Are Infants with Bronchopulmonary Dysplasia Prone to Gastroesophageal Reflux? A Prospective Observational Study with Esophageal pH-Impedance Monitoring

Stefano Nobile, MD, PhD, Carmine Noviello, MD, PhD, Giovanni Cobellis, MD, PhD, and Virgilio Paolo Carnielli, MD, PhD

Objective To perform an observational cohort study with esophageal pH-multichannel intraluminal impedance (pH-MII) monitoring in symptomatic preterm infants with and without bronchopulmonary dysplasia (BPD).

Study design We prospectively studied 46 infants born ≤32 weeks gestational age: 12 infants with BPD and 34 infants without BPD. Each patient had symptoms consistent with gastroesophageal reflux and had 24-hour pH-MII, which were compared between BPD and non-BPD by univariate analysis and quantile regression analysis.

Results Demographic and clinical characteristics were similar between infants with and without BPD, except for fluid administration (145 vs 163 mL/kg/d, $P = .003$), length of stay (92 vs 69 days, $P = .019$), and time to achieve complete oral feeding (76 vs 51 days, $P = .013$). The analysis of 1104 hours of pH-MII tracings demonstrated that infants with BPD compared with infants without BPD had increased numbers of pH-only events (median number 21 vs 9) and a higher symptom sensitivity index for pH-only events (9% vs 4.9%); the number and characteristics of acid, weakly acid, nonacid and gas gastroesophageal reflux events, acid exposure, esophageal clearance, and recorded symptoms did not significantly differ between the 2 groups.

Conclusions The increased number of (and sensitivity for) pH-only events among infants with BPD may be explained by several factors, including lower milk intake, impaired esophageal motility, and a peculiar autonomic nervous system response pattern. *(J Pediatr 2015;167:279-85)*.

Symptomatic gastroesophageal reflux (GER) has been reported as a common condition among preterm infants and can influence growth, length of hospital stay, and respiratory outcome.[1] Bronchopulmonary dysplasia (BPD), characterized by persistent airway inflammation and/or impaired lung alveolarization and growth, is a major complication of prematurity, affecting 30% of extremely low birth weight infants.[2,3] Infants with BPD may have an increased risk of GER because of respiratory effort and transient increases in intra-abdominal pressure related to coughing, crying, and air flow obstruction, which can lead to a decrease in lower esophageal sphincter (LES) tone and an increased occurrence of transient LES relaxations.[4-6] The use of respiratory stimulants (caffeine) may increase gastric acid secretion, decrease LES pressure, and exacerbate GER.[7,8]

The role of GER in the pathogenesis and recovery from BPD is controversial.[1,6,9,10] Infants with BPD are thought to have a predisposition for GER as some studies reported a high prevalence of GER among infants with BPD, possibly because of microaspirations or reflex mechanisms. Improvements in the respiratory status of infants with BPD have been reported after medical or even surgical antireflux therapy is instituted.[5,11-15] However, there are increasing concerns about the safety and efficacy of antireflux drugs among preterm infants, which are increasingly used to treat presumed (symptomatic) but not proven GER.[16]

Combined esophageal pH-multichannel intraluminal impedance (pH-MII) has emerged as the state-of-the-art method to diagnose GER.[17] This method detects and characterizes the retrograde esophageal flow and its subsequent anterograde clearance into the stomach. Therefore, the height, duration, and clearance of refluxate can be reliably characterized to define the presence and pattern of GER events and to find out associations between symptoms and reflux episodes.

Given the unclear predisposition for GER among infants with BPD and the few studies about this topic, we used pH-MII to test if symptomatic infants with BPD had more GER than symptomatic infants without BPD.

BPD	Bronchopulmonary dysplasia	NICU	Neonatal intensive care unit
CPAP	Continuous positive airway pressure	pH-MII	pH-multichannel intraluminal impedance
GA	Gestational age	PMA	Postmenstrual age
GER	Gastroesophageal reflux	SAP	Symptom-associated probability
LES	Lower esophageal sphincter	SI	Symptom index
MII	Multichannel intraluminal impedance	SSI	Symptom sensitivity index

From the Maternal and Child Department, Salesi Children's Hospital, Ancona, Italy

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Methods

This observational cohort study was conducted with infants born ≤32 weeks gestational age (GA) between March 2010 and March 2014 at a regional tertiary-care neonatal intensive care unit (NICU). Inclusion criteria were GA ≤32 weeks at birth and clinical symptoms suspected to be GER-related (bradycardia, apnea, desaturations, and regurgitations). Bradycardia was defined as heart rate ≤80 bpm, desaturation as peripheral oxygen saturation ≤80% (measured by pulse oximeter), and apnea as cessation of breathing for at least 20 seconds (5 seconds if there was a concurrent desaturation).[18] Infants were considered for GER evaluation if they presented at least 5 symptoms per day (apnea, desaturations, bradycardia, and regurgitations close to feeds as documented by nursing charts and confirmed by the attending physician) and whose symptoms were not due to other causes (eg, sepsis, seizures, and swallowing incoordination, which were ruled out after careful clinical and laboratory evaluations). Exclusion criteria were major malformations, death or discharge to other hospitals, need for any ventilatory support (ie, nasal continuous positive airway pressure [CPAP], or endotracheal ventilation) at the time of study, and lack of parental consent. A total of 395 infants ≤32 weeks GA were born in the study period; 9 were excluded for major malformations, 23 died before 36 weeks postmenstrual age (PMA), and 144 were transferred to other hospitals before 36 weeks PMA. Of the remaining 219 patients, 44 (12.1% of live infants) were diagnosed with BPD according to Walsh et al if they failed an oxygen reduction test at 36 (±1) weeks PMA.[19] Infants who had clinical symptoms consistent with GER and whose parents agreed to the pH-MII testing were studied: 12 out of 44 infants with BPD (10 did not have symptoms, 14 were ventilated or on nasal CPAP, and 8 lacked consent) and 34 out of 175 without BPD (108 did not have symptoms, and 33 lacked consent). No surgeries were performed for GER. Local Institutional Review Board approved the study.

pH-MII Methods

Each patient had 24-hour pH-MII performed with an esophageal probe connected with a pH-MII device (Ohmega MMS, Enschede, The Netherlands). During the study, all infants were breathing spontaneously, were receiving intermittent bottle or orogastric feeds, and were not on antireflux or antacid medications, inhaled medications, or diuretics. Infants were kept supine or in lateral decubitus during pH-MII. The neonatal pH-MII probe (pHTip EI0634; Unisensor, Attikon, Switzerland) had 6 impedance channels (Z1-Z6) (7 impedance rings positioned 1.5 cm apart from each other) and 1 pH channel on the tip of the catheter. Prior to each study, the pH-MII probe was calibrated in standard pH buffer solutions of 4.0 and 7.0. The probe was then inserted nasally into the esophagus, and the position verified by chest radiograph. Proper location of the probe was identified as 2-3 cm above the left diaphragm.[20-22] The pH-MII probe was securely taped and connected to the Ohmega system; constant observation and review of the position at the end of the study were assured. pH-MII data were evaluated using manufacturer's software, and each tracing was manually reviewed and validated by the same operator (S.N.).

An acid reflux event was defined as a drop in pH <4 lasting for more than 5 seconds. Liquid reflux was evident when there was a fall in impedance greater than 50% from baseline in at least 2 consecutive channels in an aboral direction. Gas-only reflux was evident as a simultaneous increase in impedance >3000 Ω in any consecutive impedance sites, with 1 site having an absolute value >7000 Ω. Mixed reflux events met both criteria.[23] On the basis of the lowest pH value recorded during each event, reflux events were divided into acid (pH <4, or occurring when the pH was already acidic), weakly acid (pH between 4 and 7), or nonacid (pH >7). All pH drops <4 exceeding 5 seconds, excluding meal periods, registered independently from the impedance reflux events, were considered pH-only events.

Symptoms were documented in real time by NICU nurses who were blinded to the pH-MII recordings. Nurses recorded the beginning and end of each meal and the occurrence of symptoms. An association between symptoms and GER events was considered positive if a symptom occurred within 120 seconds before or after a reflux event.[24] For each study, the following variables were evaluated in accordance with the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition/European Society for Paediatric Gastroenterology, Hepatology and Nutrition GER guidelines and with other studies[6,21,25]: number and pH of reflux episodes, duration of the longest reflux event, number of reflux events lasting >5 minutes, lowest pH, esophageal clearance, acid exposure (area under curve pH <4 in minutes), pH-only events, symptom index (SI), symptom sensitivity index (SSI), and symptom-associated probability (SAP) for liquid and gas refluxes. The SI was calculated as (number of symptoms associated with reflux/number of all symptoms) × 100; the SSI was calculated as (number of refluxes associated with symptoms/total number of refluxes in 24 hours) × 100; the SAP was calculated for acid, nonacid, and gas reflux using MMS software (Medical Measurement Systems, Enschede, the Netherlands) by dividing 24-hour pH data into consecutive 2-minute segments. We determined for each segment whether reflux and/or symptoms occurred. A 2 × 2 contingency table was then constructed in which the numbers of segments with and without symptoms and with and without reflux were tabulated. A χ^2 test was used to calculate the probability (P) that the observed distribution could have been by chance. SAP was calculated as $(1 - P) \times 100\%$ and was considered to be positive when ≥95%.[26,27] The pH-MII study was defined as abnormal if the SI was ≥50%, or the SAP was ≥95%.[25] The number of reflux events reaching the proximal catheters Z1 and Z3, the number of pH-only events, and the associated number of symptoms (within 120 seconds before or after these events) were