RESEARCH ARTICLE

Variation in Care and Clinical Outcomes Among Infants Hospitalized With Hyperbilirubinemia

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ABSTRACT

OBJECTIVES: To assess hospital-level variation in laboratory testing and intravenous fluid (IVF) use and examine the association between these interventions and hospitalization outcomes among infants admitted with neonatal hyperbilirubinemia.

METHODS: We performed a retrospective multicenter study of infants aged 2 to 7 days hospitalized with a primary diagnosis of hyperbilirubinemia from December 1, 2016, to June 30, 2018, using the Pediatric Health Information System. Hospital-level variation in laboratory and IVF use was evaluated after adjusting for clinical and demographic factors and associated with hospital-level outcomes by using Pearson correlation.

RESULTS: We identified 4396 infants hospitalized with hyperbilirubinemia. In addition to bilirubin level, the most frequently ordered laboratories were direct antiglobulin testing (45.7%), reticulocyte count (39.7%), complete blood cell counts (43.7%), ABO blood type (33.4%), and electrolyte panels (12.9%). IVFs were given to 26.3% of children. Extensive variation in laboratory testing and IVF administration was observed across hospitals (all $P < .001$). Increased use of laboratory testing but not IVFs was associated with a longer length of stay ($P = .007$ and .162, respectively). Neither supplementary laboratory use nor IVF use was associated with either readmissions or emergency department revisits.

CONCLUSIONS: Substantial variation exists among hospitals in the management of infants with hyperbilirubinemia. With our results, we suggest that additional testing outside of bilirubin measurement may unnecessarily increase resource use for infants hospitalized with hyperbilirubinemia.

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Hyperbilirubinemia represents 1 of the most prevalent diagnoses for hospitalized newborns,[1] with admissions typically reserved for infants at a high risk for development of acute bilirubin encephalopathy and subsequent kernicterus. Although the overall incidence for kernicterus is low, it is a highly preventable neurotoxic brain injury that results in lifelong neurologic compromise. To prevent kernicterus, ~35 000 infants per year are hospitalized after their birth hospitalization for treatment of hyperbilirubinemia. These hospitalizations account for an estimated $361 million in charges per annum.[2]

Because of the high prevalence of hyperbilirubinemia and largely preventable complication of kernicterus, the American Academy of Pediatrics (AAP) created guidelines for the management of neonatal hyperbilirubinemia. These guidelines, which were last updated in 2004, are focused on reducing the complications as well as unnecessary treatments and costs.[3] Although recommendations regarding the utility of diagnostic laboratory testing or intravenous fluid (IVF) use among infants admitted for hyperbilirubinemia are addressed in these guidelines, they are based on low-quality evidence, and the extent to which these guidelines are followed is unclear.[3]

The absence of high-quality data within evidence-based guidelines can create a climate for significant variation in clinical care.[4–6] Previous studies have revealed that among certain disease processes (eg, pneumonia, bronchiolitis, and orbital cellulitis) high variation in resource use is associated with increased hospital length of stay (LOS) and hospital costs, without significant benefit in clinical outcomes.[7–9] However, the impact of variability in diagnostic laboratory testing and IVF use on outcomes for infants hospitalized with hyperbilirubinemia is unknown.

Knowledge of variation and outcomes may help to inform an evidence-based approach to medical decision-making for neonates with hyperbilirubinemia and high-value approach to care. Therefore, we sought to (1) describe variation in laboratory testing and IVF use among infants admitted with hyperbilirubinemia and (2) examine the association of laboratory testing and IVF use with LOS, 3-day emergency department (ED) revisits, and 3-day readmissions. We hypothesized that there would be significant hospital-level variation in both laboratory testing and IVF use and that laboratory testing and IVF use would be associated with prolonged hospital LOS.

METHODS

Study Design and Data Source

We conducted a retrospective multicenter cohort study using the Pediatric Health Information System (PHIS) database. The PHIS database includes deidentified daily billing and administrative data from 49 freestanding pediatric hospitals affiliated with the Children's Hospital Association (Lenexa, KS). Data are deidentified at the time of entry into the database and are subjected to rigorous quality checks before inclusion. Patients can be tracked across encounters by using a consistently encrypted medical record number. This study was deemed nonhuman subjects research by the institutional review board at our institution.

Study Population

We included infants aged 2-to-7 days with an observation or inpatient hospitalization to a PHIS-reporting hospital and primary diagnosis of hyperbilirubinemia between December 1, 2016, and June 30, 2018. The following *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) codes were used to identify infants with hyperbilirubinemia: Rh isoimmunization of newborn (P55.0); ABO isoimmunization of newborn (P55.1); other hemolytic disease of newborn (P55.8); hemolytic disease of newborn, unspecified (P55.9); neonatal jaundice due to other specified excessive hemolysis (P58.8); neonatal jaundice from other specified causes (P59.8); neonatal jaundice from breast milk inhibitor (P59.3); neonatal jaundice, unspecified (P59.9); and disorder of bilirubin metabolism, unspecified (E80.7). In general, we excluded infants that are not included in the AAP guidelines for hyperbilirubinemia management or who are at risk for complicated clinical courses that may warrant testing or treatment not related to hyperbilirubinemia. We excluded all infants with a hospital LOS >48 hours because the vast majority of hospitalizations are <30 hours and infants with a substantially longer LOS likely represent outliers with complicated or unique clinical courses. Additionally, we excluded infants with a gestational age <37 weeks, a birth weight <2500 g, direct admission to an ICU, a discharge diagnosis corresponding to fever and/or temperature instability, shock, sepsis and/or bacteremia, a urinary tract infection and a history of surgical procedure, major congenital anomaly, or complex chronic condition.[10] Birth hospitalizations and infants <2 days of age were excluded because we wished to study infants admitted specifically for management of hyperbilirubinemia. Nonstandard discharges (such as those infants transferred to other facilities) and infants transferred into PHIS participating sites from an outside facility were excluded because of risk of incomplete data. We also excluded infants admitted to hospitals with a mean annual volume of <10 admissions for hyperbilirubinemia (Fig 1) because of risk of bias from small sample sizes.

Resource Use: Laboratory Testing and IVF Use

We used billing codes to identify laboratory testing and receipt of IVF within the first 2 days of hospitalization. We defined supplementary laboratories as tests drawn in addition to bilirubin levels, including a complete blood cell (CBC) count (with or without differential), peripheral smear, electrolyte panel, reticulocyte count, ABO

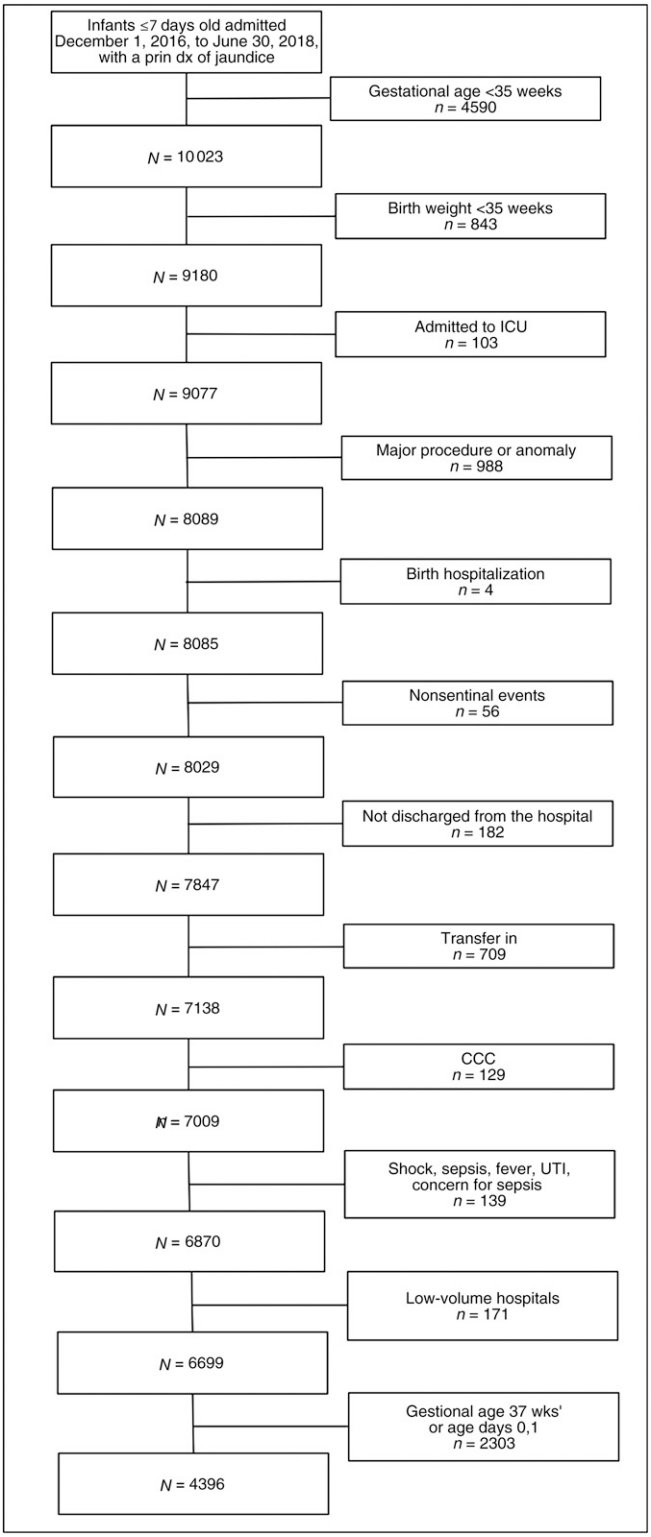

FIGURE 1 Consort diagram. CCC, complex chronic condition; prin dx, principle diagnosis; UTI, urinary tract infection.

blood type, type and screen, glucose-6-phosphate dehydrogenase activity, urinalysis, and direct antiglobulin testing (DAT). We examined hospital-level rates of use for IVFs and the top 5 most frequently obtained supplementary laboratories.

Clinical Outcomes

We included hospital LOS in hours, all-cause 3-day ED revisit and 3-day hospital readmission rates, transfer to ICU level of care, incidence of blood transfusion, diagnosis of hearing loss, and diagnosis of kernicterus as clinical outcomes. We chose to examine returns within 3 days given the acute nature of hyperbilirubinemia and risk of progression to bilirubin encephalopathy if treatment is not initiated in a timely manner. We did not specifically examine the rate of exchange transfusion in our population because billing data specific to exchange transfusion are not well detailed in the PHIS database. The incidence of blood transfusion was used as a surrogate marker for receipt of exchange transfusion. We assessed incidence of hearing loss to evaluate sequelae of extreme hyperbilirubinemia that does not progress to kernicterus.

Clinical Characteristics

The following patient-level characteristics were identified: age in days, sex, race and/or ethnicity, primary payer type, presence of a hemolytic disease process, and illness severity. Infants were identified as having a hemolytic disease process if they had an ICD-10-CM diagnosis code corresponding to any of the following: Rh isoimmunization of newborn, ABO isoimmunization of newborn, other hemolytic disease of newborn, or hemolytic disease of newborn not otherwise specified, neonatal jaundice due to other specified excessive hemolysis. Illness severity was measured by using the hospitalization resource intensity scores for kids algorithm.[11]

Statistical Analysis and Development of Laboratory Use Score

We summarized continuous variables using medians and interquartile ranges (IQRs) and categorical variables by frequencies and percentages. We used generalized linear mixed effects models to calculate risk-adjusted hospital-level laboratory testing and IVF rates after adjusting for sex, race and/or ethnicity, payer, illness severity,

and hemolytic disease. To assess hospital-level variation in risk-adjusted laboratory testing and IVF use, we used a covariance test to assess the significance of the hospital random effect. We then determined each hospital's diagnostic laboratory testing performance on the basis of their risk-adjusted laboratory use score. To determine laboratory use scores, we first ranked hospital-level laboratory and fluid use into quintiles on the basis of ordering frequency. Each laboratory and fluid quintile were then assigned a use score from 0 to 4, with a score of 0 corresponding to least frequently ordered laboratories or fluids and score of 4 corresponding to most frequently ordered laboratories or fluids. Total hospital laboratory use scores were obtained by summing the individual laboratory scores for each hospital. For each hospital, we summed the 5 individual laboratory quintiles to create a total laboratory use score. This score could range from 0 (lowest quintile on all tests) to 20 (highest quintile on all tests). We correlated both the risk-adjusted total laboratory use score and risk-adjusted IVF rate with clinical outcomes by using Pearson correlation coefficient. All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC), and P values $<.05$ were considered statistically significant.

RESULTS

We identified 4396 children hospitalized with hyperbilirubinemia from 36 PHIS-reporting children's hospitals during the study period (Fig 1). Patient- and hospital-level characteristics as well as unadjusted patient outcomes are portrayed in Table 1. The median age of infants was 4 days (IQR 3–5), and 57% were male. One-half of infants (50.2%) had private insurance, and 40% were non-Hispanic white race and ethnicity. Approximately 8% of infants had a diagnosis code corresponding to a hemolytic disease process. Overall, the median LOS was 25 hours (IQR 20–41), the 3-day ED revisit rate was 1.9%, and the 3-day hospital readmission rate was 1.4%. Among infants with a 3-day ED revisit or readmission, 77% and 74% had a primary diagnosis corresponding to hyperbilirubinemia at these repeat encounters, respectively.

TABLE 1 Demographic and Clinical Characteristics of the Cohort

Characteristics	*n* (%) or median (IQR)
Discharges, *N*	4396
Age, d, median (IQR)	4 (3–5)
Age, d, *n* (%)	
2	190 (4.3)
3	1180 (26.8)
4	1305 (29.7)
5	918 (20.9)
6	531 (12.1)
7	272 (6.2)
Sex, *n* (%)	
Male	2505 (57)
Female	1890 (43)
Race and/or ethnicity, *n* (%)	
Non-Hispanic white	1753 (39.9)
Non-Hispanic Black	389 (8.8)
Hispanic	1243 (28.3)
Asian	539 (12.3)
Other	472 (10.7)
Hospital region, *n* (%)	
Midwest	1173 (26.7)
Northeast	294 (6.7)
South	1201 (27.3)
West	1728 (39.3)
Payer, *n* (%)	
Government	1971 (44.8)
Private	2219 (50.5)
Other	206 (4.7)
Hemolytic disease, *n* (%)	
No	4050 (92.1)
Yes	346 (7.9)

Among the cohort, 3 infants were transferred to an ICU, and 6 infants received red blood cell transfusions. No infants had a diagnosis of hearing loss nor a diagnosis of kernicterus.

Laboratory Testing and IVF Use

After adjusting for patient- and hospital-level characteristics, the 5 most commonly used supplementary laboratory studies among hospitalized neonates with hyperbilirubinemia were DAT (45.7%), CBC count (43.7%), reticulocyte count (39.7%), ABO blood typing (33.4%), and electrolyte panel (12.9%). IVFs were used in 26.3% of infants. Figure 2 reveals the distribution of laboratory use and fluid use across hospitals. We found significant variation in unadjusted rates of both laboratory testing and IVF use (Fig 2). DAT and ABO blood typing were the 2 most highly variable laboratories, with IQRs between 25.2% and 59.0% and 19.5% and 46.9%, respectively. Both laboratory tests had rates of use that ranged between 0% and 96.2%. Reticulocyte count testing was the test performed with the least variation with regards to IQR but still had a wide range of obtainment, from 7.9% to 91%.

Interhospital Variation in Laboratory Use and IVF Use

We assigned hospitals quintile scores on the basis of risk-adjusted use of an individual

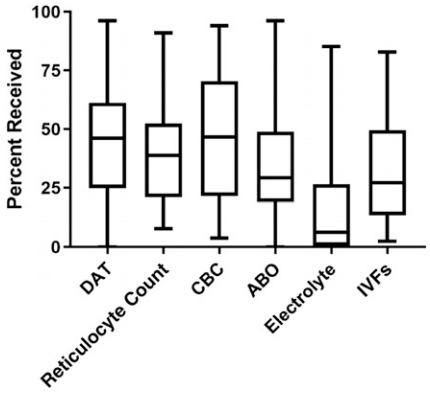

FIGURE 2 Unadjusted variation in laboratory and IVF use across the hospital.

laboratory test or IVF. Figure 3 reveals differences in the risk-adjusted use score quintile for each specific laboratory test and IVF. Hospitals are ordered from top to bottom according to the highest to lowest total risk-adjusted use score. Although no hospital performed at the lowest or highest quintile across each outcome, in general, hospitals tended to follow similar patterns of laboratory use and IVF use.

Association of Total Use Score and Clinical Outcomes

After adjusting for important demographic and clinical factors, we found higher hospital-level total laboratory use scores were associated with a longer hospital LOS ($P = .007$). There were no associations with laboratory use and either readmission rates or ED revisits. Higher hospital-level rates of IVF were not associated with LOS and had no significant associations with risk of either an ED revisit or readmission for any condition (Supplemental Fig 4).

DISCUSSION

In this multicenter retrospective cohort analysis of infants hospitalized with a primary diagnosis of hyperbilirubinemia, we illustrate considerable hospital-level variation in the inpatient management of hyperbilirubinemia. We observed that increases in laboratory use, but not IVF use, were associated with a longer LOS. Neither laboratory nor IVF use were associated with an ED revisit or hospital readmission rates. Although finding variation in the management of a common illness is not surprising, demonstrating the etiology and clinical impact of variation is 1 of the first steps toward improving diagnostic stewardship and practice standardization for infants hospitalized with hyperbilirubinemia.

Our observations of substantial hospital-level variation in laboratory testing may be a consequence of limited evidence regarding the role of laboratory evaluation in the management of patients with hyperbilirubinemia. In the latest guideline from the AAP, it is recommended that infants receiving phototherapy undergo evaluation with DAT, ABO blood typing, and CBC count with peripheral smear. These recommendations, however, are based on the lowest quality of evidence, consisting of expert opinion, case reports, and clinical reasoning.[3] Wide hospital-level variation in obtainment of these laboratories as well as the common obtainment of nonrecommended laboratories, such as electrolyte testing, draws into question the effectiveness of these guidelines. Given the lack of strong evidence-based recommendations for laboratory testing among infants admitted with hyperbilirubinemia, local expert opinions may drive differing hospital cultures of laboratory use. Additionally, a lack of integration of health-system technology likely contributes to our observations (eg, lack of availability of birth records and laboratory data on admission). Because insufficient investigation of the underlying etiology can contribute to extreme hyperbilirubinemia, in future evaluations, researchers should seek to define which infants may be safely managed with limited supplementary laboratories and evaluate the utility of novel diagnostic tests, such as genetic sequencing, in the management of these infants.[12–14]

A lack of clear evidence regarding the utility of supplemental fluids may contribute to variation in IVF use. Although the AAP states the use of routine IVFs among infants who appear well hydrated is unnecessary, in the most recent policy statement, the AAP avoids making a firm recommendation for or against routine IVF use.[2] Although several studies have revealed that IVF supplementation in term neonates decreases the duration of phototherapy and rate of exchange transfusion,[15,16] others have found no differences in bilirubin levels, the duration of phototherapy, or the rate of exchange transfusion.[17,18] In a 2017 Cochrane review of IVF use among otherwise healthy infants receiving phototherapy, the authors describe that IVF may reduce the bilirubin level at certain time points but the use of IVF was not associated with a reduction in rates of bilirubin encephalopathy. In addition, no associations between IVF use and duration of phototherapy or exchange transfusion could be determined.[19] Consequently, differences in interpretation of available evidence by clinicians and differences in provider experiences and biases may drive variation in IVF use among hospitals and highlight the need to identify which infants would benefit most from supplemental fluid administration.

Laboratory use is associated with longer LOS for other pediatric conditions.[3–5,20] Consistent with these previous reports and as we hypothesized, admission for hyperbilirubinemia to hospitals with higher testing use scores was associated with longer LOS. IVF use was not associated with LOS, and neither laboratory nor fluid use was associated with rates of readmission or revisit. Although IVF use is theorized to potentially decrease the duration of phototherapy, and thus one might argue decrease LOS, in recent research in other pediatric conditions, researchers describe IVF use to be independently associated with prolonged LOS.[21] In our cohort of term, otherwise well infants, the harms and risk of routine IVF use (pain associated with procedure, IV infiltrates, and potential electrolyte derangements) may outweigh any benefits.

Our study has several limitations. First, because, in this study, we relied on ICD-10-CM and billing codes, differences in hospital coding practices may influence our results. We attempted to mitigate differences in coding and billing practices by excluding hospitals with known poor data quality and infants seen at hospitals with a mean of <10 cases per year. Second, although we controlled for illness severity as a measure

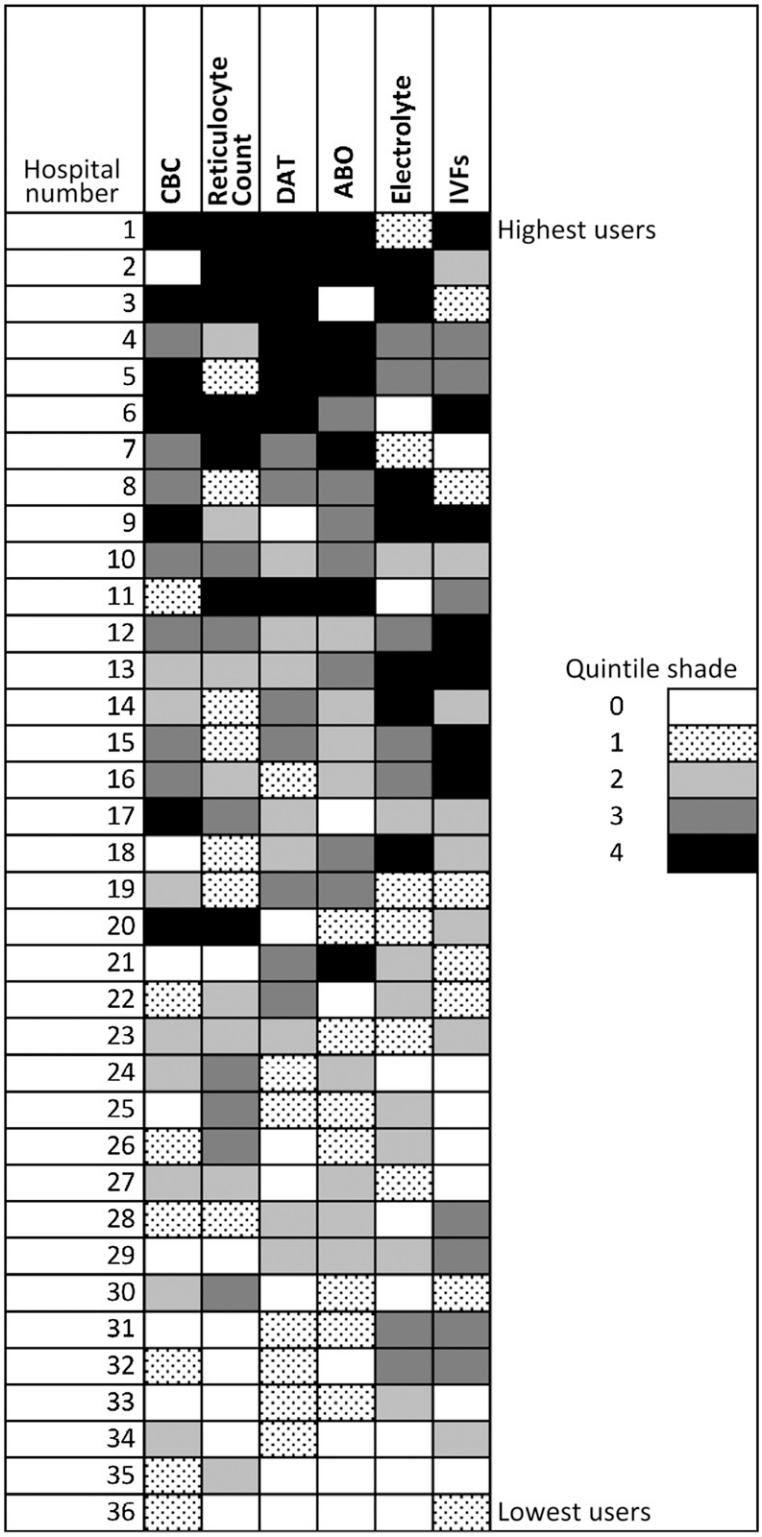

FIGURE 3 Heat map of interhospital variation in laboratory and fluid use.

of hospital resource use (hospitalization resource intensity scores for kids algorithm), using a billing database such as PHIS limits our ability to control for severity of illness. Some patient-level characteristics not attainable within the PHIS database may influence clinical decision-making, including knowledge of breastfeeding history, a family history of hemolytic processes, and physical examination findings. By looking at hospital-level variation in testing, however, we hoped to decrease the influence of these more granular clinical characteristics; however, we acknowledge some associations between laboratory and/or fluid use and clinical outcomes may be confounded by illness severity. Finally, we were unable to account for any laboratory testing performed before hospitalization that might influence in-hospital testing.

CONCLUSIONS

High degrees of variability exist between children's hospitals in the use of laboratory testing and IVFs among infants hospitalized with hyperbilirubinemia. Greater laboratory testing use was correlated with longer LOS without reductions in subsequent ED revisits or hospital readmissions. Fluid use was associated with neither LOS nor return visits. Further study into sources of practice variation is needed to inform standardization efforts.

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