Journal of Pediatric Gastroenterology and Nutrition
21:253–262 © 1995 Lippincott–Raven Publishers, Philadelphia

Reprinted from the JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION
Vol. 21, No. 3 October 1995
Lippincott–Raven Publishers Printed in U.S.A.

Statement of the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN)

Indications for Pediatric Esophageal pH Monitoring

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Gastroesophageal reflux (GER), defined as the regurgitation of gastric contents into the esophagus, is a common physiological, self-limited condition in infants (1). Half of 2-month-old infants regurgitate twice a day or more, but only 1% of 12-month-old infants do so (2). Regurgitation by an infant, even when frequent, generally is not a concern if the infant is otherwise healthy because the natural history is usually spontaneous resolution (2). However, a small percentage of infants will develop pathogenic GER, termed GER disease (GERD), with esophagitis, stricture, Barrett's esophagus, respiratory disease, apnea, or failure to thrive. GERD is often a diagnosis of exclusion. Numerous disorders can present with chronic regurgitation that mimics GERD; these disorders include hydronephrosis, brain tumor or other causes of increased intracranial pressure, intestinal obstruction, and metabolic disorders such as uremia (1,3).

While older children, like adults, with GERD often have heartburn, regurgitation with reswallowing, and a chronically acid taste, it may be difficult to establish the presence of GERD in preverbal infants or young children on the basis of symptoms and signs. Children, particularly infants, are different from adults in the manifestations of reflux disease, in the safety and ease of alternative diagnostic techniques, in the documented safety of therapies, and in the potential lifetime duration of disease or therapy.

Since its introduction in 1974, esophageal pH monitoring (EpHM), the continuous measurement and recording of intraesophageal pH, has become a test administered commonly to children with suspected or manifest GERD (1–12). It is based on the detection within the esophageal lumen of acidic gastric fluid and the measurement of the frequency and duration of episodes of acid reflux. It is the most reliable test for the detection of occult GER episodes and, in certain circumstances, for establishing a temporal relationship between GER episodes and symptoms (13–16).

The test is performed by the transnasal placement of a standardized microelectrode into the lower esophagus in the hospitalized or ambulatory patient for continuous measurement and recording of intraesophageal pH by either a strip chart or computerized device (17–19). The frequency and duration of episodes of reflux are measured manually or by computer, with computation of the number of episodes longer than 5 min; the longest episode; the percentage of time pH is less than 4; and the relationship of reflux to eating, position, sleeping, activity, and symptoms.

Although a large number of normal asymptomatic controls have not been studied to establish clearly normative data for all ages, numerous studies have demonstrated that measurement of the percentage of time pH is less than 4, called the reflux index, is a reliable, clinically useful measure when obtained under standardized conditions (20–27). When compared to a global clinical diagnosis, the reflux index has been reported to have a sensitivity and specificity of 94% or better (9,28,29). In children with endoscopically or histopathologically documented reflux esophagitis, EpHM has been reported to have a sensitivity of 93–96% (21,30–32).

Correct performance of the test requires a prop-

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erly trained technician, suitable and well-maintained recording equipment and probes, and a physician trained in the technique and interpretation of EpHM as well as in the clinical disorders under consideration (19,33,34). Even with standardized techniques, variability has been reported with sequential testing or with simultaneous recording with two pH probes (35,36).

Compared to other tests for GER, EpHM cannot determine the presence of a hiatal hernia, stricture or other anatomical abnormality, aspiration, or the presence of esophagitis. It cannot detect reflux when the gastric contents are not acid, as may occur immediately after a meal of nonacidic food, such as infant formula, or in the presence of achlorhydria or duodenogastric reflux (37,38). Nor can EpHM measure the quantity of acid refluxate (1,39).

No single test, such as EpHM, by itself should dictate a diagnosis or treatment of a patient. EpHM should be only one facet of a thoughtful and informed medical evaluation by a physician who is familiar with the patient and knowledgeable about the strengths and weaknesses of the test. The decision to perform EpHM is also influenced by the availability of the test and necessary expertise, as well as its cost. Additional research that investigates cost, risk, and benefit in comparison to other diagnostic and treatment options is needed to determine the optimal usage of EpHM in numerous clinical situations.

CLINICAL SITUATIONS WHERE EpHM IS GENERALLY USEFUL

Like all tests, EpHM should not be performed unless it will lead to a clinically important alteration in diagnosis, treatment, or prognosis. It is not necessary to perform EpHM when the diagnosis of GERD is already established by symptoms and signs or other tests. If reflux esophagitis has been diagnosed by endoscopy or biopsy, then EpHM is not necessary to document the presence of GERD. However, EpHM can be a very useful clinical tool to detect occult GER or to demonstrate a temporal relationship between a symptom and GER episodes.

Certain nongastrointestinal symptoms caused by GER, such as stridor, can present without other clinical manifestations of GERD. If such symptoms occur frequently, then EpHM can be performed to determine if symptoms occurring during the course of the test occurred at the same time as episodes of reflux. The symptom index (number of occurrences of a symptom with pH < 4 divided by total number of occurrences of that symptom during an EpHM study) can then be calculated to assess whether the symptoms are due to GER (40–42). Patients with symptoms of chest pain, abdominal pain, or infantile irritability that persist despite antireflux therapy can be similarly studied.

Other disorders, such as recurrent pneumonia and failure to thrive, may be manifestations of occult GER. Because these disorders are continuous rather than intermittent during a 24-h study, the symptom index is not applicable. However, EpHM may be useful to detect occult GER that presents without other evidence of GER by demonstrating the presence of clinically significant, quantifiably excessive GER.

In adults EpHM is generally indicated for patients with atypical symptoms of reflux, patients with reflux symptoms who are not responsive to standard medical therapy, and in the follow-up of patients who have been treated medically or surgically (43). These three broad criteria also apply to the pediatric patient. EpHM may be useful in the pediatric patient to diagnose gastroesophageal reflux that is manifest as hoarseness, stridor, chest pain, recurrent pneumonia, and in the evaluation of therapy of reflux.

Laryngeal Symptoms

Proximal rather than distal esophageal acid exposure is more likely to lead to laryngeal symptoms and laryngoscopic findings of posterior laryngitis (44–46). In a study of 40 adult patients with gastroesophageal reflux, 25 had persistent laryngeal symptoms, including cough, sore throat, and hoarseness (47). Ambulatory dual-electrode EpHM with the proximal electrode placed just distal to the upper esophageal sphincter demonstrated significant proximal esophageal acid exposure in those patients with laryngeal symptoms. Nocturnal proximal esophageal acidification occurred in over 50% of these patients but in none of the 15 adults who served as controls. The authors concluded that increased proximal esophageal acid exposure can occur in a subgroup of adults with gastroesophageal reflux who experience laryngeal symptomatology. These adults are much more likely to exhibit laryngoscopic abnormalities consistent with acid laryngitis than patients with gastroesophageal reflux

without laryngeal symptoms. When dual-electrode EpHM was performed on 182 adults with otolaryngologic disorders who were suspected of having gastroesophageal reflux, 55 (30%) had gastroesophageal reflux into the pharynx (48).

In a pediatric study, eight children (2 months to 7.5 years old) who had recurrent laryngotracheitis including episodes of croup had dual-electrode EpHM with the upper probe placed in the pharynx (49). The symptoms in these children included nocturnal stridor, chest retraction, and barking cough. Six control children (1 month to 13 years old) were also evaluated. There was significantly greater total reflux time in the lower esophagus and a greater number of reflux episodes in the pharynx in the children with laryngeal symptoms than in the control group. In a study of laryngoscopically demonstrated laryngitis, three of five children (<11 years old) had irritability and intermittent inspiratory stridor when 0.1 *N* HCl was infused into the esophageal body, suggesting that gastroesophageal reflux can provoke stridor in certain children (50). These studies provide evidence to support the concept that proximal acid reflux can induce recurrent laryngeal symptoms in the pediatric as well as the adult patient.

Chest Pain

Of 16 children with chest pain and asthma, 11 had endoscopical and histological evidence of esophagitis, four had a positive Bernstein test, seven had significant GER on EpHM, and nine (56%) responded to medical therapy with cessation of chest pain (51). EpHM can be performed to detect significant reflux, but since chest pain may not occur in all patients during the study, the Bernstein test can be performed to determine if the chest pain is related to esophageal acidification.

Recurrent Pneumonia

Establishing a definite relationship between GER and recurrent pneumonia is problematic (1,52–55). When microaspiration is suspected, radiographic evaluation of the oropharynx and esophageal body is usually the first screening test indicated. It is difficult to know precisely the importance of microaspiration or the role of esophageal-respiratory reflexes as a cause of recurrent respiratory disease (56). Patients with aspiration tend to reflux more to the proximal esophagus (57). Nocturnal reflux is statistically correlated with chronic aspiration. Delayed clearance of refluxed material and clustering of reflux events may precipitate respiratory symptoms in pediatric patients (58,59).

Physicians have long recognized the relationship between recurrent pneumonia and reactive airway disease and their association with GER (60). Recently, of 23 patients (3–25 months old) with recurrent bronchopulmonary infections (61), 21 had abnormal EpHM and 14 of the 21 had a reflux index greater than 10%. The study concluded that EpHM was the best single test for diagnosing GER and its association with recurrent bronchopulmonary disease. There was no control population.

In a retrospective study, 93% or 128 children with reflux-related respiratory symptoms had a prolonged mean duration of reflux episodes during sleep, compared to none of 131 children with respiratory symptoms due to other causes (62). The authors concluded that the measurement of the mean duration of reflux during sleep was the best single method to identify correctly the presence or absence of respiratory symptoms associated with GER. Other investigators, who examined the effectiveness of Nissen fundoplication in children with bronchopulmonary dysplasia, also concluded that EpHM was the definitive test to predict which patient would have an improvement in respiratory symptoms after surgery (63). These investigators found that the mean duration of nocturnal episodes of reflux was longer in patients responding favorably to surgery for GER than in those who did not improve. A study of 11 adults with recurrent pneumonia, chronic cough, and morning hoarseness, who had respiratory symptoms within 3 min after a reflux episode, demonstrated that they also had a reflux index greater than 11.4% (64).

Because it is difficult to establish a causal relationship between GER and recurrent respiratory disease, it is important to consider other diagnostic modalities (65). Endoscopy and esophageal biopsy can document evidence of chronic esophagitis (10). Bronchoscopy can document the lack of a tracheoesophageal communication, identify laryngeal or tracheal abnormalities, exclude the presence of a foreign body, and obtain tracheal aspirates for lipid-laden macrophages (18). A modified Bernstein test can demonstrate whether cough, bronchospasm or stridor occur during the infusion of acid. Newer methods to look at oropharyngeal aspiration such as the radionuclide salivagram may help further identify these patients (66).

Evaluation of the Treatment of GER

EpHM can be performed to verify the success of a particular drug or surgical therapy in improving or ameliorating GER. It has been shown in adults and children with Barrett's esophagus that EpHM performed at intervals following treatment with fundoplication or omeprazole is valuable in assessing success of therapy (67–70). Of 24 children with severe GER and respiratory symptoms who were treated with cisapride, GER was controlled in 22, as indicated by an improvement in their EpHM and clinical course, and 18 patients showed a definite improvement in their pulmonary disease (71).

In a double-blind controlled study, the efficacy of sodium alginate to reduce GER in infants was assessed by EpHM, which demonstrated improvement in all variables including the percent of total reflux time and the mean duration of reflux during sleep (72). In addition, in a double-blind placebo-controlled trial, the efficacy of domperidone in 17 children (5–11 years old) was assessed by EpHM, which demonstrated a reduction in the total number of reflux episodes in the 2-h postprandial period (73).

CLINICAL SITUATIONS WHERE EpHM IS GENERALLY NOT USEFUL

Regurgitation in Infants

Regurgitation is a manifestation of GER in infancy, although it does not necessarily represent reflux disease. If simple regurgitation is the sole manifestation of reflux, diagnostic or therapeutic measures are generally unnecessary. If regurgitation is associated with failure to thrive or other symptoms, diagnostic evaluation and therapy are usually indicated, but EpHM often does not contribute to the diagnostic evaluation (74).

Reflux Esophagitis

Having diagnosed reflux disease by demonstrating esophagitis (endoscopical erosions or histological esophagitis; 75–77), it is unnecessary to quantify acid reflux except possibly to evaluate inadequate response to therapy (30,32,78–82).

Untreated Common Symptoms of Reflux: Chest or Epigastric Pain

Older children who describe typical heartburn and pyrosis are often treated, as adults are, with an 8-week course of pharmacological therapy with an H_2-receptor antagonist and/or cisapride, despite the lack of FDA approval (83). Intractability or recurrence of these symptoms is generally evaluated initially by endoscopy rather than by EpHM. Although the pros and cons of empiric therapy for adults have been identified (84), empiric therapy in children—comparing costs, risks, and benefits—has not been evaluated. Chronic therapy without any diagnostic evaluation is generally not recommended.

Dysphagia

Esophageal dysphagia in pediatric patients is more likely to be secondary to neuromuscular disorders or intrinsic and/or extrinsic mechanical lesions. Occasionally, dysphagia may be secondary to GER (85–87). A barium esophagram, esophageal motility, and endoscopy are generally considered the preferred diagnostic tests in most children with dysphagia.

CLINICAL SITUATIONS WHERE EpHM IS GENERALLY CONDITIONAL

Infantile Apnea

Reflux may be the underlying cause in up to 20% of cases of infantile apnea (88). EpHM has been used in infants with apnea to quantify reflux, to identify possibly hazardous reflux patterns, and to document a temporal association between reflux episodes and apneic episodes. Such studies have been particularly difficult because of the lack of clear criteria for diagnosing reflux-associated apnea. The resultant subjectivity of the studies makes their evaluation particularly difficult.

Since quantitatively greater-than-normal reflux and apnea can coexist without being causally related (89,90), simply quantifying reflux is of limited value in these patients. Reflux during sleep, particularly prolonged episodes of reflux, have been found to occur more frequently in infants with apnea believed to be due to reflux (91,92). However, there have been no studies evaluating the efficacy of pharmacological treatment of GER to prevent apnea in infants with abnormal EpHM.

Apnea related to reflux usually occurs when the infant is awake, within 1–2 h following a meal, in the supine or seated position and appears to be obstructive (with persistence of respiratory effort) rather

than central (absence of respiratory effort), and it may occur in infants with no history of regurgitation (92–96). Documentation of a temporal association between reflux and apnea requires concurrent pneumocardiography, with simultaneous multichannel recording of heart rate, oxygen saturation, chest wall movement and ventilation as recorded by nasal thermister or end-tidal CO_2 (94), as well as esophageal pH. This technique can quantify GER and identify GER patterns, temporal associations between reflux and apnea, types of apnea (central, obstructive, or mixed), and the occurrence of hypoxemia or bradycardia. The usefulness of this test is limited if apnea does not occur during the monitoring. Detection of postprandial reflux by EpHM also requires that acid meals (e.g., apple juice) be fed (37,38). Although a multichannel test has a somewhat greater cost than simple EpHM, it may be offset by the much greater amount of information obtained. In infants monitored for cardiorespiratory events at home, unexplained hypoxia has been a frequent and sometimes lethal event (97,98); some of these episodes are likely to have been obstructive apnea with reflux as the underlying cause.

EpHM generally will not be useful when apnea is clearly central or when, although obstructive, it occurs in conjunction with an upper respiratory illness; such apnea is unlikely to be caused by GER. Nor will EpHM be useful when there has been a single episode of apnea, which is unlikely to recur during monitoring. Nor is EpHM generally indicated when apnea is clearly related to reflux—e.g., the postprandial infant placed supine for a diaper change who has formula appear at the mouth or nose during an episode of apnea.

Infantile Irritability, Intractable Crying, and Refusal to Eat

These symptoms may be infantile correlates of adult complaints of pyrosis, heartburn, and dysphagia, but the nonverbal nature of infants makes these symptoms far less easily characterized as having reflux as their cause (99–101). Feeding difficulties or excessive irritability ("atypical colic") can be due to GER and may be unresponsive to antireflux therapy (1,80,102). Of infants presenting to an emergency room with acute, unexplained crying, 2% were diagnosed with reflux as the cause (100); the prevalence of reflux as a cause of more prolonged symptoms and with other indications of GERD is much higher (99). In another study, only 15% of crying episodes during EpHM occurred at the time of an episode of reflux (80). While esophageal suction biopsy is a more efficient means of identifying the infant with esophagitis (103), in some cases EpHM may be necessary to establish a causal relationship between episodic crying and GER. The validity of such an approach to this problem, and the value of empiric therapy of such cases, has not been studied.

Reactive Airways Disease

Patients with asthma are probably a heterogeneous group (104,105). Bronchospasm may have identifiable precipitants which differ among patient groups: some may wheeze in response to inhalant allergens, some to ingested allergens, some during viral infections, and some to reflux. It has been suggested that patients with reflux-induced bronchospasm have not only reactive airways but also esophagitis and that having either one alone is not sufficient for reflux-induced bronchospasm (104–106). As many as half of asthmatic children have esophagitis (31,107) and an even higher proportion of those with predominantly nocturnal wheezing have abnormal EpHM (108). However, the proportion of asthmatics in whom reflux is a cause, rather than a result, of the airway obstruction is unclear. Reported responses to antireflux therapy depend on the patients selected and the efficacy of therapy and vary widely (59,109–111).

Diagnostic approaches to identify reflux as an etiology for otherwise intractable asthma include (9) modified Bernstein test (with pulmonary function testing after saline and after acid infusions; 59,104, 105,109,112–114), (b) endoscopy and/or esophageal histology (104,105,109,110,113) (c) EpHM with documentation of temporal relationship to wheezing episodes (59,108,114), (d) EpHM to quantify reflux (either in terms of total reflux time or sleep reflux time; 31,58,59,108,110,113,114), or (e) trial of empiric therapy for reflux.

The modified Bernstein test linked with pulmonary function testing is an efficient method to document the association between reflux and bronchospasm, although it has not been thoroughly evaluated (104,105,115). Endoscopy and esophageal histology showing esophagitis (32) document both the presence of reflux disease requiring therapy and the presence of the esophageal inflammation, which may be necessary for reflux-associated bronchospasm. EpHM may be used with pulmonary func-

tion testing or with close observation for wheezing episodes if those episodes are intermittent (116) or simply to document abnormal quantity of reflux (117) or abnormal quantity of sleep reflux (58,62, 118) to justify chronic therapy. A 2-month course of empiric treatment with acid suppression could also be considered (113). Because of the ambiguity of the relationships between asthma, asthma medications, and reflux (52), the optimal approach to diagnostic evaluation has not yet been established and varies from case to case, dependent on clinical judgment.

Prior to Fundoplication

Intractable reflux disease in children, as in adults, may require surgery (119,120). Some surgeons have reported that prolonged reflux during sleep (mean duration of nocturnal reflux episodes >4.5 min) predicts a favorable response to fundoplication in up to 95% of children operated (63,121), but normal pH probe studies have also been found in children who nonetheless had esophagitis and seemed to respond to surgery (122). In each of these situations, EpHM was not the only criterion used in selection for surgery. Prior to medical therapy EpHM should not be the sole indicator for this major and irreversible therapy since it does not reliably predict medical intractability, at least in adults (123–126). However, following medical therapy, it is one of several ways to document intractability of reflux to medical therapy; symptoms alone are inadequate for this purpose. Thus, candidates for surgery, whose symptoms have been intractable to therapy and in whom there is doubt about the presence or etiological role of GER, may certainly benefit from EpHM. In this group, EpHM may identify patients whose reflux is indeed controlled by medical therapy and whose persistent symptoms have a cause other than reflux; these patients would be saved an unnecessary surgery. EpHM is also useful in the unfortunate postoperative patient with persistent or recurrent symptoms to determine whether reoperation is necessary.

SUMMARY RECOMMENDATIONS FOR ESOPHAGEAL pH MONITORING IN INFANTS AND CHILDREN

The North American Society for Pediatric Gastroenterology and Nutrition (NASPGN) recognizes the need to develop a medical position statement on the indications for EpHM in infants and children to promote optimal patient care, to foster learning and to guide practitioners, as well as to facilitate peer and other review of clinical practices. The following recommendations were prepared by the authors, with the critique and endorsement of the Subcommittee on Endoscopy and Procedures, the approval of the Patient Care Committee, and the authorization of the Executive Council of NASPGN. In addition, they have been endorsed by the American Gastroenterological Association Patient Care Committee and the American College of Gastroenterology Practice Parameters Committee. These recommendations are subject to change based on periodic review of subsequent research. Nonetheless, the authors provide the following recommendations, written in the context of the preceding literature review, as a tool for improving the outcomes of patient care and to advance our understanding of them.

1. For infants with simple regurgitation it is generally not necessary to perform EpHM.
2. If reflux esophagitis has been diagnosed by endoscopy or biopsy, then EpHM is not necessary to document the presence of GERD.
3. EpHM is useful if it will lead to a clinically important alteration in diagnosis, treatment, or prognosis.
4. EpHM has little role in the evaluation of dysphagia. Similarly, it is only occasionally useful in the management of chest or abdominal pain when features are typical of GERD.
5. Certain nongastrointestinal symptoms caused by GER, such as laryngeal symptoms or atypical chest pain, can present without other clinical manifestations of GERD. If such symptoms occur frequently, then EpHM can be useful to demonstrate a temporal relationship between symptoms and GER.
6. In cases of unexplained recurrent pneumonia, it can be useful to perform EpHM to detect occult GER.
7. EpHM may be indicated to determine whether the dosage of medication is optimal in Barrett's esophagus and in selected cases of severe intractable GERD. Similarly, EpHM can be useful after fundoplication to evaluate the effectiveness of surgery when symptoms persist or recur.
8. When a causal relationship between GER and apnea is suspected but not otherwise clinically evident, EpHM can be useful when it is part of a multichannel pneumocardiography test.
9. The optimal approach to the diagnostic evalu-

ation of intractable reactive airways disease has not yet been established; EpHM can be useful in some cases, dependent on clinical judgment.

10. Prior to fundoplication, candidates for surgery whose symptoms have been intractable to medical therapy and in whom there is doubt about the presence or etiological role of GER, can benefit from EpHM.

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