose lower than 35 mg/kg/day, and no previously documented myelosuppression at doses higher than the current dose. The secondary outcomes were to evaluate if the number of pharmacist encounters had any association with immunization completion and health maintenance metrics. For the health maintenance metric analysis, retinopathy and microalbuminuria screening during 2014 and echocardiogram screening for pulmonary hypertension during the past 5 years were assessed.

Statistical Analysis

The baseline patient characteristics and pharmacist intervention types were analyzed by using descriptive statistical analysis, and the univariate analysis was conducted by using either the Mann-Whitney U test or the χ^2 test based on the variables. To assess the quality metrics, potential influential factors including age, sex, number of clinic visits, and number of pharmacist encounters were entered into a multivariate logistic regression model to compare patients who underwent hydroxyurea dose escalation or completed immunization or health maintenance screening with patients who did not. SYSTAT 13 statistical analysis software (Systat Software Corp., Chicago, IL) was used for the analyses.

Results

A total of 424 adults with SCD were prescribed at least one medication at the Sickle Cell Outpatient Center at UIC from January 1–December 31, 2014. Thirty-nine of these patients were prescribed medications without a clinic visit in 2014 and were therefore excluded, leaving 385 patients for inclusion in the analysis.

Hydroxyurea Dose Escalation

Among the 385 patients with SCD included in this analysis, the median age was 33 years (interquartile range [IQR] 25–45 years), 40% were male, and 74% had Hb SS or S β^0 -thalassemia genotypes. The patient characteristics were listed based on whether they underwent hydroxyurea dose escalation or completed immunization or health maintenance screening in Table 1. A total of 161 patients (42%) were taking hydroxyurea, and 97 of them were eligible for dose escalation. Among the 97 eligible patients, 42 patients (43%)

underwent dose escalation. The number of pharmacist encounters was associated with improved dose escalation rate after adjusting for other variables (OR 1.48, 95% confidence interval [CI] 1.07–2.05, $p = 0.02$; Table 2).

Immunization Completion

The influenza vaccination rate was 62% in 2014, and 47% and 66% of patients were up to date on PCV-13 and PPSV-23 immunizations, respectively. Thirty-four percent of patients were up to date for all three immunizations. The number of pharmacist encounters was associated with improved immunization completion rates for influenza and PCV-13 (Table 3). The number of pharmacist encounters was also associated with improved completion rates of all three immunizations (OR 1.38, 95% CI 1.17–1.62, $p < 0.001$).

Health Maintenance Metrics

Routine health maintenance metrics in patients with SCD includes microalbuminuria screening for nephropathy, retinal evaluation for sickle retinopathy, and echocardiogram screening for pulmonary hypertension. Table 4 shows that the number of pharmacist encounters was associated with improved screening rate for microalbuminuria (OR 2.14, 95% CI 1.60–2.86, $p < 0.001$), and a trend for an association with the retinopathy screening rate was also observed (OR 1.16, 95% CI 1.00–1.35, $p = 0.05$). The number of clinic visits was associated with improved echocardiogram screening rate (OR 1.19, 95% CI 1.06–1.33, $p = 0.003$).

Clinical Pharmacist Interventions

During the 100 randomly selected pharmacist encounters, a total of 312 interventions were made with a median of 3 interventions per encounter (IQR 2–4). The most frequent pharmacist interventions included referral to other specialists (38%), laboratory test ordering for medication monitoring and health maintenance screening (20%), immunizations (20%), and changing pharmacotherapy (16%).

Discussion

Initiation and dose escalation of hydroxyurea is one of the most important quality measurements in treating SCD (7, 24), although hydroxyurea is still underused in this patient population (25). In the Sickle Center Outpatient Center at UIC, dose escalation is an area where more efforts are needed, as 97 (60%) of 161 patients taking hydroxyurea were eligible for dose escalation. During dose escalation, patients need to be closely monitored due to the risk of myelosuppression. The clinical pharmacist is equipped with knowledge in clinical pharmacology and can be a facilitator for escalating the hydroxyurea dose and helping manage safety issues. Our results indeed showed that the number of pharmacist encounters was associated with improved rate of dose escalation (Table 2), which may translate to better clinical outcomes in patients with SCD.

Immunization is essential for patients with SCD to reduce the risk of infections, especially those caused by encapsulated organisms such as *Streptococcus pneumoniae* (7). Published literature showed that the PPSV-23 immunization rates in other adult SCD centers ranged

from 21–44%, whereas influenza vaccination rates are 12–50% (26–28). In the Sickle Cell Outpatient Center at UIC, higher immunization rates for PPSV-23 (66%), PCV-13 (47%), and influenza (62%) were achieved. By educating patients on the importance of immunization, facilitating vaccine procurement, and entering immunization orders based on a written protocol, the number of pharmacist encounters was associated with improved immunization rates as shown in Table 3. Furthermore, clinical pharmacists also assisted in monitoring the safety of immunization and reporting of severe adverse events related to vaccination in patients with SCD (29).

Our report has limitations because of its retrospective nature, and certain confounding factors such as patient socioeconomic status were not measured. Patients may have different types of insurance coverage, which may affect the presented measurements. Second, the analyzed measurements were mostly process outcomes for SCD management, although hydroxyurea dose escalation and immunization completion are expected to lead to improved clinical benefits. Third, an independent investigator conducted the data collection, but the clinical pharmacist practicing in the Sickle Cell Outpatient Center was involved in analyzing the results, which potentially introduces subjective bias. Fourth, medication adherence, an important quality measurement, was not evaluated due to the retrospective nature of this report. Future prospective evaluations of clinical outcomes such as emergency department visits and hospitalizations, medication adherence, opioid use, and financial impact are warranted.

Conclusion

We used a quantitative approach to measure quality metrics in a rare disease, SCD, and demonstrated that a newly implemented clinical pharmacy service was associated with improved hydroxyurea dose escalation rate, immunization completion rates, and health maintenance metrics. The future direction of this service includes developing written protocols and collaborative practice agreements to give pharmacists autonomy to adjust medication dosages. It is also a consideration to create standing orders to have other disciplines involved in improving the quality measurements.

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Figure 1.
Clinical pharmacy service implementation framework in the sickle cell disease outpatient center.

Table 1

Characteristics of Patients Who Completed versus Those Not Completed Each Quality Metric

Quality Metric															
Covariate	Hydroxyurea Dose Escalation			Immunization Completion			Microalbuminuria Screening			Retinopathy Screening			Echocardiogram Screening		
	Yes (n=42)	No (n=55)	p-value	Yes (n=129)	No (n=256)	p-value	Yes (n=308)	No (n=69)	p-value	Yes (n=119)	No (n=266)	p-value	Yes (n=238)	No (n=147)	p-value
No. of pharmacist encounters per patient, median (IQR)	2 (1-4)	1 (1-3)	0.03	2 (1-4)	1 (1-3)	<0.001	2 (1-3)	1 (0-1)	<0.001	2 (1-4)	1 (1-3)	<0.001	2 (1-3)	1 (1-2)	0.002
No. of clinic visits per patient, median (IQR)	4 (3-7)	3 (2-5)	0.21	5 (3-7)	3 (2-5)	<0.001	4 (2-6)	3 (1-4)	<0.001	4 (3-7)	3 (2-5)	<0.001	4 (3-7)	3 (2-5)	<0.001
Age (yrs)	28 (24-36)	32 (27-45)	0.02	37 (28-47)	31 (25-44)	0.008	33 (25-45)	32 (27-47)	0.47	35 (27-49)	32 (25-43)	0.02	33 (25-47)	32 (25-43)	0.13
Sex (male)	50%	42%	0.42	35%	43%	0.13	40%	41%	0.92	40%	41%	0.84	41%	40%	0.80

IQR = interquartile range.

Table 2

Results of Logistic Regression with Hydroxyurea Dose Escalation in the 97 Eligible Patients

Covariate	Odds Ratio	95% CI	P-value
No. of pharmacist encounters	1.48	1.07–2.05	0.02
No. of clinic visits	0.94	0.79–1.24	0.94
Age (yrs)	0.95	0.90–0.99	0.02
Sex (male)	1.20	0.49–2.95	0.69

CI = confidence interval.

Table 3

Results of Logistic Regression with Immunization Completion

Immunization	Covariate	Odds Ratio	95% CI	P-value
Influenza	No. of pharmacist encounters	1.28	1.08–1.51	0.004
	No. of clinic visits	1.08	0.97–1.20	0.16
	Age (yrs)	1.00	0.98–1.02	0.96
	Sex (male)	0.71	0.46–1.10	0.13
PCV-13	No. of pharmacist encounters	1.46	1.24–1.72	<0.001
	No. of clinic visits	1.04	0.93–1.15	0.50
	Age (yrs)	1.02	1.00–1.04	0.04
	Sex (male)	0.79	0.50–1.22	0.29
PPSV-23 ^a	No. of pharmacist encounters	1.11	0.94–1.31	0.23
	No. of clinic visits	1.12	1.00–1.26	0.05
	Age (yrs)	1.01	0.99–1.02	0.51
	Sex (male)	0.68	0.44–1.06	0.09
All 3 immunizations (influenza, PCV-13, and PPSV-23)	No. of pharmacist encounters	1.38	1.17–1.62	<0.001
	No. of clinic visits	1.02	0.91–1.13	0.79
	Age (yrs)	1.02	1.00–1.04	0.04
	Sex (male)	0.78	0.49–1.25	0.31

CI = confidence interval; PCV-13 = 13-valent pneumococcal conjugate vaccine; PPSV-23 = 23-valent pneumococcal polysaccharide vaccine.

^aPatients who received at least one dose of PPSV-23 in the past 5 years or had received the PCV-13 immunization and were within the 2-month waiting period for receiving PPSV-23 at the end of the evaluation period were considered PPSV-23 immunization completion.

Table 4

Results of Logistic Regression with Health Maintenance Metrics

Metric	Covariate	Odds Ratio	95% CI	P-value
Microalbuminuria Screening	No. of pharmacist encounters	2.14	1.60–2.86	<0.001
	No. of clinic visits	1.02	0.90–1.16	0.76
	Age (yrs)	0.99	0.97–1.01	0.31
	Sex (male)	1.10	0.61–1.99	0.74
Retinopathy Screening	No. of pharmacist encounters	1.16	1.00–1.35	0.05
	No. of clinic visits	1.05	0.94–1.17	0.38
	Age (yrs)	1.02	1.00–1.04	0.02
	Sex (male)	1.09	0.69–1.72	0.72
Echocardiogram Screening	No. of pharmacist encounters	1.02	0.87–1.20	0.78
	No. of clinic visits	1.19	1.06–1.33	0.003
	Age (yrs)	1.01	0.99–1.03	0.24
	Sex (male)	1.20	0.77–1.86	0.41

CI = confidence interval.