

# Early severe hypoalbuminemia is an independent risk factor for intestinal failure in gastroschisis

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Accepted: 26 April 2011 / Published online: 20 May 2011  
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## Abstract

**Objective** This study attempted to evaluate the association of early hypoalbuminemia with the risk of intestinal failure in gastroschisis patients.

**Patients and methods** Neonates with gastroschisis treated at a tertiary children's hospital over a 10-year period were initially categorized into groups based on the lowest serum albumin measurement during the first 7 days of life. Based on preliminary analysis, patients with serum albumin <1.5 g/dL were considered to have early severe hypoalbuminemia. Intestinal failure was defined as inability of the patient to wean from parenteral nutrition (PN) during the initial hospital admission, thus requiring home PN. Logistic regression modeling was performed to adjust for sex, gestational age, birth weight, and concomitant intestinal complications.

**Results** One hundred and thirty-five gastroschisis patients were included, of whom 21% had early severe hypoalbuminemia. Patients with early severe hypoalbuminemia had a significantly higher risk of intestinal failure compared to those with higher albumin levels (26 vs. 8%,  $p = 0.015$ ). On multivariable logistic regression modeling, early severe hypoalbuminemia was strongly associated with intestinal failure (OR 6.4, 95% CI 1.8–23.3,  $p = 0.005$ ).

**Conclusions** Early severe hypoalbuminemia appears to be an independent risk factor for long-term intestinal compromise rather than merely an indicator of overall illness. Further interventional studies are needed to determine whether clinical protocols utilizing judicious fluid administration, exogenous albumin, and early enteral feeding can improve clinical outcomes in gastroschisis.

**Keywords** Gastroschisis · Hypoalbuminemia · Parenteral nutrition · Intestinal motility · Critical care

## Introduction

Despite survival rates of 90–95% with modern pediatric surgical care, gastroschisis remains a highly morbid and costly condition to treat. Neonates with gastroschisis demonstrate prolonged intestinal dysfunction and require parenteral nutrition for an average of 28 days after abdominal wall closure [1–4]. Some patients progress to intestinal failure, in which full enteral feeding cannot be attained and long-term parenteral nutrition must be provided. Intestinal failure in gastroschisis is usually multifactorial, arising from dysmotility, associated intestinal anomalies, and loss of intestinal length due to necrosis or surgical resection [5, 6].

Neonates with gastroschisis commonly present with low levels of serum albumin, which are thought to result from fetal protein loss into amniotic fluid through exposed intestine [7]. Hypoalbuminemia has been shown to be associated with bowel edema, prolonged intestinal ileus, and poor outcomes in multiple gastrointestinal conditions [8–11], but the effect of various degrees of hypoalbuminemia on intestinal dysfunction in gastroschisis is unclear. The purpose of the present study was to evaluate the effect

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of severe hypoalbuminemia on gastroschisis outcomes, attempting to identify a threshold value of serum albumin below which clinical outcomes are affected.

## Methods

This was a retrospective cohort study of gastroschisis patients admitted to The Children's Hospital of Alabama (TCH), the largest pediatric tertiary care center in the state of Alabama. All neonates with gastroschisis admitted to TCH from 1999 through 2009 with at least one serum albumin measurement during the first week of life were included.

Patient characteristics, albumin levels, and clinical outcomes were determined by chart review. Complex gastroschisis was defined as concomitant intestinal atresia, necrosis, perforation, trauma, or volvulus. Outcomes of interest included time to abdominal wall closure, time to first enteral feeding, number of in-hospital parenteral nutrition days, and intestinal failure defined as a long-term parenteral nutrition (PN) requirement continuing after hospital discharge (i.e. home parenteral nutrition). Although there was no written protocol in place, patients were routinely sent home on PN if they were not tolerating goal feeds 3–4 weeks after closure, had no immediately correctable causes for feeding intolerance, and were not expected to achieve goal feeds within the near future. This approach did not change throughout the study period.

The primary independent variable of interest was the lowest serum albumin level during the first week of life. To identify a threshold albumin value at which clinical outcomes changed, patients were initially categorized into four groups, roughly corresponding to the quartiles of the serum albumin nadir distribution: <1.5, 1.5 to 1.9, 2.0 to 2.5, and >2.5 grams per deciliter (g/dL). Outcomes were compared between the four groups using Wilcoxon rank-sum tests and Fisher's exact tests for continuous and categorical variables, respectively. Based on these initial comparisons, early severe hypoalbuminemia was defined as a serum albumin <1.5 g/dL during the first week of life. Characteristics and outcomes were compared for patients with and without early severe hypoalbuminemia using the statistical tests described above.

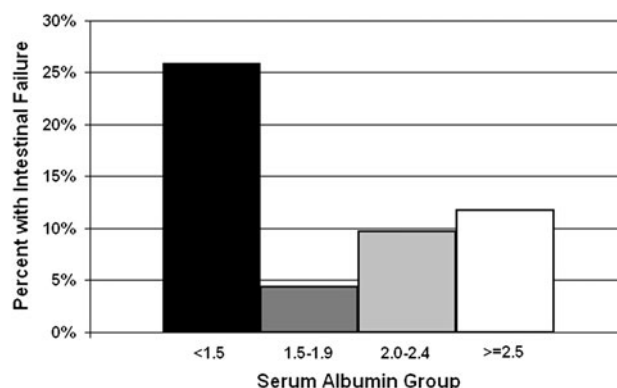
Logistic regression was used to investigate the independent association of early severe hypoalbuminemia with intestinal failure. The regression model included all clinically significant variables, regardless of statistical significance on bivariate analysis: complex versus simple gastroschisis, birth weight, gestational age, and sex. Additional models were also evaluated, using alternate definitions of severe hypoalbuminemia as albumin <2.0 and <2.5 g/dL, in order to verify the uniqueness of the 1.5 g/dL threshold.

## Results

During the 10-year study period, 177 neonates with gastroschisis were admitted to TCH. One hundred and thirty-five (81%) had at least one serum albumin measurement during the first week of life and were included in this study. Overall, the median albumin nadir during the first week of life was 1.9 g/dL (range <1.0–3.3 g/dL). Twenty-nine patients (21%) with serum albumin measurement <1.5 g/dL during the first week of life, approximately corresponding to the lowest quartile, were categorized as having early severe hypoalbuminemia. When patients were categorized into four groups based on albumin levels, the incidence of intestinal failure in the <1.5 g/dL group was significantly higher than the other three groups (Fig. 1).

Patient characteristics and outcomes for those with and without early severe hypoalbuminemia are shown in Table 1. There were no significant differences in baseline characteristics between the two groups. Patients with severe hypoalbuminemia required more days to definitive closure (median 7 vs. 5 days,  $p = 0.029$ ), had delayed initiation of enteral feeding (median 21 vs. 16 days,  $p = 0.050$ ), and were much more likely to progress to intestinal failure and home parenteral nutrition (26 vs. 8%,  $p = 0.015$ ).

Table 2 provides results of logistic regression modeling for the risk of intestinal failure, using a model that included early severe hypoalbuminemia, complex versus simple gastroschisis, birth weight, gestational age, and sex. Early severe hypoalbuminemia was strongly associated with intestinal failure (OR 6.4, 95% CI 1.8–23.3,  $p = 0.005$ ). Complex gastroschisis was the strongest predictor of intestinal failure (OR 6.7, 95% CI 1.6–28.9,  $p = 0.011$ ), whereas sex, low birth weight (<2,500 g), and pre-term delivery (gestational age <35 weeks) did not reach significance. Results of the model were similar when birth weight and gestational age were modeled as continuous variables. When alternate threshold values for severe



**Fig. 1** Risk of intestinal failure by serum albumin group

**Table 1** Comparison of patients with and without early severe hypoalbuminemia ( $n = 135$ )

	Severe hypoalbuminemia ( $n = 29$ )	No severe hypoalbuminemia ( $n = 106$ )	$p$
<i>Characteristics</i>			
Gestational age, weeks	37 (27–39)	37 (29–40)	0.902
Birth weight, g	2,395 (800–3,860)	2,490 (850–3,800)	0.123
Female sex	59	56	0.835
Complex gastroschisis	10	13	1.0
Atresia	3	7	
Necrosis	3	2	
Perforation/trauma	0	1	
Volvulus	0	0	
Some combination of above	3	4	
<i>Outcomes</i>			
Days to abdominal closure	7 (0–11)	5 (0–56)	0.029
Days to first enteral feeding	21 (9–41)	16 (4–92)	0.050
Hospital days on parenteral nutrition	37 (12–150)	33 (2–135)	0.170
Necrotizing enterocolitis after closure	7	8	1.0
Sepsis	14	19	0.784
Length of hospital stay, days	50 (12–150)	39 (7–150)	0.372
Intestinal failure <sup>a</sup>	26	8	0.015
Death	3	2	0.519

Serum albumin <1.5 during the first week of life. Continuous and categorical variables presented as median (range) and percentage, respectively

<sup>a</sup> Requirement for home parenteral nutrition

hypoalbuminemia were modeled, neither an albumin threshold of <2.0 g/dL (OR 1.3, 95% CI 0.4–4.3,  $p = 0.689$ ) nor <2.5 g/dL (OR 0.9, 95% CI 0.2–5.0,  $p = 0.905$ ) was predictive of intestinal failure. Of the 17 patients with complicated gastroschisis, three had severe hypoalbuminemia and 14 did not. Four patients (one with and three without severe hypoalbuminemia) required resection of long segments of intestine; the remainder required either no resection or short-segment resection. Including estimates of remaining intestinal length in the models did not change the substance of the results.

## Discussion

Our data demonstrated that gastroschisis patients whose serum albumin fell below 1.5 g/dL during the first week of life were much more likely to progress to intestinal failure than those whose albumin levels remained at or above

1.5 g/dL. Other cutoff values for low serum albumin had no effect on outcome. Although complex gastroschisis (i.e. the presence of other intestinal abnormalities) was the strongest predictor of intestinal failure, the effect of severe hypoalbuminemia remained strongly significant after adjustment for concomitant intestinal anomalies and other clinically important variables.

The underlying reason for this association is unclear. Severe hypoalbuminemia may simply represent a marker for more extensive amniotic fluid exposure with its associated inflammatory intestinal peel and malnutrition. It is also possible that hypoalbuminemia reflects over-aggressive fluid resuscitation with resulting intestinal edema and increased intraabdominal pressure. However, severe hypoalbuminemia may also play a causative role in prolonged intestinal dysfunction.

We observed that severely hypoalbuminemic patients required, on average, 2 days longer to achieve abdominal wall closure and 5 days longer to the first attempt at enteral

**Table 2** Results of logistic regression model for intestinal failure

Risk factor	Odds ratio	95% Confidence interval	$p$
Early severe hypoalbuminemia <sup>a</sup>	6.4	1.8–23.3	0.005
Complex gastroschisis	6.7	1.6–28.9	0.011
Gestational age <35 weeks	2.0	0.4–9.9	0.411
Low birth weight, <2,500 g	1.1	0.3–4.2	0.902
Female sex	0.4	0.1–1.4	0.167

<sup>a</sup> Serum albumin <1.5 g/dL during the first week of life

feeding, suggesting that hypoalbuminemia produced intestinal edema and prolonged ileus. Previous studies have shown that low albumin levels ( $<3.0$  g/dL) are associated with poorer enteral feeding tolerance in pediatric surgical patients [8], whereas other studies have shown no difference in weight gain or nutritional parameters for hypoalbuminemic patients ( $<2.8$  g/dL) on parenteral nutrition [12]. Interventional studies of albumin replacement in pediatric surgical patients have been inconclusive and limited by small sample size, low power, variable definitions of hypoalbuminemia, and heterogeneous study populations [13, 14].

Our study has several limitations. First, 20% of patients treated at TCH during the study period could not be included in the study because no serum albumin measurements were obtained. We were also missing time of first feeding and abdominal wall defect size data for approximately 10% of patients. Second, exogenous albumin was given to some patients in this study, but it was not routinely administered and we were not able to access records that would allow us to include this variable in the analysis.

## Conclusion

In conclusion, while low serum albumin levels are nearly universal in gastroschisis, patients with albumin levels  $<1.5$  g/dL during the first week of life appear to experience worse outcomes. Because the characteristics of the severe hypoalbuminemia group did not differ from the rest of the study cohort, severe hypoalbuminemia appears to represent an independent risk factor for prolonged intestinal compromise rather than merely an indicator of overall illness. Interventional studies are justified to determine whether clinical protocols utilizing judicious fluid administration, exogenous albumin, and early enteral feeding can improve clinical outcomes for gastroschisis patients.

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