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Outcomes in Neonates with Gastroschisis in U.S. Children's Hospitals

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Abstract

Our objectives are to report patient characteristics, comorbidities, and outcomes for gastroschisis patients and analyze factors associated with mortality and sepsis. Using Pediatric Health Information System data, we examined neonates with both an *International Classification of Diseases*, 9th Revision diagnosis (756.79) and procedure (54.71) code for gastroschisis (2003 to 2008). We examined descriptive characteristics and conducted multivariate regression models examining risk factors for mortality, during the birth hospitalization, and sepsis. Analysis of 2490 neonates with gastroschisis found 90 deaths (3.6%) and sepsis in 766 (31%). Critical comorbidities and procedures are cardiovascular defects (15%), pulmonary conditions (5%), intestinal atresia (11%), intestinal resection (12.5%), and ostomy formation (8.3%). Factors associated with mortality were large bowel resection (odds ratio [OR] 8.26, 95% confidence interval [CI] 1.17 to 58.17), congenital circulatory (OR 5.62, 95% CI 2.11 to 14.91), and pulmonary (OR 8.22, 95% CI 2.75 to 24.58) disease, and sepsis (OR 3.87, 95% CI 1.51 to 9.91). Factors associated with sepsis include intestinal ostomy (OR 2.94, 95% CI 1.71 to 5.05), respiratory failure (OR 2.48, 95% CI 1.85 to 3.34), congenital circulatory anomalies (OR 1.58, 95% CI 1.10 to 2.28), and necrotizing enterocolitis (OR 4.38, 95% CI 2.51 to 7.67). Further investigation into modifiable factors such as small bowel ostomy and prevention of sepsis and necrotizing enterocolitis is warranted to guide surgical decision making and postoperative management.

Keywords

Gastroschisis; outcomes; mortality; sepsis; comorbidities

Gastroschisis is a common birth defect, with an increasing incidence both in the United States and abroad.[1–5] This disease has an obvious and significant impact on patients, families, and the health care system in general. These newborns require lengthy birth hospitalization with a mean number of hospital days reported between 25 and 50, at a mean cost between $70,000 and $150,000 per patient.[6–10] Because greater than 95% of patients born with gastroschisis can expect to survive to discharge from the hospital, further improvements in the care of these neonates should focus on in-hospital morbidity and mortality.[6,11,12]

Some reports have evaluated this population to identify factors associated with poor outcomes. One study analyzed 4344 neonates from 13 years of patients from both the National Inpatient

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Sample[5] and the Kids' Inpatient Database.[11,13] Using a previous definition of complex gastroschisis (presence of atresia, necrotizing enterocolitis [NEC], perforation, and volvulus), [14] the infants with complex gastroschisis were more likely to have cardiac disease, gastrointestinal, respiratory, and infectious disease complications; increased length of stay[15]; cost of hospitalization; and mortality.[11,13] Using that population, this team developed a scoring system to predict mortality.[12] Intestinal atresia, NEC, cardiac anomalies, and lung hypoplasia were associated with an increased likelihood of death. Sepsis was the most common complication in their study, a finding echoed in other studies.[10,16–18]

Whereas certain factors in patients with gastroschisis such as congenital anomalies and intestinal atresia cannot be altered, there may be factors in the management of this complex group of patients that will affect outcomes. Specifically, modifiable factors may include the decision to perform a particular procedure, such as an ostomy, or it may be the specific way that a disease condition is treated, in the case of NEC. The purpose of this study is to confirm factors previously associated with poor outcomes (such as those already defined as part of complex gastroschisis: atresia, NEC, perforation, and volvulus) and evaluate potentially modifiable patient-level factors and procedures that impact morbidity and mortality in patients with gastroschisis.

METHODS

Data Source and Study Population

We used the Pediatric Health Information System (PHIS), created by the Child Health Corporation of America (Kansas City, MO), that contains demographic, clinical, and charge data for all inpatient discharges from 43 freestanding, noncompeting children's hospitals in the United States. This represents 17 of 20 major metropolitan areas and 70% of freestanding children's hospitals. This analysis included those 41 hospitals that contributed to the expanded dataset with information on diagnostic testing, intensive care unit (ICU) utilization and clinical services (i.e., ventilation). Subjects were identified as neonates (≤30 days old) with an *International Classification of Diseases*, 9th Revision (ICD-9) diagnosis code for gastroschisis (756.79) and an ICD-9 procedure code for gastroschisis repair (54.71), with hospital discharge dates between January 2003 and March 2008. We chose to use both ICD-9 diagnosis and procedure codes in an effort to minimize misclassification.

Outcomes and Variables of Interest

The primary outcome of interest in this analysis was inhospital mortality, as coded by the hospitals in the discharge data. The secondary outcome was bacterial sepsis (ICD-9 code 771.8). Other covariates hypothesized as possible predictors of the outcomes of mortality and sepsis included patient characteristics as reported in the hospital discharge demographic data (gestational age, sex, birth weight, and race), comorbid conditions as measured by ICD-9 discharge diagnosis codes (congenital cardiac, circulatory, and pulmonary anomalies as well as neonatal intestinal conditions such as atresia and NEC), and related surgical procedures as measured by ICD-9 procedure codes (intestinal resection and intestinal ostomy). Comorbid conditions were further categorized as "intestinal" if related to feeding or any anatomic intestinal malformation or event and "systemic" if otherwise. The variable of days in ICU was defined as spending any hospital day in an ICU setting. All outcomes and covariates were analyzed from the initial hospitalization.

Statistical Analysis

Covariates that commonly have skewed distributions (length of stay and charges) are described using medians and interquartile ranges (IQRs). Two multivariate logistic regression analyses were performed to examine covariates associated with in-hospital mortality and bacterial

sepsis. Covariates hypothesized to be associated with each outcome were selected a priori for each model, based on clinical hypotheses (see Table 3).[12,14] Some covariates utilized in the mortality model could not be included in the sepsis model, as the limitations of the data meant that we could not ascertain whether those covariates represented events that happened prior to or after the onset of bacterial sepsis. All covariates included in the models are presented in Table 3, and both models were adjusted for Medicaid status. Each regression analysis modeled hospital as a fixed effect, so patients were compared within but not across hospitals. This methodology allows us to control for unmeasured hospital-level confounding, such as differences in referral patterns or treatment preferences. As a result of the statistical model employed, only data from hospitals with both positive and negative outcomes were utilized in the analysis. All analyses were conducted using Stata/SE, version 10 (College Station, TX).

This study was approved by the institutional review board at the Children's Hospital and Regional Medical Center in Seattle, Washington #12538.

RESULTS

We identified 2490 neonates with gastroschisis (52% male, 40% <36 weeks' gestation; Table 1). Approximately half had birth weights less than 2500 g. The median length of stay was 35 days (IQR: 24 to 58) with median adjusted total hospital charges of $172,000 (IQR: $109,000 to 293,000). Ninety-two percent of all subjects were admitted to the ICU during their hospitalization and 57% spent between 75 and 99% of their hospitalization in the ICU (median 89%; IQR: 31 to 97). The percentage of neonates requiring any mechanical ventilation during their hospitalization was 73%. The overall inhospital mortality was 3.6%.

Patient comorbidities were classified as systemic and intestinal (Table 2). Among the systemic comorbidities, 13%, 5%, and 2% had a circulatory, pulmonary, and cardiac anomaly, respectively. Thirty-six percent developed either bacterial or fungal sepsis, and 27% developed respiratory failure. Sixteen percent of patients had at least one ICD-9 diagnosis code for any of the previously defined "complex" conditions, and a few patients had multiple. Congenital conditions such as intestinal atresia and volvulus were found in 10% and 5%, respectively. The acquired conditions of NEC (<1%) and intestinal perforation (4%) occurred less often. Segments of the small bowel were resected in 10% of patients and large bowel in 2%. Six percent of the population (i.e., 60% of patients that had a small bowel resection) had a small intestine stoma created, and 2% had a large intestine stoma placed.

In the regression analysis, we found that large bowel resection was significantly associated with increased odds of mortality (OR = 8.26, 95% CI = 1.17 to 58.17; Table 3). Other significant risk factors in the model included congenital circulatory and pulmonary anomalies, respiratory failure, and bacterial sepsis. Interestingly, the presence of any type of intestinal atresia, perforation, and NEC were not independently associated with mortality after controlling for other covariates. In our sepsis regression analysis, large bowel resection, congenital circulatory anomalies, and respiratory failure were significantly associated with this outcome (Table 3). Additional covariates that were statistically significant in the regression model for sepsis include the creation of an intestinal ostomy and NEC.

DISCUSSION

Of the 2490 neonates with gastroschisis between 2003 and 2008 in the PHIS database, we identified both unalterable and potentially modifiable factors associated with poor outcomes. Unalterable factors for mortality included the presence of either a congenital circulatory or pulmonary anomaly. Potentially modifiable factors associated with mortality include the performance of a large bowel resection, development of respiratory failure, and presence of

bacterial sepsis. Although unalterable factors associated with sepsis also included congenital circulatory anomalies, potentially modifiable factors included the performance of a large bowel resection, development of respiratory failure, creation of any stoma, and the development of NEC.

Superficially, it would be easy to view the modifiable factors of bowel resection and stoma formation as a surrogate for patients with complex gastroschisis. It has been shown that complex patients have more severe disease and poor outcomes.[13] These complex patients, however, may do better with different clinical management similar to peritoneal drainage instead of laparotomy in premature neonates with NEC[19,20] or modified ventilator management in patients with congenital diaphragmatic hernia.[21] The optimal management of NEC is still unclear, and improvements in the timing of initiation of feeds, their caloric density, and the rate of advancement may subsequently also lead to improvements in caring for patients with gastroschisis.

It is difficult to accurately qualify how modifiable the above factors truly are. The purpose of our study, however, was to identify associations with an outcome that can lead to improving the direction and design of future studies. To this end, we have identified crucial decision points in the clinical management of gastroschisis at which we should carefully examine our options.

The major limitation of our study lies in the use of an administrative database, reliant upon accurate data entry. The use of ICD-9 codes to correctly identify patients with gastroschisis in large databases has been validated.[22] At the same time, inaccurate entry would result in misclassification and bias our results toward the null hypothesis. These data represent an entire hospitalization, and the timing of procedures during a hospitalization cannot be addressed. Knowing the timing of procedures and events would assist with assessing relationships and the possibility of causality (i.e., whether sepsis occurred either before or after the creation of an intestinal stoma). Finally, the PHIS database represents large freestanding children's hospitals that serve as tertiary referral centers. As such, we cannot make any population-based inferences from these data. Gastroschisis, however, is a complex disease, and it has been suggested that a large percentage of neonates with gastroschisis are likely transferred postnatally to hospitals with a children's designation.[6] Studying gastroschisis at children's hospitals allows for a better understanding of outcomes specific to children's institutions.

This study provides information useful to clinicians in their counseling of families of patients with gastroschisis. Specifically, their child will spend a median of 35 days in the hospital with the majority of that time spent in the ICU. During the hospital stay, almost one-third of these children will develop some form of infectious sepsis, and in-hospital mortality would average 3.6% with the majority of that occurring in children with complex gastroschisis. We have also identified potentially modifiable factors associated with both mortality and sepsis that deserve further study. Although the results from a large database study do not necessarily inform us as to the correct clinical pathway in the management of a disease as do the results of a randomized clinical trial, they can identify associations, both obvious or subtle, that can help to design future studies, and identify branch points in our algorithms that will benefit from more intensive evaluation.

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Table 1

Patient Demographics and Hospitalization Statistics among 2490 Subjects

	n **(%)**
Sex	2490 (100)
Male	1294 (52)
Female	1196 (48)
Missing	0 (0)
Gestational age (wk)	
21–33	195 (13)
34–35	412 (27)
36–37	647 (42)
38–46	288 (19)
Missing	948 (38)
Birth weight (g)	
<1000	25 (1)
1000–1499	72 (3)
1500–2499	1186 (48)
2500+	1121 (45)
Missing	86 (3)
Length of stay (d)	
1–14	118 (5)
15–29	859 (35)
30–59	898 (36)
60–99	330 (13)
100+	273 (11)
Missing	12 (0.5)
Median, IQR (d)	35, 24–58
Adjusted charges ($)	
1–74,999	184 (7)
75,000–99,999	310 (12)
100,000–199,999	967 (39)
200,000–499,999	743 (30)
500,000–999,999	219 (9)
1,000,000+	67 (3)
Missing	0 (0)
Median, IQR ($)	172,002, 109,579–293,030
Days in ICU >0	2280 (92)
% of hospitalization in ICU	
0%	210 (8)
1–25%	346 (14)
26–50%	255 (10)
51–75%	261 (10)
76–99%	1418 (57)

	n **(%)**
Missing	210 (8)
Median, IQR (percentile)	89, 31–97
Mechanical ventilation	1813 (73)
In-hospital mortality	90 (3.6)

Table 2

Comorbidities and Procedures among 2490 Subjects

Comorbidities	***n* (%)**
Systemic	
Chromosomal anomaly	9 (0.36)
Congenital heart anomaly	48 (1.93)
Congenital circulatory anomaly	327 (13.13)
Congenital pulmonary anomaly	125 (5.02)
Respiratory failure	680 (27.31)
Sepsis, bacterial	766 (30.76)
Sepsis, fungal	126 (5.06)
Hemolytic disease	366 (14.70)
Neonatal jaundice	551 (22.13)
Intestinal	
Newborn feeding problems	798 (32.05)
Ileus	302 (12.13)
Esophageal reflux	401 (16.10)
Volvulus	7 (0.28)
Small bowel atresia	188 (7.55)
Large bowel atresia	81 (3.25)
Other intestinal anomalies	211 (8.47)
Necrotizing enterocolitis	127 (5.10)
Intestinal perforation	100 (4.02)
Complex: atresia, NEC, perforation or volvulus	406 (16.31)
Procedures	
Small bowel resection	257 (10.32)
Large bowel resection	55 (2.21)
Small bowel ostomy	148 (5.94)
Large bowel ostomy	60 (2.41)
Central line placement	225 (9.04)

Table 3

Logistic Regression Models for the Risk Mortality and Bacterial Sepsis, Using Hospital as a Fixed Effect

	Model 1: Mortality (*n* = 1270 Subjects in 24 Hospitals)			Model 2: Bacterial Sepsis (*n* = 1546 Subjects in 33 Hospitals)		
	OR	**95% CI**	***p* Value**	**OR**	**95% CI**	***p* Value**
Birth weight	0.99	0.99–1.00	0.077	0.99	0.99–1.00	0.722
Gestational age	0.90	0.78–1.03	0.139	0.94	0.89–1.00	0.073
Age (d) on day of operation	1.04	0.99–1.08	0.054	—	—	
Small bowel resection	1.96	0.53–7.17	0.308	1.50	0.90–2.50	0.119
Large bowel resection	8.26	1.17–58.17	0.034	2.56	1.09–6.02	0.030
Small bowel ostomy	0.74	0.14–3.68	0.714	2.94	1.71–5.05	0.000
Large bowel ostomy	6.22	0.97–39.83	0.054			
Congenital heart anomaly	0.71	0.07–7.00	0.771	—	—	—
Congenital circulatory anomaly	5.62	2.11–14.91	0.001	1.58	1.10–2.28	0.013
Congenital pulmonary anomaly	8.22	2.75–24.58	0.000	—	—	—
Respiratory failure	3.31	1.24–8.84	0.017	2.48	1.85–3.34	0.000
Sepsis, bacterial	3.87	1.51–9.91	0.005	—	—	—
Sepsis, fungal	2.49	0.59–10.53	0.214	—	—	—
Hemolytic disease	0.77	0.21–2.28	0.707	—	—	—
Neonatal jaundice	0.70	0.26–1.86	0.480	—	—	—
Newborn feeding problems	0.25	0.07–0.87	0.029	—	—	—
Ileus	1.15	0.27–4.84	0.842	—	—	—
Esophageal reflux	0.27	0.06–1.29	0.103	—	—	—
Small bowel atresia	1.47	0.37–5.82	0.577	0.98	0.57–1.67	0.949
Large bowel atresia	0.34	0.02–5.13	0.438	0.86	0.40–1.86	0.718
NEC	1.58	0.42–5.95	0.497	4.38	2.51–7.67	0.000
Intestinal perforation	0.80	0.15–4.30	0.797	1.41	0.73–2.72	0.297
Volvulus	—	—	—	1.58	0.22–11.13	0.642
Central line insertion	—	—	—	1.49	0.91–2.42	0.107

CI, confidence interval; OR, odds ratio; NEC, necrotizing enterocolitis.