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Preventive Care Delivery to Young Children with Sickle Cell Disease

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Abstract

Preventive services can reduce the morbidity of sickle cell disease (SCD) in children but are delivered unreliably. We conducted a retrospective cohort study of children ages 2–5 years with SCD, evaluating each child for 14 months and expecting that he/she should receive 75% of days covered by antibiotic prophylaxis, 1 influenza immunization, and 1 transcranial Doppler ultrasound (TCD). We used logistic regression to quantify the relationship between ambulatory generalist and hematologist visits and preventive services delivery. Of 266 children meeting inclusion criteria, 30% consistently filled prophylactic antibiotic prescriptions. Having 2 generalist, non-well child care visits or 2 hematologist visits was associated with more reliable antibiotic prophylaxis. Forty-one percent of children received 1 influenza immunizations. Children with 2 hematologist visits were most likely to be immunized (62% versus 35% among children without a hematologist visit). Only 25% of children received 1 TCD. Children most likely to receive a TCD (42%) were those with 2 hematologist visits. One in twenty children received all three preventive services. Preventive services delivery to young children with SCD

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Conflicts of interest:

No conflict of interest with the present manuscript is perceived by the authors.

SUPPLEMENTAL DIGITAL CONTENT

Supplemental digital content—Table 1—Recommended services

Supplemental digital content—Table 2—Codes

was inconsistent but associated with multiple visits to ambulatory providers. Better connecting children with SCD to hematologists and strengthening preventive care delivery by generalists are both essential.

Keywords

sickle cell anemia; antibiotic prophylaxis; influenza vaccines; transcranial Doppler ultrasonography; preventive health services

INTRODUCTION

Sickle cell disease (SCD) affects nearly 100,000 individuals in the US¹ and substantially increases the risk of severe infections^{2–4} and stroke⁵ among affected children. Preventive services, including antibiotic prophylaxis,^{6,7} influenza immunization,⁸ and transcranial Doppler (TCD) screening,^{9,10} could reduce SCD-related infectious and neurologic morbidity if reliably delivered and are recommended by evidence-based national guidelines (Supplemental Digital Content—Table 1).^{11–13} Measuring preventive services delivery has been proposed as one component in the overall assessment of the quality of care delivered to children with SCD.¹⁴

Existing evidence suggests children with SCD receive preventive services inconsistently. Antibiotic prophylaxis, known for 30 years to substantially reduce the incidence of invasive pneumococcal disease in children with SCD,^{6,7} is received only half the time.^{15–17} While influenza-related hospitalizations are >50 times more common among children with SCD than those without,⁴ fewer than 1 in 3 children with SCD receive influenza immunization annually.^{17–19} Although annual TCD screening has been shown to reliably identify children with SCD at elevated risk for stroke,⁹ chronic transfusion of at-risk children reduces stroke risk by >90%,¹⁰ and single institution studies show that effective screening and treatment is possible,^{20,21} annual TCDs still occur less than half the time in some reports.^{22–24}

A significant gap in our understanding of preventive services delivery to children with SCD concerns the relative contribution of generalists and specialists (i.e., hematologists). Unlike many other serious chronic conditions of childhood (e.g., cystic fibrosis, inflammatory bowel disease), the care of children with SCD is often driven largely or exclusively by generalists.^{25,26} We have shown previously that 2 in 5 Medicaid-insured Maryland children with SCD never saw a hematologist in the first 2 years of life,²⁷ despite long-standing recommendations for comprehensive hematologist evaluations at least annually.¹² How ambulatory care patterns of children with SCD affect their receipt of recommended preventive care is largely unknown.

The objectives of our study, therefore, were to use a statewide Medicaid claims database to 1) measure the proportion of Medicaid-insured children with SCD receiving 3 recommended preventive services; and 2) determine whether patterns of generalist and hematologist ambulatory care predict receipt of these services. We hypothesized that generalist ambulatory visits would drive non-specialized SCD preventive care delivery (i.e., antibiotic

prophylaxis and influenza immunization) and that hematologist ambulatory visits would drive specialized SCD preventive care delivery (i.e., TCD screening).

MATERIALS & METHODS

Data source

Study data were Maryland Medicaid claims data, collected by the Maryland Department of Health and Mental Hygiene during normal operations from 2002–2008. Analysts from the Hilltop Institute at the University of Maryland, Baltimore County extracted study data and provided a limited, de-identified dataset to the research team. Data included demographic and enrollment information, as well as claims for medical, pharmacy, and other health-related services.

Case definition

Children with SCD were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes (Supplemental Digital Content—Table 2). Concordant with previous research, children were designated as having SCD if they had one inpatient visit or two outpatient visits more than 30 days apart that were associated with a primary diagnosis code for SCD.^{15,25}

Enrollment

Our study involved children between the ages of 2 years (the youngest age at which annual TCD screening is recommended) and 5 years (the oldest age at which antibiotic prophylaxis is universally recommended). Annual influenza immunization is recommended throughout this age window. Children with SCD in this age group were included in analyses if they had 14 months of continuous enrollment from June 1 of one study year to July 31 of the following study year (e.g., June 1, 2007 to July 31, 2008). The 14 month duration was selected to allow for a 1-month “grace period” on both ends of a 12 month window during which a minimum of 1 TCD would have been expected. The calendar window was selected to include exactly one influenza season, during which a minimum of 1 influenza immunization would have been recommended. For children with multiple years’ worth of data available, we chose the earliest 14 month window to include in the final dataset.

Measures

Antibiotic prophylaxis—Consistent with prior studies,^{15–17} we used pharmacy claims to count the number of days of prophylactic antibiotic coverage dispensed during the enrollment window. While most such prescriptions were for medications in the penicillin class (primarily penicillin and amoxicillin), we also accepted pharmacy claims for macrolides, since erythromycin is the recommended alternative for penicillin-allergic individuals. We assumed all days dispensed to be non-overlapping, whether or not a given dispensing occurred during or after the end of a previously dispensed supply, yielding a best-case estimate of the number of days covered. We assessed antibiotic prophylaxis both as the proportion of total days enrolled that were covered by an antibiotic dispensing and as the proportion of children with 75% of days covered by an antibiotic prescription, a cut-off

used in other studies of medication adherence.^{28–30} Individuals with >100% coverage were capped at 100%.

Influenza immunization—We purposefully selected our enrollment windows to include exactly one influenza season. Despite somewhat complex recommendations that determine whether a young child needs 1 or 2 influenza immunizations during a given season, we considered a child to have been immunized against influenza if they received 1 influenza immunization at any time during an influenza season.

Transcranial Doppler—TCD is recommended at least annually for children ages 2 to 16 years. While conditional (170 to 199 cm/sec) or abnormal (≥ 200 cm/sec) TCDs demand follow-up TCDs at shorter intervals, we did not have access to TCD results and therefore considered a child to have been up-to-date for TCD if they received 1 TCD at any time during the 14 month window (i.e., the 1-year window with a 1-month grace period on either end).

Composite—In order to assess whether children received all recommended care, we created a composite (i.e., “all-or-none”) outcome that was met if the child received at least 75% antibiotic prophylaxis coverage and had 1 influenza immunization and 1 TCD in their study year. If any of these were lacking, the composite outcome was not met. We also analyzed what proportion of children received at least 2 of the 3 recommended services in the composite.

Ambulatory visits

Ambulatory visits were categorized by self-reported provider type (generalist versus specialist) and purpose (well child care (WCC) versus non-WCC) (Supplemental Digital Content—Table 2). Providers were considered generalists if they self-reported as pediatricians, family physicians, or internists; other providers were treated as specialists. Visit purpose was determined using ICD-9-CM and Current Procedural Terminology codes. When applicable, our coding scheme mirrored National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set criteria.³¹

Analysis

We tabulated patient demographics and ambulatory healthcare utilization. For the latter, we analyzed the number of generalist (well child care and non-well child care) and hematologist visits in 3 categories: none, 1, or 2 visits within the 14-month window. We estimated the effect of outpatient visits on each preventive service outcome using logistic regression, calculating the odds ratio of receiving a preventive service for a given category of visits (e.g., 2 well child care visits) versus the baseline of no such visits, after adjusting for gender, age, and other visits (e.g., hematologist visits and generalist non-well child care visits). We calculated the confidence interval using a standard Wald interval. P-values were calculated using likelihood ratio tests for the type of visit (e.g., well child care visits). All analyses were performed in Stata (Version 13, StataCorp, College Station, TX). This study was approved by the Institutional Review Boards of the Johns Hopkins University School of

Medicine, the Maryland Department of Health and Mental Hygiene, and the Hilltop Institute at the University of Maryland, Baltimore County.

RESULTS

Study subjects & ambulatory healthcare utilization

There were 266 children with SCD whose age and enrollment patterns met our inclusion criteria (Table 1). Approximately half were female and 80% resided in 1 of 4 urban counties surrounding Baltimore, MD (43%) and Washington, DC (37%). Eighty-two percent of children had one or more generalist visits, with a mean of 3.8 generalist visits per child. Of these generalist visits, an average of 0.79 well child care visits occurred annually, compared with 3.0 non-well child care visits annually. Almost 60% of children went unseen by a hematologist; 22% had a single visit and the remainder had 2 or more.

Antibiotic prophylaxis

Overall, 30% of children filled prophylactic antibiotic prescriptions covering at least 75% of study days (Table 2). Child gender, age at study entry, and number of WCC visits were not associated with consistent receipt of antibiotic prophylaxis in adjusted models. In contrast, having 2 or more non-WCC visits with a generalist (adjusted odds ratio (aOR) 2.54 [95% confidence interval: 1.28–5.01]) or 2 or more visits with a hematologist (aOR 2.76 [1.40–5.45]) was associated with increased odds of consistent receipt of antibiotic prophylaxis. Overall, study children were covered for a mean of 53% of study days. The highest proportion of days covered by antibiotics in any subgroup was found among children with 2 or more hematologist visits (65% of days covered).

Influenza immunization

Overall, 41% of children received at least 1 influenza immunization during the study period. The subgroup most likely to be immunized, and the only one statistically significantly different from its comparators in the adjusted model, was those children with 2 or more hematologist visits (62% immunized, compared to 35% among children without a hematologist visit; aOR 2.64 [1.32–5.28]).

TCD screening

TCD screening was the least reliably delivered preventive service, with only 25% of children receiving at least one TCD during the study period. As with antibiotic prophylaxis and influenza immunization, the children most likely to receive a TCD (42%) were those with 2 or more hematologist visits (aOR 2.03 [1.02–4.04]). Children with no well child care visits (19%), no non-WCC generalist visits (22%), and no hematologist visits (20%) were the least likely to receive a TCD in each of the 3 visit type groupings.

Composite

Only 14 of 266 children (5.3%) received all three preventive services (data not shown). All 14 had a generalist visit of some type (1: 1 visit; 13: 2 visits) and 10 had a hematologist visit (2: 1 visit; 8: 2 visits). An additional 55 children received exactly 2 of the 3 services.

Of the 69 children who received either 2 or 3 of the 3 preventive services, only 2 (2.9%) did so in the absence of any generalist visit, while 30 (43%) did so in the absence of a hematologist visit.

DISCUSSION

Reliably delivered preventive services reduce the morbidity of SCD in young children. Despite this, we found that only 1 in 20 Medicaid-insured Maryland children with SCD received 3 recommended preventive services during the study period. Only one-quarter received at least 2 of the 3 services. Preventive services delivery was best among children with 2 or more non-WCC generalist visits or 2 or more hematologist visits. Our hypothesis that generalist ambulatory visits would drive non-specialized SCD preventive care delivery (i.e., antibiotic prophylaxis and influenza immunization) was not supported; our hypothesis that hematologist ambulatory visits would drive specialized SCD preventive care delivery (i.e., TCD screening) was. For each of the 3 services, it was those children seen 2 or more times by the hematologist who had the greatest likelihood of receiving the preventive service. The causal direction of this association remains unknown. It is possible that hematologist visit increase a patient's likelihood of being offered and undertaking recommended preventive services. It is also possible that the type of parents and children who seek out 2 or more hematologist visits are also the type of parents and children who more aggressively seek out and undertake preventive services.

Antibiotic prophylaxis

Antibiotic prophylaxis to prevent invasive bacterial infection was one of the first preventive treatments definitively proven effective in the SCD population.^{6,7} A landmark trial, stopped 8 months early and published in 1986, demonstrated an 84% reduction in septicemia among children with SCD treated with daily penicillin prophylaxis.⁶ Despite the introduction of the 7-valent pneumococcal conjugate immunization in 2000 and the 13-valent update in 2010, antibiotic prophylaxis remains essential, as breakthrough cases of invasive pneumococcal disease persist.^{32,33} Prior research on antibiotic prophylaxis adherence is concerning, and our findings echo this concern. In a study of Medicaid-insured children from 2 states, Cox et al. found that only 41% of days were covered with an antibiotic prescription, and only 22% of children had 75% or more days covered in a year,¹⁵ slightly lower than our measured adherence. In other Medicaid-insured populations of children with SCD, Patel et al. found 55% coverage for antibiotics, which was similar to the compliance observed in the same population for other medications (range: 59–61%),¹⁶ and Beverung et al. observed a mean of 45% of days covered with antibiotics, with fewer than 1 in 5 children meeting their full adherence threshold of 80%.¹⁷

We hypothesized that generalist visits would be associated with receipt of antibiotic prophylaxis, based on our and others' previous studies suggesting that ambulatory care for many children with SCD is provided primarily by generalists²⁷ and our belief that antibiotic prophylaxis has been widely known, not just to specialists, to be the standard of care for decades. Our finding that, among generalist visits, only non-WCC visit attendance was associated with antibiotic prophylaxis delivery suggests that patient-level factors, including

severity of illness, may be more important. Prior studies of prophylaxis adherence have suggested that the burden of picking up refills and simple forgetting were also patient-level drivers of non-adherence.³⁴ Our finding that the most robust antibiotic coverage was found among children with 2 or more hematologist visits suggests that even antibiotic prophylaxis, despite its long history and being widely available in the community, remains a service most strongly promoted by hematologists.

We measured antibiotic adherence using the so-called “medication possession ratio”, which is one of the most commonly employed measures of medication adherence.³⁵ This “best-case” methodology assumes that all dispensed doses of a medication are used by recipients and that overlapping days of coverage are remedied by patients holding newly dispensed doses until previously dispensed doses are utilized. It also does not account for expired medications, which can be particularly problematic for liquid penicillin formulations which are typically considered expired after 14 days. As a result, our estimates of antibiotic adherence should be considered “best-case”; true adherence is likely lower.

Influenza immunization

Children with SCD are at substantially increased risk for influenza-related complications and hospitalizations compared to children without SCD.^{3,4} The mechanism underlying this enhanced risk is incompletely understood, but may involve influenza: 1) compromising respiratory tract mucosal immunity;³⁶ 2) causing acute chest syndrome;³⁷ and 3) provoking fever which results in precautionary admission to rule out bacterial sepsis. Fortunately, influenza immunization is both safe^{38,39} and immunogenic^{39,40} in children with SCD, and is efficacious in children generally.⁸ Influenza immunization has been recommended for children with SCD by the Advisory Committee on Immunization Practices of the CDC since 1978,⁴¹ and is now recommended for all children over 6 months of age.⁴² Fewer than half of children overall receive the influenza immunization in a given influenza season,⁴³ however, and in a multi-site 1999 study, only 20% of adolescents with SCD received influenza immunization.¹⁸ Influenza immunization rates of children with SCD appear to be similar to the low rates observed for children with other high-risk chronic conditions.¹⁹

Few obvious barriers exist to influenza immunization of children with SCD. Influenza immunization is widely available, typically low or no cost, quick and simple to administer, and associated with minimal side effects. In our study, only repeated contact with a hematologist was associated with increased likelihood of influenza immunization. Our data cannot shed light on whether provider-side barriers, in particular among generalists (e.g., failure to offer or recommend influenza immunization) or patient-side barriers (e.g., refusal to immunize) were more influential in perpetuating low immunization rates. Alternative influenza immunization approaches, such as using hospitalizations as immunization opportunities⁴⁴ and quality improvement methods to implement multicomponent ambulatory strategies,⁴⁵ warrant further exploration.

Transcranial Doppler

Stroke is one of the most debilitating complications of SCD and occurs more than 200 times as frequently among children with SCD as those without.⁵ TCD identifies children with

SCD at increased risk for stroke,⁹ and chronic transfusion of such children substantially reduces subsequent stroke risk in both controlled¹⁰ and “real world”^{20,21,46} settings. Yet only 45–68% of children with SCD receive TCDs annually,^{22–24} despite TCDs being strongly recommended by prior¹¹ and current¹³ national evidence-based guidelines.

We observed low rates of TCD screening (25% overall), but did find that repeated non-WCC generalist or hematologist visits was associated with improved odds of receiving a TCD screen, which mirrored a similar association between hematologist visits and TCD screening we observed in a prior intervention study.⁴⁷ We hypothesized that hematologist visits would spur TCD delivery based on published evidence suggesting greater awareness of TCD guidelines, self-efficacy regarding discussing TCDs with patients and families, and overall TCD knowledge among pediatric hematologists, compared with generalists.⁴⁸

Unfortunately, patient-related barriers to TCD screening may dampen positive effects of physician contact. In one study of 36 caregivers of children with SCD, 22% had no knowledge of TCD screening and another 42% did not know TCD screening was annual.⁴⁹

Composite

Perhaps most discouragingly, when viewed from an all-or-none perspective, only a tiny minority of children received all 3 recommended services. We studied children at an age window (2–5 years) where receipt of preventive services is particularly critical, raising the concern that preventive services delivery to older populations with SCD, where the benefits of preventive services have been less clearly demonstrated, may be worse.

Limitations

Our study has several noteworthy limitations. First, using ICD-9-CM codes to identify patient genotypes for SCD is inherently imperfect.⁵⁰ We chose the most inclusive ICD-9-CM definition for SCD in order to increase patient capture. Population prevalence data suggest that our study sample comprised a mixture of children with hemoglobin SS (65%), hemoglobin SC (25%), hemoglobin S β^+ -thalassemia (8%), and hemoglobin S β^0 -thalassemia (2%).¹² At the time of our study, the National Heart, Lung, and Blood Institute recommended antibiotic prophylaxis for children with HbSS, HbS β^0 , and HbSC (an estimated 92% of our study sample), influenza immunization for 100% of genotypes in our study sample, and TCD for children with HbSS and HbS β^0 (an estimated 67% of our study sample). Nonetheless, even if all children with HbS β^+ -thalassemia and HbSC in our sample were (correctly) not screened with TCD, our residual TCD screening rate in the target population would remain low (approximately 37% instead of our reported 25%).

Our claims data-derived outcome measures were also imperfect. For antibiotic prophylaxis, our measure of days of prophylaxis dispensed may not correlate precisely with days of prophylaxis prescribed (e.g., due to lost or unfilled prescriptions) or days of prophylaxis consumed (e.g., due to lost or untaken medication). For influenza immunization, we likely missed unreimbursed immunizations delivered via health department or school-based programs, although the latter is likely rare in this age group. For TCD, we may have missed TCDs provided at no cost, for example as part of research studies. Therefore, our measure of antibiotic prophylaxis represents a best-case estimate, while our measures of influenza

immunization and TCDs represent a worst-case estimate. We were unable to examine true health outcomes (e.g., stroke, invasive pneumococcal disease) due to the rarity of these conditions. Lastly, administrative data have inherent limitations stemming from, among other challenges, potential coding inaccuracies and a lack of patient- and family-level demographic information (e.g., parental educational attainment). Nonetheless, administrative data have the advantage over chart review data in that administrative data can span multiple venues of care across large geographic areas.⁵¹

CONCLUSION

Reliable delivery of preventive services to young children with SCD is essential. Our study confirms that the present state of preventive care delivery to this population is inadequate. Hematologist visits, perhaps not surprisingly, were associated with improved care delivery, but fewer than 50% of children with SCD interacted with a hematologist regularly. A two-pronged approach, therefore, aimed at 1) engaging more children with SCD with hematologists; and 2) promoting reliable preventive care delivery to children with SCD by generalists, is warranted. Failing this, the chasm between “what is” and “what could be” in the care of children with SCD is likely to remain wide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

aOR	adjusted odds ratio
CI	confidence interval
ICD-9-CM	International Classification of Diseases, 9 th Revision, Clinical Modification
SCD	sickle cell disease
TCD	transcranial Doppler
WCC	well child care

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TABLE 1

Patient Demographics and Non-emergency Department Ambulatory Healthcare Utilization(N=266)

	n(%)
Gender	
Female	126 (47)
Male	140 (53)
Age at study entry	
2–3 years	229 (86)
3–4 years	37 (14)
County of residence	
Baltimore City	76 (29)
Prince George's	66 (25)
Baltimore County	39 (15)
Montgomery	32 (12)
Other	53 (20)
Total generalist visits	
Mean number of visits (sd) ^a	3.8 (3.6)
Median number of visits (IQR) ^b	3 (1 – 6)
0	48 (18)
1	41 (15)
2	177 (66)
Well child care visits	
Mean number of visits (sd)	0.79 (0.95)
Median number of visits (IQR)	1 (0 – 1)
0	116 (44)
1	109 (41)
2	41 (15)
Non-well child care visits	
Mean number of visits (sd)	3.0 (3.2)
Median number of visits (IQR)	2 (0 – 5)
0	69 (26)
1	53 (20)
2	144 (54)
Hematologist visits	
Mean number of visits (sd)	0.85 (1.6)
Median number of visits (IQR)	0 (0 – 1)
0	157 (59)
1	59 (22)
2	50 (19)

^{a)} standard deviation,^{b)} interquartile range

Receipt of Preventive Services by Medicaid-insured Maryland Children with Sickle Cell Disease(N=266)

TABLE 2

	Proportion covered by prophylactic antibiotics for 75% of days in the year	Adjusted odds ratio (95% CI) ^a	Proportion immunized against influenza	Adjusted odds ratio (95% CI)	Proportion screened by TCD ^b	Adjusted odds ratio (95% CI)
Overall	0.30		0.41		0.25	
Gender						
Female	0.29	1.0	0.39	1.0	0.26	1.0
Male	0.31	1.16 (0.69–1.96)	0.42	0.82 (0.46–1.47)	0.24	1.02 (0.59–1.76)
Age at study entry						
2–3 years	0.31	1.0	0.42	1.0	0.25	1.0
3–4 years	0.27	0.54 (0.24–1.18)	0.30	0.94 (0.41–2.17)	0.24	0.85 (0.38–1.90)
Generalist visits (WCC^c only)						
0	0.23	1.0	0.34	1.0	0.19	1.0
1	0.38	1.41 (0.79–2.54)	0.49	1.62 (0.84–3.14)	0.29	1.55 (0.83–2.87)
2	0.29	0.90 (0.40–2.03)	0.39	1.71 (0.71–4.14)	0.29	0.99 (0.42–2.35)
Generalist visits (non-WCC only)						
0	0.17	1.0	0.26	1.0	0.22	1.0
1	0.24	1.71 (0.76–3.84)	0.38	1.06 (0.44–2.57)	0.24	1.38 (0.56–3.42)
2	0.38	2.54 (1.28–5.01)	0.49	1.02 (0.49–2.13)	0.26	2.57 (1.22–5.40)
Hematologist visits						
0	0.24	1.0	0.35	1.0	0.20	1.0
1	0.36	0.98 (0.52–1.86)	0.37	1.11 (0.53–2.32)	0.22	1.65 (0.85–3.21)
2	0.42	2.76 (1.40–5.45)	0.62	2.64 (1.32–5.28)	0.42	2.03 (1.02–4.04)

^a confidence interval,^b transcranial Doppler,^c well child care