Emergency Laboratory Evaluations for Patients With Inborn Errors of Metabolism

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Background: Children with inborn errors of metabolism (IEM) are at risk for metabolic crises triggered by acute illnesses. Crises are identified through laboratory evaluations.

Objectives: Our objective was to determine national adherence to minimum laboratory evaluations for patients with IEM in emergency departments (EDs), as well as factors associated with laboratory evaluation adherence.

Methods: Using the Pediatric Health Information System, we identified visits to 48 EDs from 2012 to 2017 by children with IEM. We analyzed visits for catabolic conditions (dehydration, gastroenteritis, or vomiting) and determined variation in minimum laboratory evaluation adherence. Multivariable models were created to determine predictors of adherence.

Results: Among the visits by children with disorders of the urea cycle, organic acid metabolism, and fatty acid oxidation, 1457 (76.3%) of 1909 adhered to the minimum laboratory evaluation. Median ED-level adherence was 78.2% (interquartile range, 67.4–92.5). Factors associated with adherence were disorder [fatty acid oxidation vs urea cycle disorder; adjusted odds ratio (aOR), 9.35; 95% confidence interval (CI), 4.07–21.47], annual ED volume of patients with IEM (quartile 4 vs 1; aOR, 3.58; 95% CI, 1.51–8.49), and presence of a biochemical genetics fellowship (aOR, 0.29; 95% CI, 0.14–0.62).

Conclusions: Patients with IEM frequently did not receive minimum laboratory evaluations for catabolic conditions. Measures to improve laboratory use in children with IEM should be undertaken.

Key Words: genetics, metabolic disease, laboratory evaluations, inborn errors of metabolism

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Inborn errors of metabolism (IEM) are genetic disorders characterized by defects in cellular energy production or accumulation of toxic metabolites. Inborn errors of metabolism occur in 1 in 800 to 2500 births, and many diagnoses are identified by state newborn screening programs.[1–4] Some IEM place affected patients at risk for acute metabolic crises, which can be triggered by intercurrent stressors, such as insufficient nutritional intake, vomiting, or gastroenteritis, or overconsumption of offending dietary products such as protein.[5] Laboratory evaluation is needed to identify the presence and severity of a metabolic crisis. If high-quality emergency care of metabolic crises is delayed, children face increased risks for complications including hypoglycemia, metabolic acidosis, and hyperammonemia, which in turn may lead to poor outcomes such as stroke, cerebral edema, seizure, and death.[6] Although standardized clinical management plans for some IEM have been proposed, no prior study has assessed how often pediatric emergency departments (EDs) perform these evaluations.[7–15]

The objectives of this study were to (1) describe the characteristics and hospital use of children with IEM presenting to pediatric EDs; (2) define a minimum laboratory evaluation recommended for children with catabolic conditions who have a disorder of the urea cycle, organic acid metabolism, or fatty acid oxidation; and (3) determine the between-ED variability and predictors of adherence to these minimum laboratory evaluations.

METHODS

Data Source and Patient Population

We used the Pediatric Health Information System (PHIS) database (Children's Hospital Association, Lenexa, Kansas). The PHIS administrative database contains clinical and billing data from 48 freestanding, tertiary care children's hospitals. Data quality is ensured through a joint effort between the Children's Hospital Association and participating hospitals. The Boston Children's Hospital Institutional Review Board deemed this study exempt from review.

We included patients younger than 18 years who presented to a pediatric ED between July 1, 2012, and June 30, 2017, with an *International Classification of Diseases, 9th* or *10th Revision* (*ICD-9* or *ICD-10*) diagnosis code of an IEM (Table A.1, Supplemental Digital Content 1, http://links.lww.com/PEC/A470).[16] For a given patient, if the same IEM diagnosis appeared in more than 50% of the ED visits that included any IEM diagnosis, we assigned that majority diagnosis to the patient. We excluded patients with an ambiguous underlying IEM, defined as no single IEM diagnosis occurring in more than 50% of the ED visits with any IEM diagnosis for that patient.

Description of Patients With IEM

We first described all visits to pediatric EDs made by patients with IEM. For each IEM, we reported the following variables: number of ED visits, unique patients, visits per patient, hospitalization rates [including reporting intensive care unit (ICU) and non-ICU hospitalization rates], lengths of hospital stay in integer days, and in-hospital deaths. We also summarized the demographic characteristics of each visit, including the age, season, and year. We expressed these characteristics as proportions.

Use of Minimum Laboratory Evaluations

Using a modified Delphi approach (Figure A.1, Supplemental Digital Content 2, http://links.lww.com/PEC/A471), 3 physicians specializing in the care of children with IEMs generated a

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consensus minimum laboratory evaluation necessary for the identification of metabolic crises in 3 categories of IEM: disorders of the urea cycle, organic acid metabolism, and fatty acid oxidation, selected because they are the 3 most common IEM managed in pediatric EDs and have the potential to lead to metabolic crises.[17]

Each of the 3 Delphi participants was provided with a list of the diagnoses and diagnosis codes for each IEM.[16] For each of the 3 IEM categories, each participant generated a list of the laboratory tests required for the minimum laboratory evaluation of all disorders within the category. Although broader evaluation than the minimum set is often necessary, the goal was to define a common set of laboratory tests required for all diagnoses within an IEM diagnosis category. Thus, laboratory tests were not included if they applied only to one or a subset of disorders within an IEM diagnosis code category.

In the second round, we collected more information about the discrepancies in laboratory studies suggested by participants. Individuals who recommended a test that was not suggested by the other 2 participants were asked for their rationale. For laboratory tests recommended by 2 of the 3 participants, the additional participant was asked to consider if the inclusion of this laboratory test was necessary. After this round, tests that were recommended by all participants were included in the final iteration of the minimum laboratory criteria (Table 1).

National Variation and Predictors of Adherence to Minimum Laboratory Evaluations

Using the PHIS database, we analyzed visits of patients with IEM and a concurrent *ICD-9* or *ICD-10* code for a catabolic condition (Table A.3, Supplemental Digital Content 3, http://links.lww.com/PEC/A472), as these patients are at high risk of acute metabolic crisis.[7,18] We excluded patients transferred from a referring facility and those with unknown transfer status, given that they may have undergone laboratory evaluation before arrival. Tests were considered obtained if they were obtained within 1 day of arrival. We subsequently determined the proportion of visits per ED in which the minimum laboratory evaluation occurred. Finally, we calculated the proportion of discharged patients with and without the minimum laboratory evaluation who made a return visit to the ED within 3 days.

We designed a prediction model to identify patient and ED characteristics associated with the completion of minimum laboratory tests, analyzing possible predictors that we theorized might influence obtaining minimum laboratory tests. These predictors included 6 patient characteristics: IEM type, age (0–2.9 years, 3–10.9 years, and 11–18 years), sex, race, ethnicity, and insurance status. The additional 3 predictors analyzed were characteristics of the ED and hospital in which the patients were treated, including quartile of annual absolute volume of all patients with IEM seen in the ED (quartile 1, 2.8–22.2 visits per year; quartile 2, 23.2–29.2; quartile 3, 29.6–59.0; and quartile 4, 60.0–121.4); presence of one or more hospital faculty members with American Board of Medical Genetics and Genomics certification in clinical or medical biochemical genetics (as of April 2018); and the presence of an Accreditation Council for Graduate Medical Education–accredited fellowship in medical biochemical genetics. We generated the model using logistic regression with SEs adjusted for within-ED clustering using robust sandwich estimators.

For all quantitative analyses, we defined statistical significance as a 2-sided $P < 0.05$. For comparisons, we provided odds ratios (OR) or risk differences as appropriate, with 95% confidence intervals (CIs). For statistical computing, we used R 3.4.4 (R Foundation, Vienna, Austria) and Stata 14 (Stata Corp, College Station, Texas).

RESULTS

We identified 9439 pediatric ED visits made by patients with IEM (Table A.2, Supplemental Digital Content 4, http://links.lww.

TABLE 1. Diagnosis Codes for Inborn Error of Metabolism Diagnoses and Minimum Laboratory Evaluations for Emergency Department Management

Diagnosis Category	*ICD-9* Codes	*ICD-10* Codes	IEM	Recommended Laboratory Tests
Organic acid disorders	270.3	E71.0	Maple syrup urine disease	• Chemistry (includes serum bicarbonate) • Urine ketones or serum β-hydroxybutyrate level
		E71.110	Isovaleric acidemia	
		E71.120	Methylmalonic acidemia	
		E71.19	Other disorders of branched-chain amino acid metabolism	
		E71.2	Disorder of branched-chain amino acid metabolism, unspecified	
Urea cycle disorders	270.6	E72.20	Disorder of urea cycle metabolism, unspecified	• Chemistry (includes serum bicarbonate) • Ammonia
		E72.21	Arginemia	
		E72.22	Argininosuccinic aciduria	
		E72.23	Citrullinemia	
		E72.29	Other disorders of urea cycle metabolism	
		E72.4	Disorders of ornithine metabolism	
Disorders of fatty acid oxidation	277.85	E71.310	Long-chain/very-long-chain acyl CoA dehydrogenase	• Chemistry (includes serum glucose) or glucose
		E71.311	Medium chain acyl CoA dehydrogenase deficiency	
		E71.312	Short chain acyl CoA dehydrogenase deficiency	
		E71.313	Glutaric aciduria type II	
		E71.314	Muscle carnitine palmitoyltransferase deficiency	
		E71.318	Other disorders of fatty acid oxidation	

CoA indicates coenzyme A.

com/PEC/A473). The largest number of visits were by patients with urea cycle disorders (n = 2436, 25.8%). The median age of patients with IEM at the time of visit was 3.8 years [interquartile range (IQR), 1.5–9.0]. Hospitalization occurred following 5259 (55.7%) ED visits. The highest rates of hospitalization occurred at visits for patients with disorders of organic acid metabolism (1147/1750, 65.5%), adrenoleukodystrophy and peroxisomal disorders (n = 193/323, 59.8%), and urea cycle disorders (n = 1444/2436, 59.3%). Among patients who were hospitalized, the highest rates of ICU admission occurred at visits for patients with disorders of purine and pyrimidine metabolism (n = 11/17, 64.7%) and mucopolysaccharidoses (n = 45/133, 33.8%). For all hospitalizations, the median length of stay was 2 days (IQR, 1–4). A total of 22 (0.2%) of 9439 in-hospital deaths occurred.

Defining the Minimum Laboratory Evaluation

Delphi participants defined the minimum laboratory criteria for organic acid disorders as a serum bicarbonate measurement plus either urine ketones or a serum β-hydroxybutyrate. For urea cycle disorders, the minimum laboratory evaluation included serum bicarbonate and ammonia levels. For fatty oxidation disorders, the minimum laboratory evaluation was defined as either a serum glucose or a whole-blood glucose measurement.

National Variation in Performance of Minimum Laboratory Evaluation

We analyzed 1909 ED visits of children with disorders of the urea cycle, organic acid metabolism, and fatty acid oxidation with a catabolic condition. Patients with these disorders visited 42 of the 48 EDs included in the PHIS. Overall, 1457 (76.3%) visits included the minimum laboratory evaluation. Across 44 pediatric EDs, the median hospital-level minimum laboratory evaluation percentage was 78.2% (IQR, 67.4%–92.5%; Fig. 1).

Overall, in 191 (31.4%) of 609 visits by patients with urea cycle disorders, the minimum laboratory evaluation was not completed, with 87 (14.2%) of 609 lacking a chemistry and 139 (22.8%) of 609 lacking an ammonia level. At 223 (32.6%) of 684 visits for patients with organic acid disorders, patients did not receive minimum laboratory evaluations, including 79 (11.5%) of 684 who did not have a chemistry and 183 (26.8%) of 684 who did not have urine ketones or a serum β-hydroxybutyrate level. Patients with fatty acid oxidation disorders did not receive the minimum laboratory evaluation, defined as only a glucose level, at 38 (6.2%) of 616 visits. Specific laboratory tests obtained are shown in Table 2.

Among all patients with disorders of the urea cycle, organic acid metabolism, and fatty acid oxidation with catabolic conditions, hospitalization occurred following 1482 (66.0%) visits, with 189 (8.4%) to an ICU. Among the 468 patients who were discharged from the ED, 152 (32.5%) did not receive minimum laboratory evaluations. Rates of return visits to the same ED within 3 days did not significantly differ between patients who did not receive minimum laboratory evaluations and patients who did (18.4% vs 13.9%; risk difference, −4.5%; 95% CI, −11.7% to 2.8%).

Predicting Adherence to Minimum Laboratory Evaluation

Predictors of obtaining the minimum laboratory evaluation are shown in Table 3 and included the IEM diagnosis [adjusted

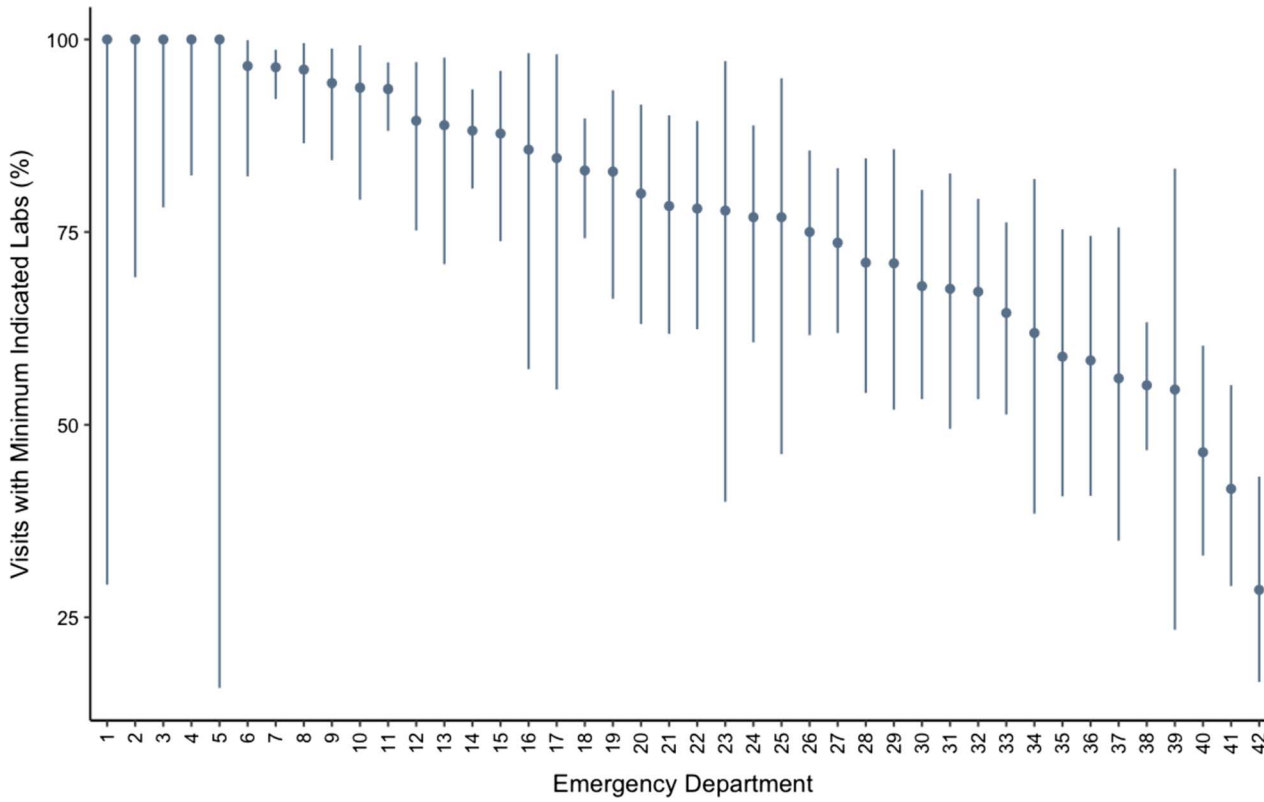

FIGURE 1. National interhospital variability in the use of minimum laboratory evaluations for patients with urea cycle disorders, organic acid disorders, and fatty oxidation disorders (N = 1909). Bars indicate 95% CIs.

TABLE 2. Specific Laboratory Tests Obtained in Each Condition

Condition	Laboratory Test	n (%)
Fatty acid oxidation disorder	Entire minimum laboratory evaluation	578 (93.8)
	Glucose	578 (93.8)
	Point of care glucose	405 (65.7)
	Serum glucose	4 (0.6)
	Basic metabolic panel	216 (35.1)
	Complete metabolic panel	353 (57.3)
Organic acid disorders	Entire minimum laboratory evaluation	461 (65.7)
	Bicarbonate	605 (88.5)
	Serum bicarbonate	65 (9.5)
	Basic metabolic panel	372 (54.4)
	Complete metabolic panel	332 (48.5)
	Ketone	501 (73.2)
	Serum ketone	64 (9.4)
	Urine ketone	180 (26.3)
	Urine chemistry	132 (19.3)
	Urinalysis	312 (45.6)
Urea cycle disorders	Entire minimum laboratory evaluation	418 (68.6)
	Bicarbonate	522 (85.7)
	Serum bicarbonate	73 (12.0)
	Basic metabolic panel	237 (38.9)
	Complete metabolic panel	325 (53.4)
	Ammonia	470 (77.2)

OR (aOR) comparing fatty acid oxidation disorders to urea cycle disorders, 9.35; 95% CI, 4.07–21.47], annual IEM volume (aOR comparing highest volume quartile to lowest volume quartile, 3.58; 95% CI, 1.51–8.49), and the presence of an ACMGE-accredited biochemical genetics fellowship affiliated with the ED hospital (aOR, 0.29; 95% CI, 0.14–0.62). The presence of at least 1 faculty member with American Board of Medical Genetics and Genomics accreditation in clinical biochemical genetics or medical biochemical genetics was not associated with obtaining minimum laboratory evaluations (aOR, 1.45; 95% CI, 0.69–3.01).

DISCUSSION

In this nationally representative sample, nearly one quarter of patients at risk for acute metabolic decompensation did not undergo a minimum laboratory evaluation when presenting to a pediatric ED. The EDs that had the highest annual volume of patients with IEM were most likely to perform minimum laboratory evaluations. The presence of a biochemical genetics fellowship was associated with a lower rate of performance of minimum laboratory tests, and the presence of board-certified biochemical genetics faculty was not associated with use. Taken together, our findings suggest that patients with the most common IEM treated in pediatric EDs do not uniformly receive minimum laboratory evaluations for metabolic crises.

There are several possible ways to address high variability and low rates of obtaining laboratory evaluations in EDs. Although many institutions distribute emergency protocol cards or letters to families of children with IEM diagnoses, families may not bring these cards with them to ED visits when their child is acutely ill.[6] The finding that higher volume of patients with IEM is associated with adherence to laboratory evaluations suggests a hospital's familiarity with IEM may lead to higher performance. In EDs that treat fewer patients with IEM, high-quality education or protocols relating to metabolic crises may help close the gap in care. Prior studies have demonstrated that clinical education regarding acute decompensation of patients with IEM may be limited. In a survey of junior physicians in Ireland, fewer than 15% selected the correct steps in the emergency management of patients with IEM, and most indicated that they had no training focused on IEM treatment.[19] The inclusion of education on IEM for pediatric residents and pediatric emergency medicine fellows as well as the availability of well-publicized online resources represent steps toward improving rates of appropriate laboratory evaluations. Some institutions have begun to record patients' evaluation and management plans in the electronic medical record system, which provides an ED-level intervention at the point of care. As this system becomes more widely used, outcomes should be systematically assessed to determine if this intervention improves rates of laboratory use and patient outcomes.

Of concern, the presence of a biochemical fellowship was associated with a lower likelihood of performing minimum laboratory evaluations. The presence of hospital faculty specializing in IEM was not associated with significantly improved ascertainment of laboratory evaluations. It is unclear why fellowships were associated with lower rates of laboratory test use, but a possible explanation could be reliance on fellow consults in place of an ED-based workflow. Across diseases, high management variability often represents an opportunity to standardize care to improve overall system performance for children visiting EDs, as in anaphylaxis and head injury.[20–22] Condition-specific protocols or electronic medical record notification messages offer a potential solution to guide clinicians to optimal management and have standardized care in other rare but high-morbidity conditions.[23–25]

We observed no significant difference in the rate of return visits to the ED within 72 hours between individuals who did and did not receive minimum laboratory evaluations. This observation merits closer study than a secondary database can provide and may be best studied using data gleaned from institutions' electronic medical records. In particular, a study of this nature could more clearly assess the characteristics of individuals who did and did not have return visits, the possibility that these patients may have sought care elsewhere, and the use of subsequent services such as clinic visits and telephone communication with metabolism providers.

To our knowledge, this is the first study to describe a national cohort of patients with all IEM who were treated in pediatric EDs. Disorders associated with a risk of metabolic decompensation in the setting of acute childhood illnesses were most highly represented among all IEM. The median age of patients presenting to the ED was 3.5 years, similar to previous observations and suggesting that the youngest children are at the greatest risk of metabolic crises.[6] Over half of patients with IEM who were treated in pediatric EDs were hospitalized, although only a small subset required intensive care. Patients with chronic progressive conditions such as adrenoleukodystrophy and peroxisomal disorders had the highest per patient ED visit counts. Our findings include the new observation that patients with disorders of purine and pyrimidine metabolism (such as the Lesch-Nyhan syndrome) were hospitalized most frequently and most commonly required intensive care. This descriptive information can assist EDs in anticipating the care needs of patients with IEM, as well as pediatric IEM specialists seeking prognostic information for newly diagnosed patients.

The strengths of this study are its national representativeness and large number of patients, which provide the power to assess risk factors for inadequate laboratory evaluations.[6,16] With this study, we build upon quality improvement initiatives for children

TABLE 3. Unadjusted ORs and aORs with 95% CIs for Outcome of Obtaining Minimum Laboratory Evaluations in Patients Presenting for a Catabolic Condition

Predictors	Minimum Laboratory Tests, %	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
ED volume of patients with IEM			
Quartile 1 (2.8–22.2 visits/y)	154/215 (71.6)	Reference	Reference
Quartile 2 (23.2–29.2 visits/y)	220/307 (71.7)	1.00 (0.40–2.50)	1.14 (0.56–2.34)
Quartile 3 (29.6–59.0 visits/y)	325/461 (70.5)	0.94 (0.43–2.10)	1.33 (0.54–3.28)
Quartile 4 (60.0–121.4 visits/y)	758/926 (81.9)	1.79 (0.72–4.46)	3.58 (1.51–8.49)
Biochemical genetics faculty			
No	126/179 (70.4)	Reference	Reference
Yes	1331/1730 (76.9)	1.40 (0.74–2.66)	1.45 (0.69–3.01)
Biochemical genetics fellowship			
No	932/1152 (80.9)	Reference	Reference
Yes	525/757 (69.4)	0.53 (0.3–1.15)	0.29 (0.14–0.62)
Diagnosis			
Urea cycle disorder	418/609 (68.6)	Reference	Reference
Fatty acid oxidation disorder	578/616 (93.8)	6.95 (3.03–15.95)	9.35 (4.07–21.47)
Organic acid disorder	461/684 (67.4)	0.94 (0.53–1.68)	0.84 (0.48–1.48)
Age			
0–2.9 y	692/868 (79.7)	Reference	Reference
3–10.9 y	571/754 (75.7)	0.79 (0.58–1.08)	0.87 (0.62–1.22)
11–18 y	194/287 (67.6)	0.53 (0.27–1.04)	0.89 (0.48–1.67)
Sex			
Female	775/993 (78.1)	Reference	Reference
Male	682/916 (74.5)	0.82 (0.56–1.19)	0.81 (0.57–1.17)
Race			
Caucasian	889/1175 (75.7)	Reference	Reference
American Indian	8/9 (88.9)	2.6 (1.3–5.3)	1.97 (0.60–6.49)
Asian	52/70 (74.3)	0.93 (0.30–2.90)	0.99 (0.23–4.14)
Black	147/212 (69.3)	0.73 (0.46–1.14)	1.07 (0.68–1.67)
Pacific Islander	10/15 (66.7)	0.64 (0.14–2.97)	0.96 (0.27–3.42)
Other	351/428 (82.0)	1.47 (0.69–3.11)	1.8 (0.95–3.51)
Ethnicity			
Hispanic	278/359 (77.4)	Reference	Reference
Not Hispanic	1097/1449 (75.7)	0.91 (0.57–1.45)	0.86 (0.48–1.54)
Unknown	82/101 (81.2)	1.26 (0.49–3.22)	1.21 (0.54–2.72)
Insurance			
Public	809/1072 (75.5)	Reference	Reference
Private	617/800 (77.1)	1.10 (0.76–1.58)	0.99 (0.67–1.46)
Unknown	15/17 (88.2)	2.44 (0.93–6.39)	1.21 (0.54–2.73)
Self-pay	14/18 (77.8)	1.14 (0.44–2.95)	0.84 (0.33–2.13)
Free care	2/2 (100.0)	*	*

*Could not be calculated due to insufficient observations.

with IEM by providing national baseline data on the current standard of emergency care for these patients.[6,11–13,19,26]

LIMITATIONS

This study has several limitations. First, our minimum laboratory analysis assessed only a subset of IEM diagnoses, which are not necessarily representative of all disease classes. Second, because of diagnosis code limitations, we were only able to analyze groups of disorders rather than individual diagnoses, which limited the precision with which we could assign a set of minimum laboratory criteria. However, even with the use of "common denominator" minimum laboratory evaluation criteria, our reported rates of obtaining laboratory tests were lower than anticipated and represent the best-case performance of our system. Third, the participants in the development of the minimum laboratory evaluations were from a single center, and clinicians at other centers could differ in practice approach. Finally, the data came from an administrative billing database. Some EDs may not bill for tests such as a glucose measurement, leading to an underestimate of the proportion of visits with minimum laboratory tests. In addition, we were unable to distinguish between laboratory testing completed in the ED versus the inpatient ward for patients hospitalized. However, we believe the timely performance of a laboratory evaluation is more important than the location in which it is performed.

In the future, repeating this analysis using *ICD-10* codes would allow for more precision in the identification of performance

on minimum laboratory evaluations for specific IEM diagnoses. Assessing nonpediatric EDs would also improve our understanding of the quality of care in nonspecialized hospitals for patients with highly specialized needs.

Our results suggest that there is national variation in the laboratory testing of children with IEM presenting to pediatric EDs at risk for metabolic decompensation. This study serves as a broad description of the emergency care of patients with IEM and offers insight into the patients most at risk for receiving insufficient evaluations for metabolic crises. At nearly one quarter of visits to pediatric EDs, patients with IEM did not receive the minimum laboratory evaluation. Given the life-threatening nature of metabolic crises, measures to improve laboratory use in children with IEM and catabolic conditions should be undertaken.

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