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Improving Care for Children with Bloody Diarrhea at Risk for Hemolytic Uremic Syndrome

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Introduction: Children with infectious bloody diarrhea are at an increased risk for developing hemolytic uremic syndrome (HUS). Early intervention may improve outcomes. This study evaluated the impact of a clinical pathway designed to identify those at risk for HUS, guide initial management, and provide decision support regarding patient disposition. **Methods:** We performed a retrospective cohort study of children 4 months to 19 years of age who presented with the acute onset of bloody diarrhea or other HUS risk factors to the pediatric emergency department (ED) from September 2015 through July 2020. A rapid stool polymerase chain reaction (PCR) test became available in May 2017. The clinical pathway was implemented in January 2018. We used Fisher's exact tests and statistical process control charts to analyze patient- and system-level changes following pathway implementation. **Results:** Three hundred five patients were included. Postimplementation, stool PCR use increased (78%–91%), hospitalization decreased (49%–30%), and mean total charges decreased ($7715–$6797). There were increases in length of stay (226–288 minutes) and charges ($2651–$3524) for patients discharged from the ED. All changes met rules for special cause variation. There was no change in early IV fluid administration, inpatient length of stay, ED return visits, hospital readmissions, or patients with Shiga toxin-producing *Escherichia* coli (STEC), acute kidney injury (AKI) or HUS. **Conclusions:** For children presenting to the ED with bloody diarrhea, introduction of a rapid stool PCR test and clinical pathway correlated with decreased hospitalizations and overall costs without adverse clinical outcomes. *(Pediatr Qual Saf 2022;7:e517; doi: 10.1097/pq9.0000000000000517; Published online January 21, 2022.)*

INTRODUCTION

Problem Description

Children with infectious bloody diarrhea, especially those with Shiga toxin-producing *Escherichia coli* (STEC) infection, are at an increased risk for developing hemolytic

uremic syndrome (HUS).[1,2] HUS is a rare but serious condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury, with potential long-term consequences such as kidney failure.[1,2] Early identification of patients with diarrhea and STEC infection, and treatment with intravenous (IV) fluids, is needed to both reduce the severity and potentially prevent the development of HUS.[1] However, many physicians disagree on how to manage children with infectious bloody diarrhea, in part because it is relatively common, and HUS is uncommon. STEC was previously diagnosed by stool culture, which could require several days for final results.[3] This led to the hospitalization of many children for IV fluids while awaiting results to reduce morbidity among the few children who would potentially develop HUS.[1] However, the development of a rapid stool bacterial polymerase chain reaction (PCR) diagnostic test allows clinicians to detect STEC infection in real time in the emergency department (ED).[4] Stool PCR test results, in conjunction with other risk factors such as exposure history and laboratory signs of hemolysis, enable clinicians to quickly identify children at an increased risk for the development of HUS.[4]

Available Knowledge

STEC is most often transmitted via undercooked meat, contact with animals and their environment, or contact with another individual with diarrhea due to STEC infection.[5] Diagnosis of STEC infection can be made via

isolation of the organism or Shiga toxin in stool, identification of Shiga toxin-producing genes by PCR, or isolation of antibodies against STEC or Shiga toxin in the blood.[6] Stool PCR tests have excellent sensitivity and specificity as compared with stool cultures in detecting STEC and other infectious etiologies of bloody and nonbloody diarrhea.[7] Diagnosis of HUS requires evidence of hemolytic anemia (hemoglobin < 10 g/dL and presence of schistocytes), thrombocytopenia (platelets < 150,000 per microliter), and AKI (serum creatinine 1.5 times the age and gender matched standard values for the laboratory).[6] Antibiotic administration among those with STEC infection has been associated with increased risk for development of HUS, and thus antibiotics are not recommended.[8] Intravenous infusion of isotonic solution in STEC-infected patients should be administered before the development of HUS to prevent oliguria.[6] One systematic review demonstrated that patients with STEC infection who received IV fluids within the first 4 days of symptom onset developed less severe HUS; there was no evidence of harm from appropriate use of IV fluids after 4 days of symptoms; and nonrandomized trials showed that IV fluids may potentially prevent HUS altogether in patients at increased risk.[9]

Rationale

Based on chart review, we found that approximately 50% of children who presented to our institution's ED with bloody diarrhea before pathway implementation were admitted; the other half were discharged home. In response to this variability in management and availability of a new rapid stool PCR panel at our institution, a multidisciplinary committee developed a clinical pathway to standardize the management of patients at an increased risk for HUS as part of a quality improvement initiative. Clinical pathways are tools used to disseminate evidence-based care and can decrease unnecessary interventions, decrease length of stay, and halt rising healthcare costs without negatively impacting clinical outcomes.[10] The pathway includes recommendations for the initial diagnostic workup and management for patients with bloody diarrhea and HUS risk factors, including hospital admission criteria, and an inpatient phase with recommendations to assess for concerning trends or reassuring findings indicating it is safe to discharge the patient with outpatient follow-up (https://www.seattlechildrens.org/pdf/HUS-Risk-Bloody-Diarrhea-Pathway.pdf).

Specific Aims

The primary aim of this study was to compare the relative changes in hospital admission for patients who presented to the ED with bloody diarrhea before and after the implementation of the clinical pathway. Secondary outcomes included changes in early IV fluid administration, ED and hospital length of stay, hospital charges, readmission, and diagnoses of STEC, AKI, and HUS.

METHODS

Context

The setting is a freestanding, university-affiliated, academic, tertiary care children's hospital with approximately 50,000 annual ED visits and 350 inpatient beds. Medical students, residents, nurse practitioners, and physician assistants provide direct patient care under the supervision of fellows and attending physicians. Since 2002, multidisciplinary hospital teams have implemented over 70 clinical pathways for common pediatric conditions based on evidence-based literature reviews and expert consensus. Each pathway consists of a decision-making algorithm and electronic order set. Each pathway group conducts quarterly reviews to ensure the pathways are consistent with national guidelines and current high-quality medical literature. Pathways are accessible on the hospital intranet homepage, through the electronic medical record order set, and as printed copies in provider workspaces. As such, hospital staff are well acquainted with the process of pathway development and implementation. Pathways are also externally facing and can be accessed worldwide by providers not associated with the hospital.

In May 2017, a multiplex rapid stool PCR test (Film Array gastrointestinal panel) became available at the institution. Concurrently, a multidisciplinary hospital committee comprised of pediatric subspecialists in emergency medicine, hospital medicine, infectious diseases and nephrology, as well as microbiologists and informaticists, began to develop a clinical pathway and electronic order set to guide management of ED and hospitalized patients with bloody diarrhea.

Intervention

The hospital implemented the pathway on January 10, 2018. Hospital leaders announced the pathway implementation at division meetings and distributed information on the pathway via electronic newsletters at the start of the intervention. The pathway includes recommendations for patients 4 months of age or older with bloody diarrhea or nonbloody diarrhea and other HUS risk factors. HUS risk factors include physical examination findings such as petechial rash, edema, pallor, or hypertension, as well as history of eating raw or undercooked meat, farm visits or farm animal contact, and close contact with a person infected with STEC. The pathway excludes patients with prior diagnosis of HUS, malignancy, hemorrhagic shock, inflammatory bowel disease, renal disease, or intussusception. The pathway consists of 2 phases: ED and inpatient. In the ED phase, it recommends performing a visual rectal examination, obtaining a stool PCR and laboratory studies to assess risk for HUS, including a CBC with differential, electrolytes, blood urea nitrogen, creatinine, and urinalysis. The ED phase also recommends assessing hydration status and administering normal saline boluses as needed. It also specifies criteria for hospital admission (any of the following in children with STEC infection: symptoms less than or equal to 4 days, ill-appearing,

unable to tolerate oral fluids, use of antibiotics during illness, laboratories concerning for HUS, unable to complete outpatient follow-up plan), nephrology consultation, and return to the ED. In the inpatient phase, the pathway recommends close monitoring of hydration status, suggests repeating laboratory tests, defines laboratory values concerning for HUS, and provides nephrology consultation as well as hospital discharge criteria.

Study of Interventions
We assessed the impact of the intervention by performing a retrospective study of patients who presented to the ED from September 1, 2015, to July 31, 2020. We obtained data from the electronic health record system at the hospital [PowerChart (Cerner Corporation, Kansas City, Mo.), and Epic (Epic Systems Corporation, Verona, Wis.)]. We included patients aged four months to 19 years who presented to the hospital ED during the timeframe of interest with any International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code relating to bloody diarrhea (see Appendix A, **Supplemental Digital Content 1**, which described ICD-10 codes relating to bloody diarrhea, *http://links.lww.com/PQ9/A353*). We then performed a manual review of all charts to exclude patients based on pathway inclusion and exclusion criteria, only including patients with bloody diarrhea or nonbloody diarrhea and other HUS risk factors, and excluding patients with prior known HUS, malignancy, hemorrhagic shock, inflammatory bowel disease, prior renal disease, or intussusception. For analysis of length of stay and hospital charges of hospitalized patients, we excluded patients admitted to any service other than general pediatrics or nephrology, developed HUS, or whose hospital stay required intensive care or dialysis at any point. We excluded these patients to limit analysis to care recommended by the pathway.

Measures
Process, outcome, and balancing measures were analyzed. Process measures included IV fluid bolus administration in the ED, stool PCR utilization, ED and hospital length of stay, and hospital admission. Outcome measures included percentages of patients with AKI, STEC infection, and HUS diagnoses. We selected balancing measures to assess for unintended consequences of pathway recommendations, such as cost or additional healthcare utilization. Balancing measures included hospital charges adjusted for inflation to 2017 US dollars, return to the ED resulting in hospital admission within 72 hours, and hospital readmission within 7 and 30 days.

Analysis
We analyzed data 28 months before and 31 months after pathway implementation. We used statistical process control charts to analyze the process measures and the balancing measure of hospital charges over time. Centerlines and upper and lower control limits were set using mean and three-sigma values, respectively, with the preimplementation phase data and extended into the postimplementation phase to assess for special cause variation.[11] We used bimonthly subgroups on the charts to optimize subgroup sample size, number of data points, and size of control limits. We used Fisher's exact tests to compare the diagnoses and return visits of patients in the preimplementation and postimplementation periods due to relative infrequencies of diagnoses and return visits. We performed data analysis using Excel (Microsoft Corporation, Redmond, Wash.), Stata (StataCorp, College Station, Tex.) and QI-Charts Add-in for Excel (Process Improvement Products, Austin, Tex.).

Ethical Considerations
The hospital institutional review board approved this study.

RESULTS
There were 518 index patient encounters with qualifying age and diagnoses (see Appendix A, **Supplemental Digital Content 1**, which described ICD-10 codes relating to bloody diarrhea, *http://links.lww.com/PQ9/A353*). Two hundred thirteen encounters were excluded during the manual chart review per prespecified criteria. Of the included 305 encounters, 109 (36%) occurred in the preimplementation period and 196 (64%) occurred in the postimplementation period. Patients in the preimplementation and postimplementation periods had similar demographic characteristics and medical complexity per the Pediatric Medical Complexity Algorithm (Table 1).[12]

During the preimplementation period, 58% of patients with bloody diarrhea received an IV fluid bolus in the ED. There were no changes meeting special cause variation in the postimplementation period. The stool PCR became available at the hospital in May 2017, and stool PCR usage increased to 83%, with special cause variation occurring in May 2017 (Fig. 1). The proportion of patients admitted to the hospital decreased from 49% to 30%, with special cause variation occurring in November 2017 (Fig. 2). The mean length of stay for patients discharged from the ED increased from 209 to 277 minutes in the postimplementation period, with special cause variation occurring in January 2018 (Fig. 3). The mean length of stay for patients hospitalized with bloody diarrhea was 2 days and did not change after pathway implementation.

During the study period, 54 patients were diagnosed with an STEC infection (18%), 13 patients with AKI (3%), and 28 with HUS (28%). There was no significant change in percentages of patients with STEC (18/109, 16.5% versus 36/196, 18.4%; *P* = 0.76), AKI (7/109, 6.4% versus 6/196, 3.1%; *P* = 0.24), or HUS (14/109, 12.8% versus 14/196, 7.1%; *P* = 0.10) diagnoses from the preimplementation to postimplementation periods.

Among patients discharged from the ED, mean charges increased from $2,651 to $3,524 from the preimplementation to postimplementation periods, with special cause

Table 1. Demographic and Clinical Characteristics by Time Period (Prepathway vs Postpathway Implementation)

	Pre	Post	Total
	n = 109	n = 196	n = 305
Sex			
Female	56 (51%)	82 (42%)	138 (45.2%)
Male	53 (49%)	114 (58%)	167 (54.8%)
Race			
White or Caucasian	53 (49%)	80 (41%)	133 (43.6%)
Black or African American	10 (9%)	27 (14%)	37 (12.1%)
Asian	10 (9%)	22 (11%)	32 (10.5%)
American Indian, Alaska Native, Native Hawaiian and other Pacific Islander	3 (3%)	2 (1%)	5 (1.6%)
2 or more races	9 (8%)	11 (6%)	20 (6.6%)
Other	17 (16%)	42 (21%)	59 (19.3%)
None provided	7 (6%)	12 (6%)	19 (6.2%)
Ethnicity			
Hispanic	19 (17%)	41 (21%)	60 (19.7%)
Non-Hispanic	87 (80%)	150 (77%)	237 (77.7%)
Patient refused	3 (3%)	5 (3%)	8 (2.6%)
Insurance			
Private	55 (50%)	96 (49%)	151 (50%)
Public	51 (47%)	98 (50%)	149 (49%)
Self-pay or other	3 (3%)	2 (1%)	5 (2%)
PMCA category			
Complex chronic	20 (18%)	27 (15%)	47 (16.2%)
Nonchronic	69 (63%)	126 (70%)	195 (67.2%)
Noncomplex chronic	20 (18%)	28 (15%)	48 (16.6%)

variation occurring in May 2018 (Fig. 4). The mean charges for patients hospitalized with bloody diarrhea were $17,273 during the preimplementation period, and there was no change after pathway implementation. Overall, including discharged and hospitalized patients, there was a decrease in mean charges from $7,715 to $6,797 for all patients from the preimplementation to postimplementation periods, with special cause variation in July 2018 (Fig. 5). There were 191 patients discharged from the ED during the study period, and eight return ED visits within 72 hours resulting in hospital admission. There was no change in the frequency of return visits to the ED from the preimplementation to postimplementation periods (2/109, 1.8% versus 6/196, 3.1%; *P* = 0.72). Among the eight return visits, three patients were diagnosed with STEC during the postimplementation period, and no patients developed HUS or required dialysis or intensive care. Hospital readmissions were also rare, with no change in frequency of readmission within seven days (1/109, 0.9% versus 1/196, 0.5%; *P* = 1.0) or 30 days (3/109, 2.8% versus 3/196 1.5%; *P* = 0.67).
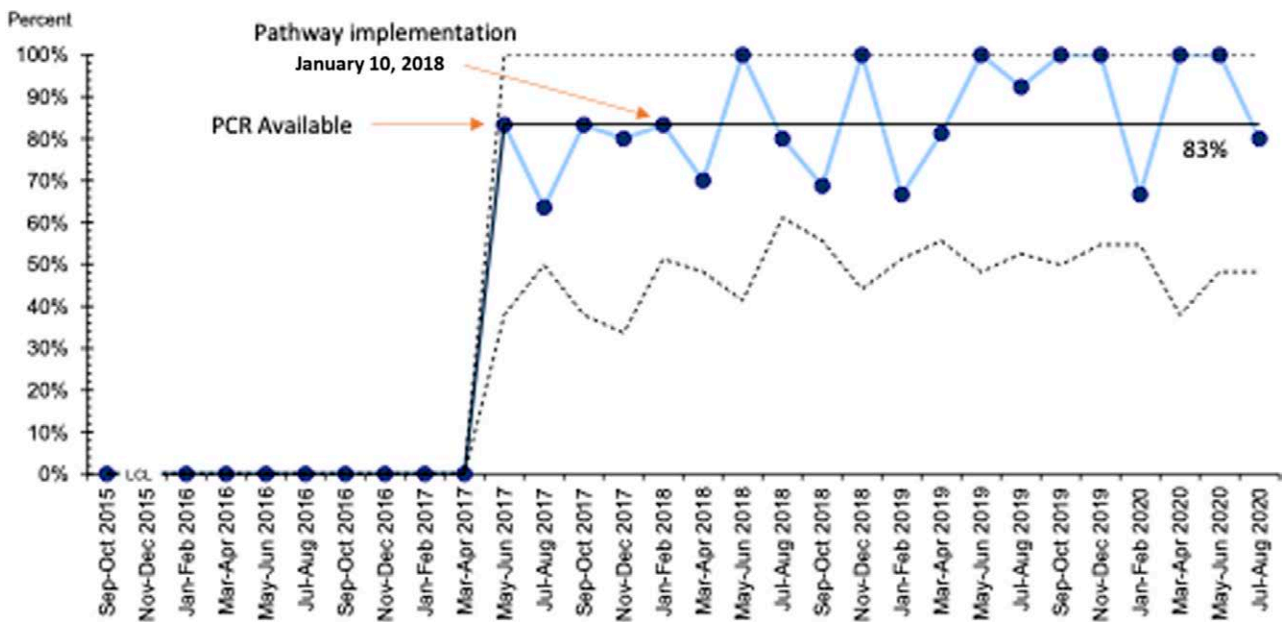

Fig. 1. Proportion of patients with bloody diarrhea who received a rapid stool PCR test over time (P chart).
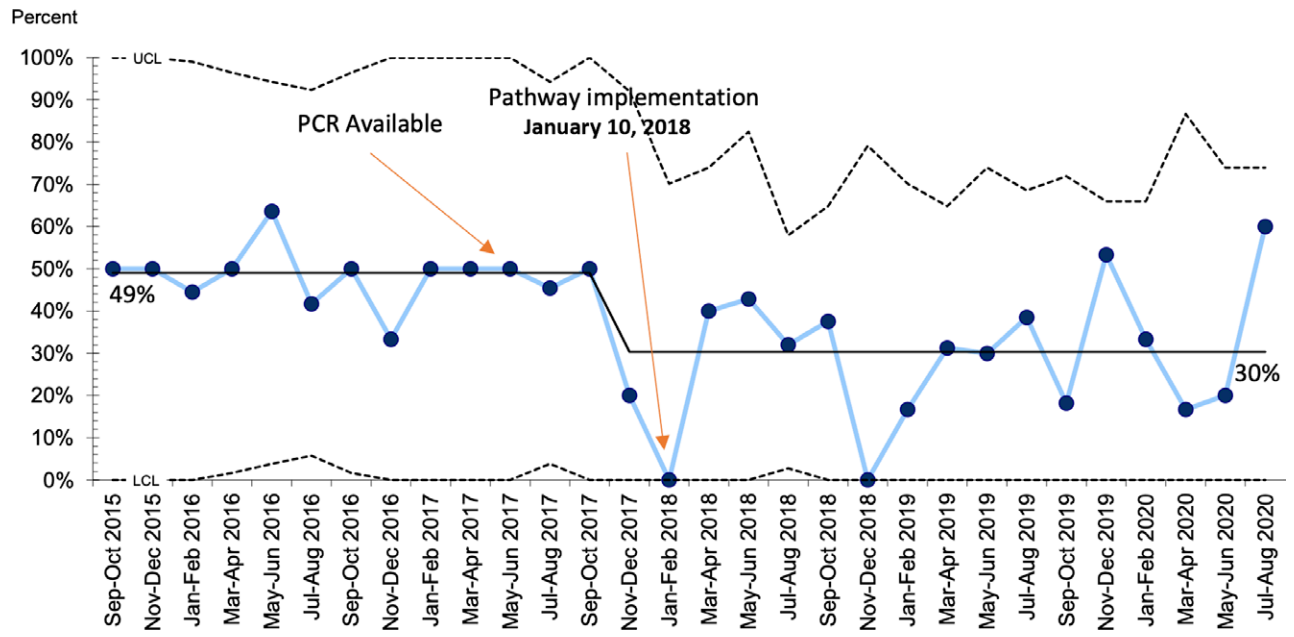
Fig. 2. Proportion of patients with bloody diarrhea admitted from the ED over time (P chart).

DISCUSSION

This is the first study on the standardization of care for children with bloody diarrhea at increased risk for HUS. Once the rapid stool PCR was available, stool PCR use increased to 83% of encounters for bloody diarrhea, and its use was sustained throughout the postimplementation period. This suggests that the availability of the new test combined with existing knowledge on indications for stool testing was sufficient to drive the behavior change, and the pathway and corresponding order set provided

continued guidance on its use. Similarly, a clinical pathway and corresponding order set for pediatric asthma exacerbations improved adherence to evidence-based care in a pediatric ED.[13]

Pathway implementation resulted in tradeoffs in key process and balancing measures. Hospitalizations decreased by almost 20% beginning 2 months before the pathway implementation date and throughout the postimplementation period. The decrease in hospitalization before pathway implementation was likely due
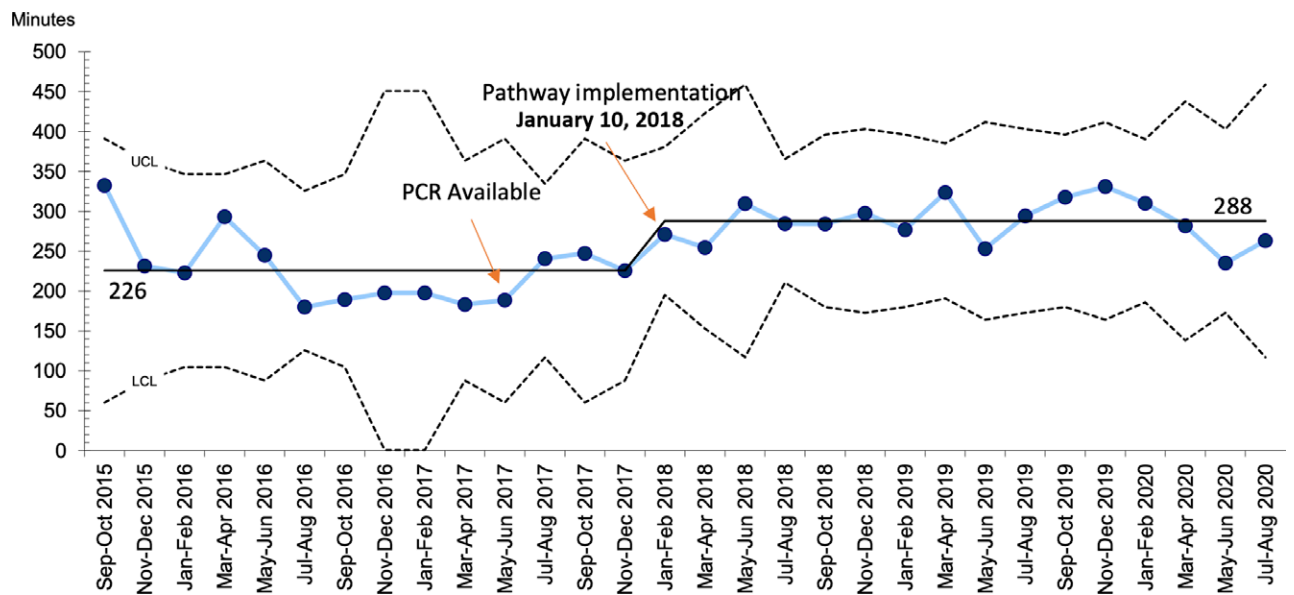
Fig. 3. Mean length of stay for patients with bloody diarrhea discharged from the ED (X-bar and S chart).
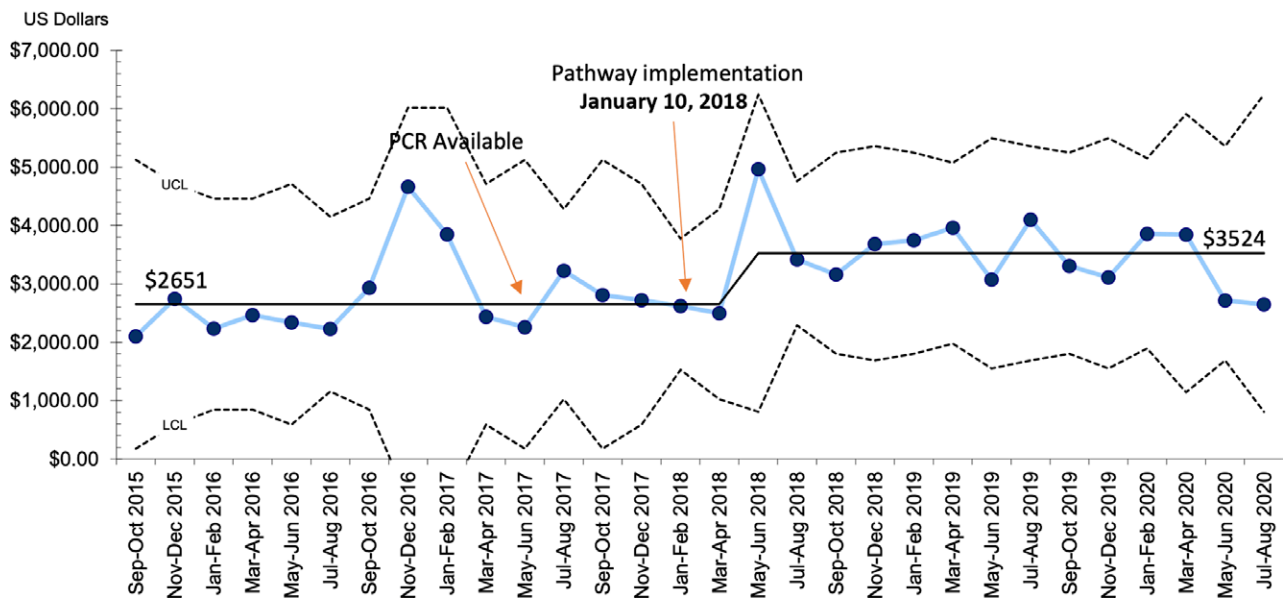
Fig. 4. Mean charges for patients with bloody diarrhea discharged from the ED (X-bar and S chart).

to the dissemination of pathway materials and department education during the months preceding the implementation date in January. It also suggests that the specific clinical and laboratory criteria in the pathway helped staff identify children at low risk for HUS and discharge them from the ED with next-day primary care follow-up, repeat outpatient laboratory testing, and strict return precautions. Likewise, pathways for intussusception and asthma led to similar decreases in hospital admission.[14,15]

There was no change in ED returns, resulting in hospital admission within 72 hours, indicating that discharge from the ED was safe for patients. Only three had an STEC infection among the eight children who were initially discharged and subsequently admitted within 72 hours. All three of these patients were discharged home, whereas stool PCR test results were pending, and all three were later contacted via phone and admitted for IV fluids. None developed AKI or HUS.

We observed a corresponding increase in length of stay and charges among patients discharged from the ED. At our institution, the rapid stool PCR and stool culture costs are approximately $600 and $411, respectively. The associated time and costs of the stool PCR recommended by the pathway likely contributed to the increased ED length of stay and charges for patients discharged from the ED. In fact, implementation of stool PCR testing correlates with increased laboratory
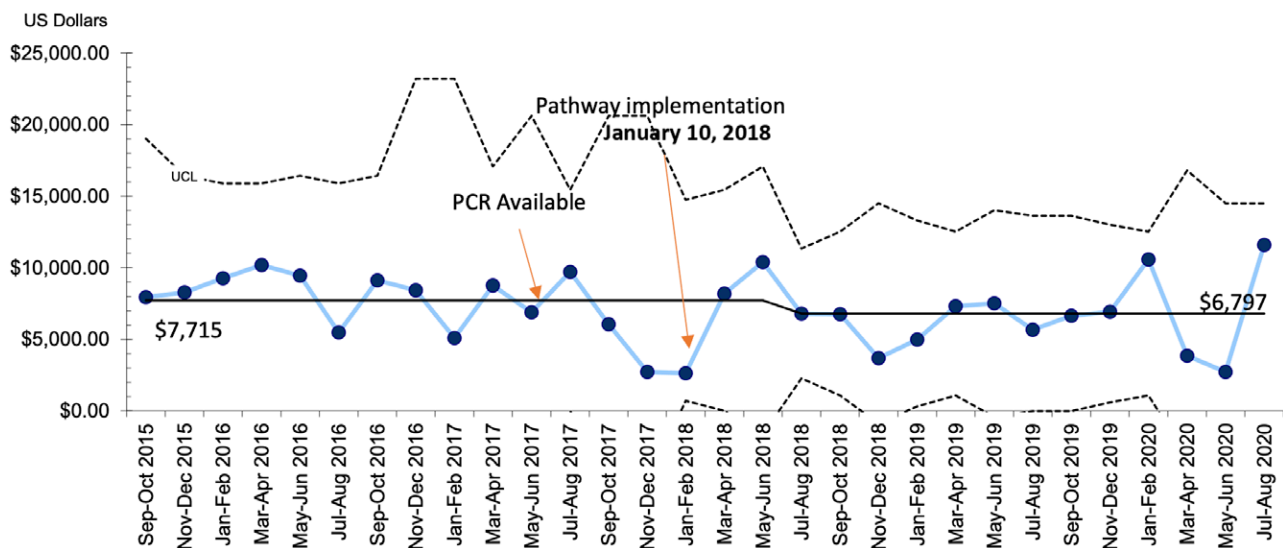

Fig. 5. Mean hospital charges for patients with bloody diarrhea over time (X-bar and S chart).

testing charges but overall decreased healthcare costs.[16] The increases in ED length of stay and ED charges should be viewed in the context of decreased overall charges and decreased hospitalizations with no change in ED return visits, hospital readmissions, or outcome measures such as AKI, STEC, or HUS diagnoses. Other institutions may consider this tradeoff as an overall net benefit in the quality, safety, and cost of care for these patients.

We did not observe a change in the proportion of patients receiving early IV fluid administration in the ED. This may be due, in part, to the wording of the pathway, which states "NS boluses as needed for poor perfusion or signs of dehydration. Most patients will require at least one NS bolus." The lack of change suggests that the pathway recommendation was consistent with existing practice patterns. Early IV fluid administration in patients infected with STEC decreases the severity of kidney injury and HUS.[9] In fact, 32 of the 39 patients infected with STEC received an IV fluid bolus in the ED during the study period. The relatively high frequency of early IV fluid administration during the preimplementation period may have also contributed to the lack of change in the frequency of AKI or HUS during the postimplementation period. Certainly, we would need a larger sample size of patients to identify changes in the frequency of AKI or HUS using this pathway.

Finally, we did not observe a decrease in charges or length of stay for hospitalized patients. Before pathway implementation, the time to obtain the final stool culture results likely determined length of stay. During the postimplementation period, however, length of stay partly depended on repeat laboratory testing 24 hours after the first set of laboratory tests, and coordinating outpatient clinic follow-up. In short, we traded one bottleneck for another. We did not observe a change in seven or 30-day hospital readmissions over the study period, which suggests that the timing of these discharges was safe for patients.

LIMITATIONS

There are several limitations to the generalizability of our results. First, our hospital has a well-established infrastructure to support the development and implementation of clinical pathways, and our staff are quite familiar with clinical pathways in general. This existing infrastructure and familiarity could affect the generalizability of our results. Second, ED returns and hospital readmissions were limited to our hospital and do not reflect return visits to other EDs, urgent care centers, hospitals, or primary care physician offices. That said, these return visits would have needed to occur at different frequencies across the study time periods to affect the study results.

CONCLUDING SUMMARY

The introduction of a rapid stool PCR diagnostic test and clinical pathway for management of patients with bloody diarrhea at an increased risk for HUS led to a significant and sustained increase in rapid stool PCR testing, and a decrease in hospitalization and hospital charges. Tradeoffs were modest increases in ED length of stay and charges for patients discharged from the ED. There was no impact on patient outcomes such as diagnoses of STEC, AKI, HUS, or ED return visits or rehospitalizations. Future studies are needed to assess the generalizability of these results.

ACKNOWLEDGMENTS

DISCLOSURE

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