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A 25-year study of gastroschisis outcomes in a middle-income country

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ABSTRACT

Background: Survival of newborns with gastroschisis is significantly higher in high-income versus low and middle-income countries. We reviewed treatment and outcomes of gastroschisis in a middle-income country setting with increasing protocolized management.
Methods: All newborns with gastroschisis treated during the period 1989–2013 at a single Brazilian academic surgical service were studied retrospectively. Protocolized diagnosis, delivery, nutrition, medical interventions, and surgical interventions were introduced in 2002. Outcomes before and after protocol introduction were studied using univariate and multivariate analysis.
Results: One hundred fifty-six newborns were treated for gastroschisis: 35 (22.4%) and 121 (77.6%) before and after 2002, respectively. When compared to the earlier cohort, patients treated after 2002 had higher rates of prenatal diagnosis (90.9% vs. 60.0%, $p < 0.001$), delivery at a tertiary center (90.9% vs. 62.9%, $p < 0.001$), early closure (65.3% vs. 33.3%, $p = 0.001$), primary repair (55.4% vs. 31.4%, $p = 0.013$), monitoring of bladder pressure (62.0% vs. 2.9%, $p = 0.001$), PICC placement (71.1% vs. 25.7%, $p < 0.001$), early initiation of enteral feeding (54.5% vs. 20.0%, $p < 0.001$), and lower rates of electrolyte disturbances (53.7% vs. 85.7%, $p = 0.001$). Mortality decreased from 34.3% before 2002 to 24.8% ($p = .27$) after 2002 despite an increase in the complex gastroschisis rate from 11.4% to 15.7% during the same period.
Conclusions: Gastroschisis outcomes in a middle-income country can be gradually improved through targeted interventions and management protocols.
Type of Study: Therapeutic.
Level of Evidence: III.

Gastroschisis is a congenital anomaly associated with high survival rates in high-resource settings, with recent studies showing survival rates well over 90% in high-income countries (HICs) [1,2]. In these settings, mortality is increasingly limited to patients with complex gastroschisis and significant bowel compromise [1,2]. In fact, in HICs, mortality is low enough that it cannot be used as an outcome measure in research studies. Morbidity outcomes, such as length of hospital stay and duration of total parenteral nutrition have become the focus for outcome improvements in HICs [1].

On the contrary, the anomaly is still associated with poor survival rates in low- and middle-income countries (LMICs), reported to vary between 0% and 50% [3,4]. Due to this large difference in outcomes between HICs and LMICs, gastroschisis has been considered a bellwether condition for adequate neonatal health care resources [4]. As a bellwether condition, outcomes of gastroschisis may adequately reflect overall outcomes of a variety of neonatal gastrointestinal anomalies, such as esophageal atresia or intestinal atresia.

Brazil, with a per capita gross national income of $14,810 in 2016, is defined by the World Bank as a middle-income country. It has a more developed health care system than low-income countries. In São Paulo, the Brazilian state with the most plentiful financial resources, three tertiary university centers reported a survival rate of 85.9%, approaching that of developed countries. [5] However, a more recent report from an academic medical center in Sao Paulo again demonstrated an overall survival rate of 75%, when accounting for all deaths [6].

Hospital das Clínicas of the Universidade Federal de Minas Gerais is a general, urban, public, university teaching hospital. Established in 1928, the hospital has 509 beds, including 60 pediatric beds, 11 pediatric

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intensive care unit (PICU) beds, and 24 neonatal intensive care unit (NICU) beds. The NICU, Center for Fetal Medicine, and Obstetric Unit are housed on the same floor and interact closely with each other. The pediatric surgical service was founded in 1977, and currently has nine pediatric surgeons who practice the entire range of urgent and elective pediatric surgical care, except trauma. The service has also hosted a pediatric surgical residency training program since 1987.

The hospital is fully integrated within the Brazilian National Health System and serves as a referral center for tertiary pediatric medical and surgical care for the State of Minas Gerais. The hospital is located in the city of Belo Horizonte, which is the sixth most populous city in Brazil with about 2.2 million residents, and also the hub of the greater metropolitan Belo Horizonte region, Brazil's third most populous area with more than 5 million people. The hospital serves a catchment area of 587,000 km^2, including 21 million people. Traveling distances to the hospital by car vary from the immediate vicinity of the hospital to 200 km.

Like many centers around the world, we have seen a rising incidence of admissions for gastroschisis over the past 25 years. Prior to 2002, no specific plan for prenatal, perinatal, or postnatal care existed. In 2002, a number of interventions were introduced, targeted at perceived causes of high mortality. These interventions became well established over the past decade. Our study had two aims. The primary aim was to test the hypothesis that these interventions had a favorable effect on mortality and morbidity. The secondary aim was to analyze the determinants of mortality before and after introduction of the interventions.

1. Methods

1.1. Patient population

All babies with gastroschisis treated at Hospital das Clínicas of the Universidade Federal de Minas Gerais / Empresa Brasileira de Serviços Hospitalares (UFMG/EBSERH) between 1989 and 2013 were included in the study. For analysis, the patient population was divided into two groups. Period 1 included patients treated from 1989 to 2001. Period 2 included patients treated from 2002 to 2013.

1.2. Outcomes

The primary outcomes were mortality and length of hospital stay. Secondary outcomes included sepsis, shock, electrolyte disturbances (abnormalities in serum level of sodium, chloride, or bicarbonate), duration of mechanical ventilation, time to first feeding, and re-operation.

1.3. Data collection

Extensive data were collected retrospectively from the patient and maternal medical charts. Maternal variables included age, delivery location (inborn vs. outborn), and delivery mode. Patient variables included sex, year of birth, birth weight, gestational age, prenatal diagnosis, 1-min and 5-min Apgar scores, the presence of simple versus complex (associated with intestinal ischemia, necrosis, perforation, stenosis or atresia) gastroschisis, and associated anomalies. Treatment variables included requirement for staged silo closure (used only when primary closure was not possible), measurement of bladder pressure, age at closure (hours), method of vascular access, use of muscle relaxants, use of total parenteral nutrition (TPN), use of mechanical ventilation, and age at initiation of enteral feeds. Variables related to complications included blood-culture confirmed sepsis, shock, electrolyte disturbances, wound infection, necrotizing enterocolitis, and other complications.

1.4. Targeted interventions

Eight targeted interventions were enacted in 2002 as a care package. This occurred through a multidisciplinary effort that included pediatric surgeons, neonatologists, obstetricians, and nurses. The team performed a literature review to delineate best practices in the care of these infants, and decide which of those practices can be adopted in our environment. The timing coincided with two main events at the hospital, namely the expansion of the Fetal Medicine Center and the inauguration of the pediatric intensive care unit of the HC-UFMG. These events provided appropriate resources for enactment of our new care package.

The elements of the care package were prenatal diagnosis, inborn delivery, monitored hydration to avoid electrolyte disturbances, placement of percutaneously inserted central catheters (PICC), early closure, primary repair when possible, measurement of bladder pressure, and early initiation of enteral feedings. These interventions can be classified under two broad categories, one related to the structuring of prenatal medical care in the regional healthcare network and another related to the logistics of pediatric intensive care within the institution.

Prior to 2001, the rate of prenatal diagnosis was low, and babies with gastroschisis were often admitted to the hospital in a delayed manner, sometimes up to 3 days after birth, with a clinical picture of dehydration, hypothermia, or sepsis associated with gastroschisis. Starting in 2002, the hospital's Fetal Medicine Service began heavily investing time in physician training aimed at prenatal diagnosis and early referral of pregnant patients to our tertiary service.

In 2002, the Pediatric Intensive Treatment Center was inaugurated on the same floor of the Pediatrics Unit of the HC-UFMG. This led to major practice changes in the care of critically ill neonates and children, who were previously treated in adult units. In 2009, the Neonatal Center was remodeled and expanded into a Neonatal Intensive Care Unit, of 10 beds, on the same floor as the Fetal Medicine Unit and High-Risk Maternity Ward. All babies with gastroschisis and other neonatal surgical disorders have since been treated in this unit by a multidisciplinary team which includes neonatologists and pediatric surgeons.

1.5. Statistical analyses

Independent variables, interventions and patient outcomes were compared between the two patient cohorts corresponding to the two time periods using the chi-square test or the Fisher Exact test (for cases with an expected frequency of less than 5) for categorical variables and the Mann–Whitney test for continuous variables. For each time period, survivors were compared to non-survivors using univariate and multivariate analyses. The univariate analysis was performed by applying the Kaplan–Meier method associated with the log-rank test. The multivariate analysis was performed by applying an adjusted form of the Cox model. Variables from the univariate analyses with p-values of less than 0.25 were included in the covariable selection process to adjust the final model. These were inserted and removed from the model until only those considered statistically significant remained. The adjustment of the model was evaluated by applying risk proportionality tests. A p value <0.05 was deemed statistically significant.

1.6. Ethics approval

The study protocols were approved by the UFMG Research Ethics Committee (ETIC 0026.0.203.000–11; and CAAE – 43,379,115.7.0000.5149).

2. Results

2.1. Patient cohort

The characteristics of the patient population are shown in Table 1. From 1989 to 2013, 156 newborns with gastroschisis were treated in the Pediatric Surgery Service of the Hospital das Clínicas of the UFMG/EBSERH (average of 6.25 cases/year). The number of patients treated increased progressively; 35 from 1989 to 2001 (2.69 cases/year), 50 from 2002 to 2007 (8.33 cases/year), and 71 from 2008 to 2013 (11.83 cases/

Table 1
Patient characteristics.

Characteristic	n	n*	Mean	SD	Minimum	Median	Maximum
Maternal age (y)	146	10	21	5.1	13	19	37
Weight (g)	156	0	2308	492.6	920	2290	3635
Gestational age (wk)	151	5	36	1.9	29	36	40
Apgar 1 min	145	11	7	2.4	0	8	10
Apgar 5 min	147	9	9	1.2	1	9	10
Age at operation (h)	151	5	7	9.8	1	4	82
TPN duration (d)	147	9	29	34.0	0	20	294
Mechanical ventilation (d)	154	2	12	11.2	1	8	68
Enteral diet begin (d)	134	22	21	21.9	0	14	180
Hospital stay-survivors (d)	114	0	46	32.2	15	38	243

n: number of observations; n*: no information; SD: standard deviation.

year). There were 79 (50.6%) girls and 77 (49.4%) boys. Average birth weight was 2308 ± 492 g (range 920–3635 g), with 102 patients (65.4%) with low birth weight (< 2500 g), and six (3.84%) with very low birth weight (< 1500 g). Seventy six children (48.7%) were born before 37 weeks gestation, and 12 (7.7%) before 34 weeks. A prenatal diagnosis was made in 131 children (84%). The majority of patients, 130 (83.3%), were born by C-section. The incidences of complex gastroschisis and associated anomalies were 23 (14.7%) and 37 (23.7%), respectively. One hundred fourteen patients survived to discharge, resulting in an overall survival rate of 73.1%. The majority of deaths, 29 (69.1%), occurred during the first 30 days. Average hospital stay for survivors was 46 ± 32.2 days. Complications included sepsis in 120 (76.9%), prolonged ileus (> 21 days) in 86 (55.1%), electrolyte disturbances in 95 (60.9%), wound infection in 24 (15.4%), and necrotizing enterocolitis in 11 (7.1%).

In terms of place of domicile of the mother, 36 (23%) were from Belo Horizonte, 63 (40%) were from communities up to 80 km from our center, 23 (15%) were from cities between 80 and 536 km from our city, and 34 (22%) had missing domicile information.

2.2. Comparison of two time periods

The comparison of patient characteristics, interventions, and outcomes between the two time periods is shown in Table 2. Due to the targeted interventions, the rates of prenatal diagnosis, inborn patients, early primary closure, PICC line use, and early feeding all increased significantly in Period 2. All secondary outcomes improved, but only avoidance of electrolyte disturbances reached statistical significance. The details of hospital stay in each period, stratified by survival, are shown in Table 3. Though not statistically significant, overall mortality decreased from 34.3% to 24.8% (p = 0.27) despite an increase in the rate of complex gastroschisis from 11.4% to 15.7%. In Period 1, the survival rates for simple and complex gastroschisis were 74.2% and 25.0%, respectively. In Period 2, the survival rates for simple and complex gastroschisis were 78.4% and 57.9%, respectively. The more than doubling in survival for complex gastroschisis from 25.0% to 57.9% did not reach statistical significance, p = 0.32.

A comparison of secondary outcomes of survivors during the two time periods is shown in Table 4. Survivors in Period 2 had a statistically significant shorter duration of mechanical ventilation and a statistically significant earlier initiation of enteral feeds. Mean hospital stay for survivors decreased from 52 + 23.4 days in Period 1 to 45 + 34.1 days in Period 2, closely approaching statistical significance (p = 0.057).

2.3. Mortality determinants during each time period

The univariate analyses comparing survivors and non-survivors in each time period is shown in Table 5. In Period 1, mortality was

Table 2
Comparison of patient characteristics and outcomes.

Characteristics	Period		p-Value
	I: 1989 – 2001 N = 35	II: 2002 -- 2013 N = 121	
	N (%)	N (%)	
Maternal characteristics			
Maternal age			0.440[1]
≤17 years	6 (21.4)	40 (33.9)	
18–21 years	11 (39.3)	38 (32.2)	
≥22 years	11 (39.3)	40 (33.9)	
Prenatal diagnosis	21 (60.0)	110 (90.9)	**<0.001[1]**
C-section delivery	21 (61.8)	109 (90.8)	**<0.001[1]**
Patients characteristics			
Inborn	22 (62.9)	110 (90.9)	**<0.001[1]**
Male	16 (45.7)	61 (50.4)	0.624[1]
Weight (<2500 g)	23 (65.7)	79 (65.3)	0.963[1]
Gestational age <37 weeks)	15 (50.0)	61 (50.4)	0.968[1]
Apgar 1 min <5	6 (21.4)	26 (22.2)	0.928[1]
Apgar 5 min <5	1 (3.3)	2 (1.7)	0.499[2]
Complex gastroschisis	4 (11.4)	19 (15.7)	0.530[1]
Associated anomalies	6 (17.1)	31 (25.6)	0.299[1]
Treatment characteristics			
Age at operation ≤4 h	11 (33.3)	77 (65.3)	**0.001[1]**
Primary closure	11 (31.4)	67 (55.4)	**0.013[1]**
Staged closure with silo	24 (68.6)	54 (44.6)	**0.013[1]**
Bladder pressure measurement	1 (2.9)	75 (62.0)	**0.001[1]**
PICC Placement	9 (25.7)	86 (71.1)	**<0.001[1]**
TPN			0,212[2]
≤14 days	7 (20.0)	35 (28.9)	
15–28 days	11 (31.4)	47 (38.8)	
≥29 days	13 (37.2)	34 (28.1)	
Not used	4 (11.4)	5 (4.2)	
Duration of mechanical ventilation			0.190[1]
≤5 days	9 (26.5)	40 (33.3)	
6–10 days	7 (20.6)	37 (30.8)	
≥11 days	18 (52.9)	43 (35.9)	
Time to first feeding			**<0.001[2]**
≤14 days	7 (20.0)	66 (54.5)	
>14 days	20 (57.1)	44 (36.4)	
Not used	8 (22.9)	11 (9.1)	
Secondary outcomes			
Pneumonia	5 (14.3)	7 (5.8)	0.096[1]
Septicemia	29 (82.9)	91 (75.2)	0.344[1]
Shock	17 (48.6)	43 (35.5)	0.163[1]
Electrolyte disturbance	30 (85.7)	65 (53.7)	**0.001[1]**
Necrotizing enterocolitis	4 (11.4)	7 (5.8)	0.267[2]
Reoperation	11 (31.4)	26 (21.5)	0.223[1]
Primary outcomes			
Death	12 (34.3)	30 (24.8)	0.265[1]
Hospital stay (days)			0.154[1]
≤28	6 (26,1)	26 (28.5)	
29–42	4 (17.4)	32 (35.2)	
≥43	13 (56.5)	33 (36.3)	

1: chi-Square test. 2: Fisher exact test.

associated with shorter period of mechanical ventilation, the inability to start enteral intake, shock, and a lower incidence of reoperations. In Period 2, mortality was associated with inability to obtain early primary closure, decreased frequency of PICC placement, inability to start enteral feeds, shock, and electrolyte disturbances.

The multivariate analysis of mortality determinants in each time period is shown in Table 6. Inability to initiate enteral feeds was an independent predictor of mortality in both periods. In Period 1, the risk of death for children who did not begin enteral intake was 20.4 times greater compared to those who began enteral intake within 14 days, and 15.9 times greater compared to those who began enteral intake after 14 days. Reoperation was associated with increased survival in Period 1.

In Period 2, staged closure with silo, lack of TPN use, and shock were independent predictors of mortality. Children who were on TPN 15–28 days had the highest chance of survival versus those who were on TPN for shorter or longer periods.

Table 3
Comparison of hospital stay between survivors and non-survivors in each period (days).

Characteristics	n	Mean	SD	Minimum	Median	Maximum	IQR	p
Period 1: 1989–2001								
Survivors	23	52.0	23	19.0	52.0	98.0	28.0–65.0	0.063[1]
Non-survivors	12	36.0	43	2.0	20.5	148.6	4.5–56.8	
Period 2: 2002–2013								
Survivors	91	45.0	34.0.0	15.0	37.0	243.0	26.0–48.0	**<0.001[1]**
Non-survivors	30	34.0	62	0.3	19.0	334.0	4.8–33.5	

IQR, interquartile range. [1]Mann–Whitney.

3. Discussion

There are great disparities in gastroschisis outcomes between HICs and LMICs. Survival from gastroschisis is still in the single or low double digits in many low resource settings. [3,4,7–9]. There is also a hidden mortality from gastroschisis represented in patients who may never seek medical care or be referred to a tertiary care center due to the perceived dismal outcomes in certain countries [4]. The Brazilian experience reported here, as well as other small series previously reported from Brazil, show overall survival from gastroschisis in the 50–80% range, outcomes which lie closer to those of high income than low income countries [5,6,10]. This supports a direct relationship between a country's neonatal care resources and gastroschisis outcomes, and strongly supports the potential use of gastroschisis as a bellwether condition for neonatal surgery capacity as recently proposed [4].

We experienced a significantly rising incidence of gastroschisis over a 25-year period, as has been reported from a number of countries. [11,12] During the period prior to 2000, one of every three babies with gastroschisis died. In response, we embarked on a process to reduce variability of care for these infants in an effort to improve outcomes. This included a plan to increase prenatal diagnosis and delivery at our tertiary center, followed by protocolized care aimed at achieving early closure, adequate vascular access and fluid resuscitation, early enteral feeding, and prevention of abdominal compartment syndrome. We believe our process can be replicated in other LMICs, at least to a certain degree. Gastroschisis survival is largely dependent on medical issues, outside the surgeon's control. Therefore, any deliberate attempt at improving outcomes should start with the assembly of a multidisciplinary team. Some targeted interventions, such as centralization of care at a regional center and early enteral feeding, may be possible without an increase in resources. In our case, centralization of care also resulted in standardization of care. We believe this was of major benefit, not only to patients, but also to medical staff who developed increased expertise in the treatment of gastroschisis.

Table 4
Comparison of secondary outcomes of survivors during the two time periods.

Variables	n	Mean	SD	Median	P value *
Entire cohort		**n**			
TPN duration (days)	112	29	26	21	
Mechanical ventilation (days)	113	12	10	8	
Initiation enteral diet (days)	111	23	22	15	
Hospital stay (days)	114	46	32	38	
Period 1: 1989–2001					
TPN duration (days)	22	29	14	28	
Mechanical ventilation (days)	23	15	10	12	
Initiation enteral diet (days)	23	29	16	25	
Hospital stay (days)	23	52	23	52	
Period 2: 2002–2013					
TPN duration (days)	90	29	28	20	0.141
Mechanical ventilation (days)	90	11	10	7	0.011
Initiation enteral diet (days)	88	21	24	14	0.002
Hospital stay (days)	91	45	34	37	0.057

* Mann–Whitney *U* test comparing Period 2 to Period 1.

Another lesson we would like to share is that efforts at improving outcome should also be targeted at regional education of health professionals. As of 2002, our Fetal Medicine Service began to invest heavily in training physicians to diagnose intrauterine gastroschisis, as well as other congenital anomalies. We expanded the contact network with obstetricians throughout Belo Horizonte and other neighboring cities. This support resulted in our current status as the high risk obstetrics and pediatric surgical referral center for the state. Currently, when a mother is found to be carrying a fetus with a congenital anomaly diagnosed at one of the Basic Health Unites, she is routinely referred to the Fetal Medicine Center at HC-UFMG for evaluation, prenatal follow-up, and birth. This is supported by the domicile data, which well represents the population density of the state.

Our data demonstrate significant success in implementation of these measures and a 15% improvement in the survival rate, an appreciable clinical effect that did not reach statistical significance. This improvement has come through improved survival of patients with complex gastroschisis, whose survival more than doubled. This was a very significant clinical improvement that did not reach statistical significance, most likely due to the small numbers of patients. Electrolyte disturbances were significantly decreased. Unfortunately the rate of sepsis remained quite high, and this still represented the main cause of mortality in such patients. Although shock rather than sepsis emerged as an independent risk factor for mortality in both periods studied, shock was almost always due to sepsis. Sepsis seems to be the common denominator for the high mortality experienced in LMICs. [4–10] It has also emerged as the highest independent risk factor for prolonged hospital stay in patients with simple gastroschisis treated in high resource settings [13].

We have attempted to address the problem of sepsis through several interventions. Our approach is to attempt primary closure within 4 h and place a customized silo developed by our group if closure cannot be obtained [14]. Silo placement in our practice, therefore, is most likely a surrogate for complex gastroschisis or simple gastroschisis with severe bowel matting. It might also contribute to increased infectious complications. [15] Use of spring-loaded silos, currently unavailable in the country, at the bedside might be less traumatic and might contribute to quicker containment of the bowel in difficult cases. [16] PICC line access has also replaced cut-downs or other invasive maneuvers that may increase the risk of central line associated blood stream infections (CLABSI). Nevertheless, sepsis remains an obvious target for further improvement if mortality in our setting is to decrease further. Towards this end, we have recently upgraded the minimum educational requirements of NICU nurses, and emphasized the importance of nursing protocols for care of PICC.

During the earlier period, inability to start enteral intake was the strongest predictor of mortality. This was not just limited to patients with complex gastroschisis as there were only four such patients in the earlier cohort. One of our interventions was targeted at early start, but slow progression, of enteral feeding. We recently published our experience with this approach, demonstrating an increase in hospital stay by 2.1% for each additional day without enteral feeding [17]. This approach shortens the duration of TPN and may help decrease the rate of sepsis. Not surprisingly, in Period 2, patients who were on TPN for 15–28 days had the best outcomes, since they were likely transitioned

Table 5
Univariate analysis comparing survivors and non-survivors in each time period.

Characteristics	Period I: 1989–2001		p-Value[1]	Period II: 2002–2013		p-Value[1]
	Death	Survival		Death	Survival	
N	**12 (34%)**	**23 (66%)**		**30 (25%)**	**91 (75%)**	
Maternal variables						
Age			0.118			0.913
≤17 years	1 (11.2)	5 (26.4)		11 (37.9)	29 (32.6)	
18–21 years	4 (44.4)	7 (36.8)		7 (24.2)	31 (34.8)	
≥22 years	4 (44.4)	7 (36.8)		11 (37.9)	29 (32.6)	
Prenatal diagnosis	5 (41.7)	16 (69.6)	0.408	28 (93.3)	82 (90.1)	0.176
C-section delivery	4 (36.4)	17 (73.9)	0.238	27 (93.1)	82 (90.1)	0.510
Patient variables						
Inborn	5 (41.7)	17 (73.9)	0.343	28 (93.3)	82 (90.1)	0.300
Male	8 (66.7)	8 (34.8)	0.212	20 (66.7)	41 (45.0)	0.079
Weight (<2500 g)	7 (58.3)	16 (69.9)	0.743	22 (73.3)	57 (62.6)	0.477
Weight (<2000 g)	4 (33.3)	8 (34.8)	0.985	8 (26.7)	20 (22.0)	0.737
Gestational age <37 week)	4 (44.4)	11 (52.4)	0.690	19 (63.3)	42 (46.2)	0.369
Gestational age <35 week)	3 (33.3)	3 (14.3)	0.164	8 (26.7)	17 (18.7)	0.364
Apgar 1 min <5)	3 (37.5)	3 (15.0)	0.253	9 (32.1)	17 (19.1)	**0.093**
Apgar 5 min <5	1 (12.5)	0 (0.0)	0.140	0 (0.0)	2 (2.3)	0.513
Complex gastroschisis	3 (25.0)	1 (4.4)	0.930	8 (26.7)	11 (12.1)	0.908
Associated anomalies	2 (16.7)	4 (17.4)	0.295	9 (30.0)	22 (24.2)	0.385
Treatment variables						
Age at operation ≤4 h	5 (41.7)	6 (28.6)	0.066	20 (69.0)	57 (64.0)	0.458
Primary closure	3 (25.0)	8 (34.8)	0.644	11 (36.7)	56 (61.5)	**0.014**
Staged closure with silo	9 (75.0)	15 (65.2)	0.644	19 (63.3)	35 (38.5)	**0.014**
PICC	3 (25.0)	6 (26.1)	0.675	16 (53.3)	70 (76.9)	<**0.001**
TPN duration			0.944			0.067
≤14 days	3 (25.0)	4 (17.4)		12 (40.0)	23 (25.3)	
15–28 days	2 (16.7)	9 (39.1)		8 (26.7)	39 (42.8)	
≥29 days	4 (33.3)	9 (39.1)		6 (20.0)	28 (30.8)	
Not used	3 (25.0)	1 (4.4)		4 (13.3)	1 (1.1)	
Mechanical ventilation			**0.006**			0.660
≤5 days	5 (45.4)	4 (17.4)		11 (36.7)	29 (32.2)	
6–10 days	2 (18.2)	5 (21.7)		4 (13.3)	33 (36.7)	
≥11 days	4 (36.4)	14 (60.9)		15 (50.0)	28 (31.1)	
Time to first feeding			<**0.001**			**0.046**
≤14 days	1 (8.3)	6 (26.1)		15 (50.0)	51 (56.0)	
>14 days	3 (25.0)	17 (73.9)		4 (13.3)	40 (44.0)	
Non-used	8 (66.7)	0 (0.0)		11 (36.7)	0 (0.0)	
Complications						
Pneumonia	2 (16.7)	3 (13.0)	0.421	3 (10.0)	4 (4.4)	0.200
Sepsis	10 (83.3)	19 (82.6)	0.272	22 (73.3)	69 (75.8)	0.274
Shock	11 (91.7)	6 (26.1)	**0.003**	23 (76.7)	20 (22.0)	<**0.001**
Electrolyte disturbances	11 (91.7)	19 (82.6)	0.583	25 (83.3)	40 (44.0)	**0.004**
Necrotizing enterocolitis	3 (25.0)	1 (4.3)	0.912	3 (10.0)	4 (4.4)	0.393
Reoperation	3 (25.0)	8 (34.8)	**0.013**	10 (33.3)	16 (17.6)	0.727

1: Log-rank test.

to enteral nutrition before early death or the development complications due to prolonged intestinal failure.

Our experience also points to the importance of practice setting in applying interventions for gastroschisis. This is quite relevant, as increased North–South collaborations are being formed to improve practice outcomes [4]. For example, the rate of Cesarean section delivery of babies with gastroschisis is quite high in our setting, currently over 90%. In fact, the rate increased significantly from the earlier period to the later one as we succeeded in increasing prenatal diagnosis and inborn delivery. While we recognize that there is little evidence to support

Table 6
Multivariate analyses (Cox model) of mortality determinants during the two periods' odds ratio (confidence interval).

Variables	Period	
	I: 1989–2001	II: 2002–2013
Staged closure with silo	X	2.3 (1.01–5.45), p = **0.049**
TPN duration		
≤14 days (*reference*)		--
15–28 days	X	0.3 (0.1–0.8), p = 0.017
≥29 days	X	0.1 (0.02–0.4), p < 0.001
Not used	X	3.8 (1.2–12.8), p = 0.029
Initiation of enteral feeds		
Not initiated (*reference*)		
≤14 days	0.049 (0.004–0.65), p = **0.022**	0.51 (0.20–1.30), p = 0.160
>14 days	0.063 (0.01–0.40), p = **0.003**	0.08 (0.01–0.41), p = **0.002**
Shock	X	4.6 (1.68–12.37), p = **0.003**
Reoperation	0.064 (0.005–0.83), p = **0.035**	X

X: not used in the model.

this approach, it is essential in our setting to plan treatment and optimize strained resources. Likewise, we recognize that attempted fascial closure in many centers has given way to staged silo closure or sutureless closure. [18,19] In our setting, our approach is aimed at obtaining maximal bowel protection as early as possible, given staged closure emerging as a risk factor for mortality in our study. In a recent randomized trial, sutureless closure was found to be inferior to fascial closure with respect to duration of ileus and hospital stay [20].

With an emphasis on reducing septic complications through the interventions above, we are currently conducting a multi-center prospective study to evaluate contemporary gastroschisis outcomes in several Brazilian institutions.

4. Conclusion

We have presented one of the largest experiences of gastroschisis from a low or middle-income country, demonstrating outcomes that are closer to those of HICs than low-income countries. Targeted interventions allowed for standardization of care and some improvement in overall outcomes, realized mostly through improvements in outcomes in patients with complex gastroschisis. Further efforts, with the principal aim of avoiding septic complications, are required to achieve the excellent outcomes currently associated with this anomaly in high resource settings.

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References

[1] Cheong LHA, Emil S. Outcomes of pediatric appendicitis: an international comparison of the United States and Canada. JAMA Surg 2014;149:50–5.
[2] Emil S, Canvasser N, Chen T, et al. Contemporary two-year outcomes of complex gastroschisis. J Pediatr Surg 2012;47:1521–8.
[3] Manson J, Ameh E, Canvasser N, et al. Gastroschisis: a multi-Centre comparison of management and outcome. Afr J Paediar Surg 2012;9:17–21.
[4] Ford K, Poenaru D, Moulot O, et al. Gastroschisis: bellwether for neonatal surgery capacity in low resource settings. J Pediatr Surg 2016;51:1262–7.
[5] Tannuri ACA, Sbragia L, Tannuri U, et al. Evolution of critically ill patients with gastroschisis. Clinics (Sao Paulo) 2011;66:17–20.
[6] Carvalho NS, Helfer TM, Serni PO, et al. Postnatal outcomes of infants with gastroschisis: a 5-year follow-up in a tertiary referral center in Brazil. J Matern Fetal Neonatal Med 2016;29:418–22.
[7] Wesonga AS, Fitzgerald TN, Kabuye R, et al. Gastroschisis in Uganda: opportunities for improved survival. J Pediatr Surg 2016;51:1772–7.
[8] Apfeld JC, Sm Wren, Macheka N, et al. Infant, maternal, and geographic factors influencing gastroschisis related mortality in Zimbabwe. Surgery 2015;158:1475–80.
[9] Niles SGM, Mitchell-Fearon K, Gill MI, et al. Mortality-related factors in gastroschisis. J Pediatr Surg 2017;52:530–3.
[10] Vilela PC, de Amorim MMR, Falbo GH, et al. Risk factors for adverse outcome of newborns with gastroschisis in a Brazilian hospital. J Pediatr Surg 2001;36:559–64.
[11] Baerg J, Kaba G, Tonita J, et al. Gastroschisis: a sixteen-year review. J Pediatr Surg 2003;38:771–4.
[12] Holland AJ, Walker K, Badawi N. Gastroschisis: an update. Pediatr Surg Int 2010;26:871–8.
[13] Youssef F, Laberge J-M, Puligandla P, et al. Determinants of outcomes in patients with simple gastroschisis. J Pediatr Surg 2017;52:710–4.
[14] Miranda ME, Tatsuo ES, Guimaraes JT, et al. Use of a plastic hemoderivative bag in the treatment of gastroschisis. Pediatr Surg Int 1999;15:442–4.
[15] Schlueter RK, Azarow KS, Hines AG, et al. Identifying strategies to decrease infectious complications of gastroschisis repair. J Pediatr Surg 2015;50:98–101.
[16] Allotey J, Davenport M, Njere I, et al. Benefit of preformed silos in the management of gastroschsisi. Pediatr Surg Int 2007;23:1065–9.
[17] Alves FMS, Miranda ME, de Aguiar MJB, et al. Nutritional management and postoperative prognosis of newborns submitted to primary surgical repair of gastroschisis. J Pediatr 2016;92:268–75.
[18] Kunz SN, Tieder JS, Whitlock K, et al. Primary fascial closure versus staged closure with silo in patients with gastroschisis: a meta-analysis. J Pediatr Surg 2013;48:845–57.
[19] Youssef F, Gorgy A, Arbash G, et al. Flap versus fascial closure for gastroschisis: a systematic review and meta-analysis. J Pediatr Surg 2016;51:718–25.
[20] Bruzoni M, Jaramillo JD, Dunlap JL, et al. Sutureless vs sutured gastroschisis closure: prospective randomized controlled trial. J Am Coll Surg 2017;224:1091–6.