

## Risk factors for gastroesophageal reflux disease in very low birth weight infants with bronchopulmonary dysplasia

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### Abstract

**Objective:** To assess risk factors for gastroesophageal reflux disease (GERD) in very low birth weight infants with bronchopulmonary dysplasia.

**Methods:** A case-control study was carried out in 23 cases and 23 control subjects with bronchopulmonary dysplasia submitted to 24-hour esophageal pH monitoring between January 2001 and October 2005. Cases and controls were compared for gestational age, birth weight, gender, use of antenatal steroids, duration of assisted ventilation, duration of oxygen therapy, length of gastric tube use, administration of xanthines, postconceptual age, and weight at esophageal pH monitoring. Multiple logistic regression analysis was used to establish the odds ratio (OR) with a 95% confidence interval (95%CI).

**Results:** None of the groups (with and without GERD) showed statistically significant differences in terms of demographic variables and postnatal outcome, use of antenatal and postnatal corticosteroids, or in terms of caffeine use and duration of mechanical ventilation and oxygen therapy. However, feeding intolerance (OR = 6.55; 95%CI 1.05-40.8) and length of gastric tube use (OR = 1.67; 95%CI 1.11-2.51) turned out to be risk factors for GERD. Postconceptual age at the time of pH monitoring (OR = 0.02; 95%CI < 0.001-0.38) was regarded as a protective factor against GERD.

**Conclusion:** The data obtained allow inferring that prolonged gastric tube use and feeding intolerance increase the risk for GERD. On the other hand, older postconceptual age at the time of pH monitoring reduces the risk for GERD in preterm infants with bronchopulmonary dysplasia weighing less than 1,500 g.

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### Introduction

Gastroesophageal reflux disease (GERD) is the most common esophageal disorder observed in the neonatal period<sup>1</sup> and accounts for prolonged hospital stay of preterm infants.<sup>2-4</sup> Its incidence ranges from 2.8 to 10% among very low birth weight (VLBW) infants.<sup>5,6</sup> The reported frequency of GERD among infants with bronchopulmonary dysplasia (BPD) is

quite high, ranging from 18.4<sup>5</sup> to 63%,<sup>7,8</sup> although diagnostic criteria have not been consistent.

Several aspects of GERD are controversial or poorly known. Some studies suggest that GERD may play a role in the pathogenicity of and recovery from BPD.<sup>9-11</sup> Nevertheless, the association of GERD with respiratory symptoms, such as apnea<sup>12</sup> or pulmonary aspiration in BPD,<sup>13</sup> is often brought into question.

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In addition to microaspiration and macroaspiration, several other mechanisms have been suggested to explain the relationship between chronic pulmonary diseases and gastroesophageal reflux, such as vagal reflex stimulation, increase in bronchial hyperresponsiveness and neurogenic inflammation due to the release of tachykinins.<sup>4,14</sup>

Multiple esophageal intraluminal impedance has recently demonstrated that healthy preterm infants often present with reflux into the proximal esophagus<sup>15</sup> and that mechanically ventilated VLBW infants often have aspiration of gastric contents into the lungs from their very first day of life.<sup>11</sup> Besides these recent bodies of evidence, the improvement of respiratory symptoms after clinical and/or surgical antireflux procedures<sup>5,10,13</sup> suggests that GERD might deteriorate the outcome of BPD.

For fear of possible clinical repercussions, several neonatologists worldwide have treated GERD in approximately 20% of preterm infants aged less than 34 weeks.<sup>16,17</sup> The vast majority of these patients are not submitted to confirmatory tests and are therefore treated based on empirical evidence.<sup>16,17</sup>

Despite the growing interest in investigating GERD in the neonatal period, there has been a dearth of information about predisposing factors in preterm infants with BPD. This information may allow for an early diagnosis as well as for more appropriate investigation and treatment. The aim of this study was to assess risk factors for GERD in preterm infants with BPD.

## Methods

An observational case-control study using unpaired data was conducted at the teaching hospital of the School of Medicine of Universidade Estadual de Campinas (UNICAMP), Brazil. All infants with birth weight  $\leq 1,500$  g and BPD by Bancalari<sup>18</sup> criteria that had clinical suspicion of GERD and were submitted to 24-hour pH monitoring of the distal esophagus during their stay in the neonatal unit between January 2001 and October 2005 were selected.

Those VLBW infants who had a reflux index (RI)  $\geq 10\%$ <sup>19</sup> were designated as cases. The control group consisted of infants with BPD who were admitted to the neonatal unit at the same time as cases, with an RI  $< 10\%$ . One control was selected for each case based on the timing of their birthdates.

Those patients whose esophageal pH monitoring lasted less than 18 hours or those under nonstandard conditions, infants on oxygen therapy around the 28th day of life due to transient deterioration of their respiratory condition, caused by other conditions such as sepsis and heart disease, and infants being treated with corticosteroids, antacids or prokinetics during examination were excluded from the study. Infants diagnosed with malformations of the digestive tract, defects in abdominal wall closure, genetic syndromes and chromosome disorders were also excluded from the analysis.

The use of xanthines (caffeine, aminophylline) at the time of examination was not an exclusion criterion.

Demographic variables such as birth weight, gestational age (GA), gender, and appropriate weight for gestational age were analyzed. Other analyzed variables included the following: use of antenatal corticosteroids, 5-minute Apgar score, abnormal neurological findings, structural central nervous system anomalies, type of respiratory failure in the first week of life (hyaline membrane disease, transient tachypnea of the newborn, pulmonary hypertension, intrauterine pneumonia), feeding intolerance, weight and postconceptual age at the time of examination, length of gastric tube use and of mechanical ventilation, length of oxygen therapy, use of postnatal corticosteroids and length of xanthine therapy. Exposure to the analyzed variables was considered up to the day of pH monitoring.

Feeding intolerance was defined as difficulty in the progression of food transition from parenteral to enteral nutrition, with consequent suspension of at least one breastfeeding in the presence of one or more episodes of (bilious or milk) vomiting, abdominal distension, or bilious or milk residuals, the latter of which account for 50% or more of the volume of the previous feeding.

## 24-hour esophageal pH monitoring

24-hour esophageal pH monitoring was performed by one of the authors under standard conditions using Digitrapper MKIII<sup>®</sup> (Synectics Medical). Esophageal pH readings were made with semidisposable 1.5-mm catheters, using an antimony electrode (Synectics Medical) in the distal third of the esophagus, 3 cm above the point at which gastric pH shifts to esophageal pH. The final position of the electrode was confirmed by chest X ray, and was maintained at the height of the T6 and T7 vertebral bodies. At the end of pH monitoring, the data were recorded into a computer and analyzed by EsopHogram<sup>®</sup> (Gastrosoft Inc).

The exam was conducted under standardized conditions: breastmilk or infant formula feeding using a volume of 130-140 mL/kg/day, given either orally or via a gastric tube every 4 hours, supine position throughout the examination, and non-mechanically ventilated infants.

## Data analysis

The chi-square test and Fisher's exact test were used to check the association with the categorical variables, whereas the Mann-Whitney U test<sup>20</sup> was used for numerical variables. Thereafter, a backward stepwise multiple univariate logistic regression analysis was carried out.<sup>21</sup>

The Statistical Analysis System for Windows, version 8.2 (SAS Institute Inc, 1999-2001, Cary, NC, EUA) was employed for data analysis. P values  $< 0.05$  were considered to have statistical significance. The study protocol was approved by

**Table 1** - Distribution of demographic variables of the study population

	Cases (n = 23)	Controls (n = 23)	p
Median BW (g)	1,036.7±230.7 (1,025.0)	914.3±241.2 (880.0)	0.075*
Range	655.0-1,470.0	520.0-1,440.0	
Median GA (weeks)	28.0±2.1 (27.0)	27.6±1.8 (27.0)	0.499*
Range	24.0-32.0	25.0-32.0	
Male (n)	15	13	0.545 <sup>†</sup>
AGA (n)	19	16	0.299 <sup>†</sup>

AGA = appropriate for gestational age; BW = birth weight; g = grams; GA = gestational age; n = number of cases.

Values expressed as mean ± SD.

\*Mann-Whitney test.

<sup>†</sup> Chi-square test.

the Research Ethics Committee of the School of Medicine of UNICAMP.

## Results

A total of 55 infants with BPD submitted to esophageal pH monitoring for the diagnosis of GERD were identified. Of these, nine were excluded: nonstandard examination procedures or due to monitoring time less than 18 hours (n = 4), medication use (n = 2), congenital malformations of the digestive tract (n = 1) and birth outside the teaching hospital of the School of Medicine of UNICAMP (n = 1). Among the 46 remaining infants, 23 were diagnosed with GERD and 23 were placed in the control group. The mean and standard deviation of the RI for cases and controls amounted to 19.7±7.0% and 4.4±2.2%, respectively.

Cases and controls were similar in terms of demographic variables, although cases tended to have a greater birth weight (Table 1).

The remaining variables showed no association with the groups (Table 2). Twenty one infants had lung disease in the first week of life (Table 2), in both groups, and four developed BPD after mechanical ventilation due to apnea.

Thirteen infants in the case group and 11 in the control group showed clinical signs of feeding intolerance, as follows: milk or bilious residuals in 12 cases and 11 controls, vomiting in one case and in none of the controls, abdominal distension in two cases and in one control. Three infants had more than one sign of feeding intolerance.

The multivariate logistic regression analysis adjusted for birth weight, GA and presence of central nervous system anomalies revealed that feeding intolerance and total length of gastric tube feeding were risk factors for GERD. Postconceptional age at the time of examination was a protective factor (Table 3).

## Discussion

This study showed that feeding intolerance and prolonged gastric tube use are risk factors for GERD in preterm infants with BPD. Older postconceptional age at the time of esophageal pH monitoring was a protective factor against GERD.

No publications with similar results were found in the review of the literature. This may be due to the fact that few neonatal units systematically investigate GERD in small preterm infants using esophageal pH monitoring.<sup>16,17</sup>

A previous case-control study did not intend to determine the risk factors, but assessed growth and length of hospital stay.<sup>2</sup> Therefore, the authors compared 23 subjects and the same number of controls, paired according to GA, birth weight, gender and severity of BPD. The study found significant differences in the time required for attainment of full oral feeding in cases, possibly due to the involvement of the oropharyngeal motor development. Hospital stay and the postconceptional age at discharge from hospital were longer among cases than among controls.<sup>2</sup> For case-control studies, it is recommendable that both groups be homogeneous (similar), especially with regard to diseases or characteristics other than the risk factors to be investigated. Since neurological diseases, which knowingly predispose to GERD,<sup>4</sup> prevail among controls, a regression analysis was used to avoid possible confounding biases that could hinder the identification of risk factors. This also applies to the adjustments made for BW and GA.

Feeding intolerance is an entity that has not been consistently defined.<sup>22</sup> In this study, not only those infants with vomiting and regurgitation were regarded as intolerant to feeding, but also those with abdominal distension and pregavage residuals during the transition from parenteral to enteral nutrition on the first 15-20 days of life. These symptoms, ascribed to preterm birth,<sup>22</sup> appeared several days or weeks before clinical suspicion of GERD (pH monitoring was performed at around the 7th week of life). Feeding intolerance results from

**Table 2** - Variables related to neonatal outcome, procedures and medications used in VLBW infants with BPD and with or without GERD

	Cases (n = 23)	Controls (n = 23)	p
Use of antenatal corticosteroids (n)	12	14	0.551*
5-minute Apgar score < 3 (n)	2	0	NP
Lung disease in the 1st week of life (n)	21	21	1.00 <sup>†</sup>
Abnormal neurological findings (n)	17	16	0.743*
Presence of CNS disorder (n)	5	9	0.199*
Presence of feeding intolerance (n)	13	11	0.555*
Use of caffeine (n)	20	21	1.00 <sup>†</sup>
Median caffeine use (days)	21.6±14.4 (22.0)	28.3±15.0 (28.0)	0.113‡
Use of gastric tube (n)	23	23	NP
Median length of gastric tube use (days)	50.9±18.4 (48.0)	60.4±20.1 (58.0)	0.078‡
Use of postnatal corticosteroids (n)	6	9	0.345*
Median length of MV (days)	15.0±17.6 (8.0)	21.1±18.6 (18.0)	0.143‡
Median length of oxygen therapy (days)	32.2±13.7 (29.0)	35.7±16.0 (42.0)	0.322‡
Median weight at the time of examination (g)	1,806.5±410.8 (1,880.0)	1,812.2±415.7 (1,820.0)	0.775‡
Median PCA at the time of examination (weeks)	35.2±2.4 (35.0)	36.4±3.3 (36.0)	0.119‡

BPD = bronchopulmonary dysplasia; CNS = central nervous system; GERD = gastroesophageal reflux disease; PCA = postconceptual age; n = number of cases; NP = not performed; MV = mechanical ventilation; VLBW = very low birth weight.

Values expressed as mean ± standard deviation.

\* Chi-square test.

<sup>†</sup> Fisher's exact test.

‡ Mann-Whitney test.

**Table 3** - Multiple logistic regression analysis adjusted for BW, GA and CNS anomalies

	95%CI	OR	P
Feeding intolerance	1.050-40.858	6.550	0.044
Length of gastric tube use	1.118-2.517	1.677	0.012
PCA at the time of examination	< 0.001-0.388	0.019	0.009

95%CI = 95% confidence interval; BW = birth weight; CNS = central nervous system; GA = gestational age; OR = odds ratio; PCA = postconceptual age.

a motor digestive disorder related to a very immature fasting and postprandial intestinal movement pattern<sup>23</sup> and to delayed gastric emptying.<sup>24-26</sup> Transient relaxations of lower esophageal sphincter (LES) associated with acid reflux caused by an increase in intra-abdominal pressure is the major mechanism implied in the pathophysiology of GERD in pre-term infants.<sup>27,28</sup> Even if some doubt is raised about delayed gastric emptying as an additional mechanism in the genesis of GERD,<sup>27,28</sup> for some individuals, delayed gastric emptying may be the triggering mechanism for transient relaxation.<sup>25</sup>

In this study, the probability of GERD increased by 1.67 times (95%CI of 1.11-2.51) for every additional day of gastric tube use. This finding is surprising, since when only the

bivariate analysis results are taken into consideration, gastric tube use duration averages 60.4±20.1 days in the control group *versus* 50.9±18.4 among cases, with a p value of 0.078. However, multiple analysis, with adjustment, eliminated possible confounding factors. The fact that gastric tube feeding is regarded as a risk factor corroborates the findings of Peter et al.,<sup>29</sup> who found a nearly twice as high number of reflux episodes as when a tube was placed in the stomach rather than in the esophagus, probably tampering with the mechanisms of lower esophageal sphincter contention.<sup>29</sup>

In our study, the statistical significance of postconceptual age at the time of esophageal pH monitoring can be explained

by the ontogeny of LES tone development, given that it is still underdeveloped at birth. The elevation in pressure occurs progressively up to the 6th or 7th week of extrauterine life when, regardless of GA or BW, a sphincter high-pressure zone builds up, which has a higher capacity to avert reflux episodes.<sup>30</sup> The antenatal use of corticosteroids predisposes to GERD in preterm infants;<sup>31,32</sup> nevertheless, the results of the present study do not ratify this finding, possibly due to the small sample size used. Moreover, xanthines are a risk factor for GERD, as they change LES tone and increase the gastric production of hydrochloric acid,<sup>4</sup> but they were not statistically significant in this study, supposedly because the sample included very immature infants with a high frequency of xanthine use (89%), characteristics that are associated with BPD.

Demographic and neonatal outcome variables were not regarded as risk factors for GERD in this study. Preterm birth is a commonly referenced predisposing factor for GERD.<sup>4,33</sup> The lack of this result in our study can be attributed to the very small variation in GA among the sampled infants, which is a specific characteristic of BPD.

Recently, a reliable method has demonstrated that there is aspiration of the gastric contents in VLBW infants during ventilatory support (28 days or more), which leads to the assumption that gastroesophageal reflux may play a role in the pathophysiology of BPD.<sup>11</sup> Previous reports exhibit discrepant results regarding the effects of ventilatory support and GERD on this age group.<sup>4,34</sup>

A prospective cohort study design would be more appropriate for the identification of disease-related factors. However, it is difficult to have a large patient population of extremely preterm infants with BPD in single-center studies, given the high mortality rate. Thus, the small number of available cases was suitable for a case-control study. The analysis of our patient population started in January 2001, when pH monitoring began to be performed in the supine position only. The small patient population, without sample size calculation, may have hindered the identification of other risk factors and also yielded wide confidence intervals.

This study allows inferring that every additional day of gastric tube use (OR 1.67; 95%CI 1.11-2.51) and the occurrence of feeding intolerance (OR 6.55; 95%CI 1.05-40.8) in VLBW preterm infants with BPD increase the likelihood of GERD. On the other hand, postconceptual age at the time of pH monitoring (OR 0.02; 95%CI < 0.001-0.38) reduces the chance of GERD diagnosis. Therefore, measures that help shorten the length of gastric tube use can reduce specific complications as well as the risk for GERD and its consequences. The same applies to nutritional measures or to the use of drugs to treat feeding intolerance.

The search for GERD markers in infants with BPD may improve diagnostic certainty and the quality of care provided by allowing for early treatment, thus reducing morbidity and the length of hospital stay.

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