How to use: a pH study

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The 24 h oesophageal pH study is considered to be the gold standard for quantifying acid reflux.[1] In this review we provide an evidence-based discussion of the role of 24 h pH studies as part of the investigation of children with suspected gastro-oesophageal reflux disease (GORD), and provide a practical guide on when a pH study is indicated, how to perform pH studies and how to interpret the results.

BACKGROUND

Gastro-oesophageal reflux (GOR) is defined as the effortless regurgitation of gastric contents into the oesophagus. GORD is defined as GOR associated with sequelae (table 1) including faltering growth.[2]

Physiological reflux is common in both primary and secondary care settings, and usually improves with age.[3] Improvement is due to a combination of factors including growth in the length of the oesophagus, a more upright posture, increased tone of the lower oesophageal sphincter, and a more solid diet. In most cases, diagnosis is based on clinical assessment without the need for invasive testing. Investigation is reserved for those children in whom, for example, there is doubt about the diagnosis, or empirical therapy is considered to have failed, or for those children with extra-intestinal manifestations, such as acute life threatening events (ALTEs), apnoeas, Sandifer syndrome, asthma or faltering growth, in whom reflux is suspected to be a contributing factor.

In children with co-existing problems, such as asthma, cerebral palsy, epilepsy or congenital heart disease, GORD may be part of a complex interaction of pathologies as a primary or secondary phenomena. In such settings children may benefit from the diagnosis and treatment of GORD, and GORD may be improved by optimal treatment of the child's co-existing problems.

Children with isolated GORD can remain symptomatic into adulthood; severe oesophagitis[4] and oesophageal strictures from GORD in childhood have been reported.[5]

Table 1 Symptoms associated with gastro-oesophageal reflux disease

Intestinal manifestations	Infants: vomiting/regurgitation, irritability, back arching Older children: heartburn, dysphagia, nausea, epigastric pain
Extraintestinal manifestations	Respiratory: recurrent pneumonia, cough, sinusitis, asthma
	Neurological: apnoeas, ALTEs/SUDI, Sandifer syndrome +faltering growth, iron deficiency anaemia

ALTE, apparent life-threatening event; SUDI, sudden unexpected death in infancy.

INVESTIGATION OF REFLUX

The investigation of reflux is difficult but multiple investigative modalities are available. The clinical situation and the clinical question being asked determine the usefulness of each test, and may therefore affect the sensitivity and specificity of the test. The 24 h pH study is currently considered to be the gold standard investigation for assessing acid reflux,[1] and we will outline its role within the investigation of GORD. Upper gastrointestinal endoscopy with biopsies is the gold standard for diagnosing oesophagitis. Other investigations include a barium meal to exclude hiatus hernia or distal obstruction (eg, malrotation), scintigraphy and intraluminal impedance.

THE PHYSIOLOGICAL BASIS OF THE PH PROBE TECHNIQUE

Acid reflux into the oesophagus occurs in all infants as a physiological phenomenon and is only significant when it occurs in excess.[2] Acid reflux has been demonstrated in premature infants, who can maintain a basal gastric pH below 4 from the first day of life.[6] By 6 months of age, an infant's ability to maintain an acid intragastric pH is similar to that of an adult.[7] Transient lower oesophageal sphincter relaxation is the most common cause of reflux, the frequency and duration of which are more marked in GORD.[8] Gastric acid may also persist in the oesophagus due to impaired luminal clearance, as seen in oesophageal dysmotility.[9]

The pH probe is designed to measure acidity (ie, acid reflux) in the lower oesophagus.

The pH probe is a microelectrode passed through the nose and down the back of the throat to sit above the lower oesophageal sphincter. The probe was first used in 1969 in adults, with an acid reflux episode defined as an oesophageal pH of <4[10] for a specified minimum duration, usually 15–30 s.[6] A set period, usually 24 h, is recorded (figs 1–3), with note made of the number of episodes, frequency of episodes, and the relationship of reflux to eating, position, sleeping or activity, and, especially, symptoms. The most sensitive marker of acid reflux on pH study is the reflux index. This is defined as the percentage of time that oesophageal pH is <4. This has been validated in several studies.[2]

The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) consensus recommendation is that the upper limit of normal of the reflux index is defined as up to 12% in the first year of life and up to 6% thereafter (table 2).[2] There is considerable debate about the upper limit of normal for the reflux index in preterm and term babies.[11]

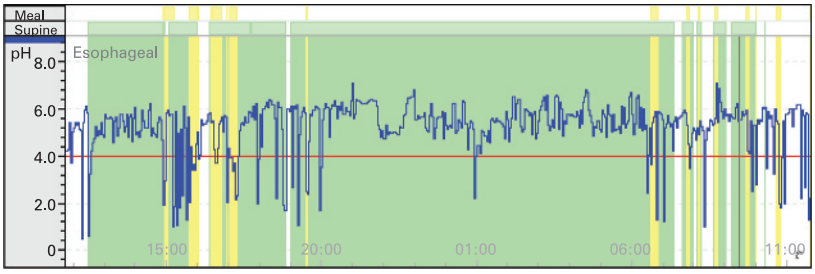

Figure 1 Example of normal 24 h pH probe; reflux index 2%.

TECHNICAL ISSUES

The patient needs to stop anti-reflux medications prior to the pH study (table 3). The child is generally monitored as an inpatient to enable supplementary observations, for example of the feeding pattern and a sleep study, and so that any technical issues that arise during the period of monitoring, such as probe displacement, can be dealt with. An ambulatory pH probe can be considered if admission to hospital is likely to significantly impact on the result.

WHERE TO SITE THE PROBE

The correct length should be estimated using the formula in table 4 and positioning should be confirmed using a chest *x* ray (CXR) or screening, due to the risk of malposition in the tracheobronchial tree or coiling in the oesophagus. The probe tip on CXR would be adequately positioned at T9. The operator should be trained in the placement of pH probes, the interpretation of CXR and the analysis of results. A pH study of <12 h duration produces less reproducible results.[12 13] A pH probe with a baseline that is rarely >4 suggests displacement into the stomach.

LIMITATIONS OF TEST

There are several limitations to pH studies, as follows:

- 1) pH studies are unable to detect anatomical abnormalities (eg, stricture, hiatus hernia or malrotation) or aspiration.
- 2) Non-acid reflux will not be detected. This should be borne in mind with non-acidic feeds such as infant formula.[14]
- 3) The changes in environment, diet and behaviour as a result of investigation and admission to hospital may impact on the result.
- 4) There is potential for technical difficulties.
- 5) pH studies provide no objective measures of inflammation, and thus are less useful than endoscopy and biopsies for the diagnosis and grading of oesophagitis.

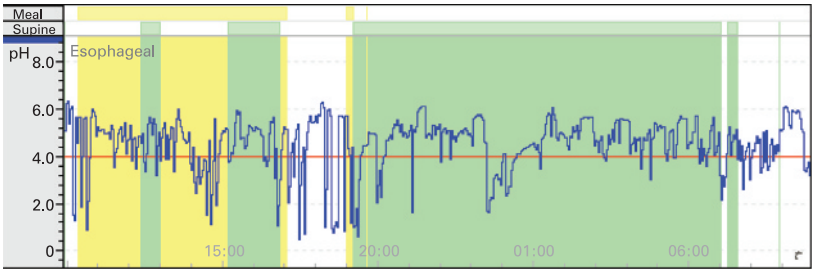

Figure 2 Example of mild acid reflux on 24 h pH probe; reflux index 8.9%.

It is crucial to have a trained operator and well-maintained equipment. The test could be misleading if, for example, the medications have inadvertently been continued, equipment is not calibrated before each test or the probe tip is misplaced or displaced.[15]

The usefulness of the test will be improved by defining a clear diagnostic question. So for a child with possible apnoeas secondary to GORD, including accurate documentation of the chronology of symptoms during the pH study is essential.

VALIDATION

Are pH studies reliable?

There is no true gold standard test for GOR, but pH studies have a sensitivity of 93–96%[1 16] in identifying acid reflux in patients diagnosed with oesophagitis on endoscopy (in both macroscopic and histological appearances). In interpreting pH studies, the most reliable marker of acid reflux is the reflux index, which has a reported sensitivity and specificity of >94%. This is significantly superior to other markers, such as the number of reflux episodes and the number of episodes of acid reflux lasting >5 min.[17 18] Normal values, used as the basis for the NASPGHAN consensus statement, were established by Vandenplas *et al*, who studied 509 healthy infants and found that the reflux index upper limit of normal (95th centile) for all infants was 12% (13% at birth, 8% at 1 year of age).[19]

Although there is a correlation between a higher reflux index and worse symptoms and endoscopy findings, there are few data to dichotomise reflux index into "mild" and "severe" (either in terms of symptom score or endoscopic appearances), so the labels of reflux index ("severe" or "mild") lie on a spectrum (figs 2 and 3).[4] There is some evidence to show that patients with a worse reflux index respond better to omeprazole compared to ranitidine.[3]

Short-term pH probes (6 h recording including up to 2 h after a meal) can be considered in selected patients. These include older children without comorbidities, for example co-existent respiratory problems. A total of 160 children (aged <12 months to 14 years) were assessed first by 6 h pH probes and then by 24 h pH probes by Barabino *et al*.[13] The authors found that the negative predictive value of the 6 h reflux index was up to 90% for selected patients, and the positive predictive value was 50–83% (lower in infants and in those with co-existing respiratory symptoms).

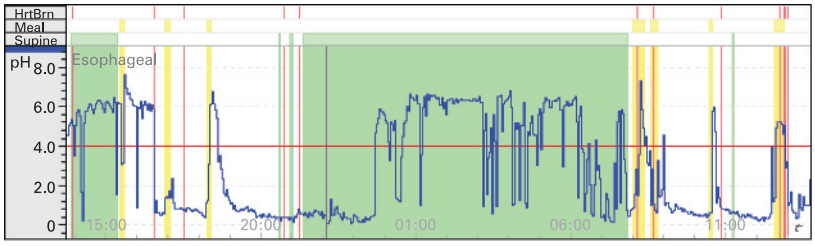

Figure 3 Example of severe acid reflux on 24 h pH probe; reflux index 48%.

Are pH studies reproducible?

In the largest study in children, Vandenplas *et al* looked at 30 children (aged 2 weeks–8 years) with a clinical diagnosis of GORD who had had two 24 h pH studies on consecutive days, using reflux index, number of reflux episodes with pH <4, longest reflux episode and the number of reflux episodes >5 min as parameters.[21] The reflux index and the number of reflux episodes >5 min were the most reproducible criteria (r = 0.97 and 0.98, respectively). They also assessed the mean difference between day 1 and day 2 readings for each parameter as a marker of reproducibility. Taking the mean difference as zero (perfectly reproducible), they expected that 95% of the differences for each parameter would fall within 2 standard deviations of the mean difference (a reproducibility coefficient adopted by the British Standards Institution).[20] Reflux index, longest reflux episode and the number of reflux episodes >5 min all satisfied this test of reproducibility. Hence the authors concluded that pH probes were reproducible.

On the other hand, Hampton *et al* looked at 13 children, 11 of whom had two 24 h pH studies on consecutive days.[22] They found that the reflux index could vary between consecutive studies; although eight children had similar reflux index results (either normal (<5%) or abnormal (>5%)) on both days, five children had one normal and one abnormal pH probe result. However, all these children had pH probes for extra-intestinal manifestations (apnoeas or respiratory symptoms) and none had undergone endoscopy. No treatments were stopped prior to the pH studies.

Wiener *et al* looked at 59 adults, with two ambulatory 24 h pH probes performed 10 days apart.[23] They assessed all pH parameters as "normal" (eg, reflux index ⩽4.4%) or "abnormal" (reflux index >4.4%) for both tests. Reflux index was the most reproducible parameter, with 93% agreement in healthy patients and patients with oesophagitis. Variability (logarithmic transformation of reflux index) between pH parameters was >90% if either very normal (reflux index <1.8%) or abnormal (>9.4%), but higher (30%) if the result was 3–4%. Murphy *et al* investigated 15 adults with GORD with two pH probes simultaneously placed 5 cm above the lower oesophageal sphincter. A number of differences were noticed between the results, and in two patients the differences were wide enough to change the clinical diagnosis.[24]

Table 2 Range of upper normal limits for age

Reflux index	Infants: 12%*
	Older: 6%*
Number of episodes of acid reflux	Infants: 72 episodes/day[18]
	1–9 years of age: 25*
Number of episodes of acid reflux lasting >5 min per day	Infants: 10 episodes/day[18]
	Children: 7*
	Adolescents/adults: 3*
Length of episode (min)	Infants: 41 min[18]
	Children: 7†

*NASPGHAN consensus[2]; †Cucchiara (n = 63).[1]
Table based on[18] Vandenplas (n = 504).

Are there alternatives to 24 h oesophageal pH studies?

Further discussion on the role of other investigations is available elsewhere[1 13 25] and pH studies should be considered as one potential modality in the diagnostic work up of GORD. Other investigations include combined intragastric and oesophageal pH monitoring, intraluminal impedance, barium swallow and scintigraphy. Combined intragastric and oesophageal pH monitoring is designed to increase the negative predictive value of a pH study by estimating the confounding impact of milk in alkalinising gastric secretions. However, no clear protocol has yet been developed in children with suspected GOR and disagreement exists as to whether a single intragastric electrode placed in the fundus or two electrodes are needed in the fundus and antrum based on evidence that the pH can be significantly different between the fundus and antrum in adult controls.[26]

Intraluminal impedance measures reflux from retrograde flow of a liquid bolus as it passes from the stomach through the oesophagus toward the oropharynx,[27] and thus is pH independent (and will detect non-acid reflux). Intraluminal impedance is increasingly being used in conjunction with pH studies.

Scintigraphy in some centres has a sensitivity of up to 59% and a specificity of up to 100% for GOR,[28] and can be used to investigate aspiration of isotope into the lungs and assess gastric emptying. A barium swallow can help to exclude surgical causes of vomiting (eg, oesophageal stricture or malrotation). The sensitivity, specificity and positive predictive value of a barium swallow for detecting GOR compared to oesophageal pH studies are 31– 86%, 21–83% and 80–82%, respectively.[2]

CLINICAL QUESTIONS

Question 1

> In children with symptoms of physiological GOR [patients], does a pH probe study [intervention] improve family satisfaction or reduce family concerns [outcome]?

A detailed history and examination is usually all that is required in this patient group to exclude

Table 3 When to stop anti-reflux medications

Medication	Pharmacokinetics	Recommended to stop
Gaviscon	Not absorbed[50] Cleared from stomach by 6 h	24 h before
Proton pump inhibitors (eg, omeprazole lansoprazole)	$t_{½}$: 1.2–2 h[51] Resumption of acid suppression 48 h[52]	72 h before
H2 receptor antagonists (eg, ranitidine, cimetidine)	Duration of action: 24 h. Plasma clearance in 6–8 h.	72 h before
Prokinetics		48 h before
Domperidone	Oral $t_{½}$: 12 h[53]	
Metoclopramide	Oral $t_{½}$: 4.5 h[54]	
Erythromycin	Oral $t_{½}$: 2 h[55 56]	

other causes. Assessment of weight gain is crucial, and a feeding history is important to exclude, for example, overfeeding. Up to 50% of infants less than 3 months old regurgitate at least one feed daily.[29] The natural history is of improvement with age; in one paediatric gastroenterology outpatient clinic, 55% of babies diagnosed with physiological GOR were symptom free by 10 months and 81% by 18 months of age.[30] A study evaluating children with GOR found no benefit in pH studies if there were no features of concern[31]; however, a pH probe may be of benefit if there is diagnostic uncertainty, or as part of the investigation of infants with a history of poor feeding or irritability. pH studies can for example be useful in demonstrating resolution of symptoms, particularly if there are continuing anxieties about feeding and it is uncertain whether reflux is a factor. The child's medications are stopped before admission. On admission the parents can be asked about symptoms off treatment, and observation of symptoms can take place over 24 h while the child is in hospital for the pH study. The pH study report and assessment of symptoms can then be used as part of the decision-making process.

Question 2

> In children with symptoms of GORD [patients], who undergo pH testing [investigation] what proportion are found to be significantly abnormal [outcome]?

An abnormal reflux index is found in 95% of paediatric patients with endoscopic oesophagitis (ulcerations or erosions) or biopsy-proven oesophagitis.[1 15]

Cucchiara looked at 24 h pH studies in 114 children (aged 1 month–12 years) and found that 45 patients had reflux without oesophagitis and 69 had reflux oesophagitis confirmed on endoscopy[1]; 63 control patients also had 24 h pH studies.

Table 4 Formula for assessing pH probe placement

Nose to diaphragm (LOS)	0.24×patient's height (cm)+5.2	Correlation r = 0.96[57]
Mouth to diaphragm (LOS)	0.226×patient's height (cm)+6.7	Correlation r = 0.97[58]

LOS, lower oesophageal sphincter.

Some 20–30% of all reflux patients had both a normal acid exposure time and a normal number of long lasting reflux episodes. Patients with oesophagitis had significantly more acid reflux than those with simple uncomplicated disease (except during sleep); however, increasing severity of oesophagitis was not associated with increasing acid exposure.

pH monitoring can be used to assess whether medication is still needed if symptoms have resolved and give an opportunity to assess current symptoms off treatment. The pH probe results can often be interpreted in the light of this.

Question 3

> In premature infants with apnoea [patients], does undertaking pH studies [investigation] or using anti-reflux medication [treatment] affect episodes of apnoea, cough or aspiration pneumonia [outcome]?

Apnoea secondary to reflux is more likely within 1–2 h after a feed, and may present with obstruction (persisting respiratory symptoms) rather than central apnoea (absent respiratory effort), which may reflect apnoea of prematurity.[32] Dhillon *et al* noted that 22% of all extremely low birth weight (<1 kg) infants received an empirical trial of prokinetics and/or Gaviscon for feeding intolerance and recurrent episodes of apnoea, bradycardia or desaturations,[32] indicating the frequency of the presentation. However, a causal relationship between reflux and apnoeas has not yet been demonstrated, either by assessing acid reflux using pH probes or the presence of refluxate using intraluminal impedance. Di Fiore *et al* (assessing 119 preterm babies with 6255 episodes of GOR)[33] and Barrington *et al* (45 infants with 10 apnoeas per pH probe recording) found no temporal relationship using pH probes.[34] Peter *et al* looked at 19 babies (524 reflux episodes and 2039 apnoeas) and found no temporal relationship using intraluminal impedance.[35] Varying the position of the pH probe does not alter sensitivity or specificity, for example upper oesophageal pH studies are no more sensitive than lower oesophageal pH studies for detecting upper airway complications of GOR.[36]

In some patients oesophageal pH monitoring may be within normal limits but brief episodes of GOR may result in complications such as persisting cough or aspiration pneumonia, or apnoea/ALTE.[1]

Question 4

> In children with asthma [patients], does undertaking pH studies [investigation] or using anti-reflux medication [treatment] affect respiratory symptoms [outcome]?

The relationship between poorly controlled asthma and acid reflux is complicated. Up to 60% of children with refractory asthma had abnormal oesophageal pH monitoring studies.[37–39] A

Clinical bottom line

- The pH probe is a generally safe, reliable test of acid reflux in children and infants.
- It does not detect alkaline reflux.
- It is part of the diagnostic work up of gastro-oesophageal reflux disease.
- Results must be interpreted in the context of clinical signs.
- The pH study is highly reliable for detecting acid reflux in oesophagitis.
- The pH study is useful in recurrent pneumonia but a poor discriminator in babies with apnoea or persistent cough.
- Always consider whether a pH study is the right investigation.
- The period when a child's medication has been stopped for a pH probe can provide useful clinical data.
- The pH study is useful in providing evidence of resolution of acid reflux.

Cochrane review evaluated 12 studies of which four addressed the role of acid reflux in children with asthma.[40] These studies identified some children in whom reflux was temporally associated with asthma[41 42] but no consistent effect of anti-reflux medication on asthma outcomes (eg, improved symptoms, FEV_1 or peak expiratory flow (PEF)) within these studies. Two studies showed a significant improvement in reported symptoms of wheeze. Other studies have failed to show an improvement in FEV_1, PEF or asthma symptoms with treatment of acid reflux, although in patients with asthma GORD symptoms lessened and the reflux index improved following administration of proton pump inhibitors (PPIs).[43]

The clinical bottom line is that it is not possible (with the current limited evidence) to recommend medical treatment of GOR as a means to control asthma. There may be a subgroup of responders, but they are difficult to identify.

Question 5

> In children with chronic cough [patients], does undertaking pH studies [investigation] or using anti-reflux medication [treatment] affect respiratory symptoms [outcome]?

Cough and GOR often co-exist. Three paediatric studies were assessed by a Cochrane review and none were suitable for inclusion for analysis.[44] One study (with eight patients) suggested that cough in association with known reflux persists when pH studies are normalised with high dose PPIs, and that cough can take a year to settle even after commencing a PPI.[45]

Little *et al*[46] looked at 222 children (aged 1 day–16 years) with a double probe (simultaneous oesophageal and pharyngeal pH monitoring) over 24 h. A total of 168 (76%) had abnormal findings in either one or both of the pH probes. Of those, 46% (78/168) had evidence of increased pharyngeal acid reflux with normal oesophageal acid exposure times. Patients with laryngeal or pulmonary manifestations had significantly more pharyngeal acid reflux ($p<0.001$) than patients with non-respiratory symptoms.

A validated clinical algorithm exists in adults to identify those whose cough is caused by GOR. A 24 h oesophageal pH study is one of these investigations[44] but has not been validated in children.

The clinical bottom line is that the relationship between reflux and cough is complex and further research is needed. More work is also needed to assess whether 24 h oesophageal pH studies can help to differentiate those subgroups of children with co-existent GOR and cough from those children with cough caused by GOR.

Question 6

> In children with recurrent pneumonia [patients], does undertaking pH studies [investigation] or using anti-reflux medication [treatment] affect respiratory symptoms [outcome]?

Chen *et al* performed pH studies on 23 children between 3–25 months of age, 21 of whom had an abnormal study (with 14 children having a reflux index of >10%).[47]

The clinical bottom line, as recommended in the NASPGHAN consensus statement, is that in cases of recurrent pneumonia where GORD is suspected, a 24 h oesophageal pH study may be indicated.[2]

Question 7

> In children with neurodisability and symptoms of GORD [patients], does investigation and treatment of GORD [intervention] improve quality of life, recurrent pneumonia or abdominal pain [outcome]?

Children with neurodisability often have a degree of global gut dysmotility as part of their clinical presentation and are more likely to have GOR, with delayed gastric emptying and raised intra-abdominal pressure from scoliosis, as well as increased transient relaxations of the lower oesophageal sphincter with impaired clearance of acid reflux from the oesophagus (oesophageal dysmotility). They can present with vomiting (and haematemesis) and recurrent pneumonia, or as unsettled and posturing. Schwarz *et al* assessed 79 patients with neurological impairment and feeding problems, and noted that 56% had an abnormal 24 h pH probe.[48] However, there is no formal consensus on whether pH probe is the gold standard test in this group, given the underlying dysmotility.[49] Consideration may be given to initial empirical treatment of symptoms with PPIs.

Competing interests: None.

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How to use: a pH study

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