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Higher rate of bronchoalveolar lavage culture positivity in children with non-acid reflux and respiratory disorders

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Abstract

The aim of the study was to determine if children with chronic cough or wheezing and more full-column, non-acid reflux have a higher likelihood of a positive bronchoalveolar lavage fluid culture. In a prospective study of 46 children with cough undergoing endoscopy, multichannel intraluminal impedance testing and bronchoscopy, we found that patients who had a positive culture, had significantly more full-column, non-acid gastroesophageal reflux than those who had a negative culture.

Keywords

Gastroesophageal reflux; non-acid reflux; respiratory infections; impedance

Recently, pediatric and adult literature has suggested that patients taking acid suppression therapy may have increased risk of pneumonia [1, 2]. A proposed mechanism of risk is a shift in gastric pH from acid to non-acid, which may result in a change in gastric flora. This change may result in pneumonia if gastric contents are refluxed and aspirated. We therefore hypothesized that patients who have a higher non-acid reflux burden are more predisposed to bacterial infections of the lower airway.

Methods

This is a prospective, cross-sectional study of children 2–18 years with chronic cough or wheezing to determine if gastroesophageal reflux burden predicts a positive bacterial culture of bronchial lavage fluid. Patients were included if they were undergoing simultaneous: (1) bronchoscopy; (2) esophagogastroduodenoscopy (EGD) with biopsies; and (3) multichannel intraluminal impedance (pH-MII) probe placement. Patients were excluded if: (1) they were

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taking antibiotics within 1 week of the procedure; or (2) they had not stopped acid suppression therapy 48 hours prior to procedures. The protocol was approved by the Institutional Review Board, and informed consent was obtained from each family and patient.

Flexible bronchoscopy and endoscopy with biopsies were performed under general anesthesia as previously described [3]. Lavaged fluid was sent for: (1) aerobic and anaerobic cultures; (2) pepsin analyses; and (3) lipid laden macrophage indices [4, 5]. Then, a pH-MII catheter (Sleuth, Sandhill Scientific, Denver, CO) was placed and the location was radiologically confirmed. All patients were admitted for the 24-hour recording.

Reflux Definitions

pH-MII tracings were manually reviewed by a single investigator (R.R.). The pH portion was considered abnormal if the pH was < 4 for $> 6\%$ of the time for children older than 1 year of age [6].

Definitions for acid, non-acid and pH only episodes have been described previously [3]. Full column reflux was defined as an episode that reached the highest pair of impedance sensors. The percentage of full column reflux was determined by dividing the number of full column events by the total number of reflux events. For each patient, the percentage of time that reflux was in the esophagus was calculated by dividing the sum of the bolus clearance times in either the proximal or distal esophagus by the total study duration. A normal pH-MII study was defined as < 73 reflux episodes per 24 hour period [7].

Means (presented with $\pm$ standard deviations) were compared using Student t-tests. Proportions were compared using Fisher exact analyses. Logistic regression was performed to determine predictors of a positive bacterial culture.

Results

Forty six patients, mean age 74 ± 46 months, were included. Twelve of 46 patients (26%) had a positive lavage culture, yielding growth of *Streptococcus pneumoniae* (4), *Moraxella catarrhalis* (1), and *Haemophilus influenzae* (7).

Fifteen percent of patients had abnormal impedance studies and 22% had abnormal findings of pH monitoring. The reflux profiles of patients with and without a positive bacterial culture are shown in Table I; patients with positive cultures had significantly more full-column, non-acid reflux.

Prior medication use in patients with and without a positive culture is shown in Table II. Patients with esophagitis tended to have a negative culture ($p=0.06$). There was no significant difference in the number of patients who were diagnosed with pneumonia in the preceding 6 months between patients with a negative culture and those with a positive culture ($p=0.3$).

After controlling for other variables including PPI and corticosteroid use, the amount of non-acid and full-column gastroesophageal reflux were independent predictors of a positive culture.

Discussion

The present study suggests that full-column, non-acid reflux may change lung flora, even in patients without clinical evidence of pneumonia, and this could be harmful particularly in children with underlying respiratory tract disease. This finding is important as prior pediatric

studies have shown that non-acid reflux can comprise 40% to 89% of reflux disease, even in children who are not taking acid suppression as children are fed frequently, and that full-column, non-acid reflux is an independent risk factor for the genesis of pulmonary symptoms [8, 9]. Our finding that non-acid reflux may change extraesophageal flora is supported by a study in nasogastric-tube fed adults that found bacterial concordance between the gastric flora and oropharyngeal flora and that, when the gastric pH was >4 in the postprandial period, there was a significantly higher rate of recovery of pathogenic bacteria in the stomach [10].

Gastric fluid also is non-acidic in patients taking acid suppressing drugs. In a study of 40 adults, 30 of whom were taking acid suppression, bacterial overgrowth in the stomach occurred in 37% of patients taking acid suppression therapy compared with 10% of patients who were not [11]. Therefore, one could postulate that, if bacteria-laden fluid was aspirated during reflux episodes, the patient could be at risk for lung infections. Pneumonia is a known complication of acid suppression therapy, which increases the amount of non-acid reflux [1, 2].

There are several limitations to the study. First, our patients may not be representative of typical children with asthma or cough presenting to a primary care clinic, but they represent patients with pulmonary symptoms referred for evaluation to a tertiary care center. Second, a high percentage of patients had been on acid suppression therapy in the 6 months prior to presentation, which may increase the likelihood of a positive culture. There were, however, no differences in the proportion of patients taking acid suppression therapy in culture-positive versus culture-negative groups. Even after adjustment for acid suppression use, non-acid reflux remained a significant predictor of a positive BAL culture.

Third, the lavage cultures were not performed quantitatively and could represent oropharyngeal contamination. However, all of our bronchoscopes were introduced into the lower airway through an endotracheal tube, so there was no direct contact with the oropharynx. Also, given that more than 50% of cultures were negative and that the isolated bacteria were not predominantly streptococci of typical oropharyngeal flora, we suggest that these are not contaminants. Additionally, although the literature on bronchoscopy in normal control children is limited, studies have shown that bronchoscopy cultures taken in a similar fashion are negative in children without pulmonary disease [12].

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Abbreviations used in this paper

pH-MII	multichannel intraluminal impedance
GERD	gastroesophageal reflux disease

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Table 1

Relationship between characteristics of reflux and culture positivity.

	Culture Negative N=34	Culture Positive N=12	P Value
Mean # acid events	25±14	24±15	0.9
Mean # non-acid events	15±14	25±16	0.06
Mean pH-only events	8±6	5±5	0.2
% full-column events	42±19	56±22	0.04
Total duration of proximal acid reflux (seconds)	417±652	685±177	0.4
Total duration of proximal non-acid reflux (seconds)	137±461	545±741	0.006
% Time pH < 4	4.1±5.0	4.3±4.3	0.9
% Time distal acid	0.9±0.8	0.7±0.5	0.5
% Time distal non-acid	0.5±0.8	0.8±1.0	0.2
% Time proximal acid	0.5±0.7	0.8±1.9	0.4
% Time proximal non-acid	0.2±0.2	0.5±0.7	0.009
Normal pH probe	27/34 (79%)	9/12 (75%)	0.8
Abnormal pH probe	7/34 (21%)	3/12 (25%)	
Normal MII	30/34 (88%)	9/12 (75%)	0.3
Abnormal MII	4/34 (12%)	3/12 (25%)	

Table 2

Clinical and historical factors associated with culture positivity.

	Culture Negative N=34	Culture Positive N=12	P Value
Mean LLMI	61±46	58±46	0.8
% BAL neutrophils	10±10	14±9	0.3
# Pepsin positive	15/34 (44%)	5/12 (42%)	0.8
# With esophagitis	7/34 (21%)	4/12 (33%)	0.06
# Taking H2 blocking agent in prior 6 months	4/34 (12%)	4/12 (33%)	0.1
# Taking proton pump inhibitor in prior 6 months	28/34 (82%)	10/12 (83%)	0.9
# Using inhaled corticosteroid in prior 6 months	30/34 (88%)	9/12 (75%)	0.2