

M. E. James · A. K. Ewer

## Acid oro-pharyngeal secretions can predict gastro-oesophageal reflux in preterm infants

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**Abstract** Acid gastro-oesophageal reflux (GOR) is common in preterm infants but there is a lack of a non-invasive technique to establish the diagnosis. The aim of this study was to identify whether the presence of acid in oro-pharyngeal secretions (OPS) was a valid indicator of clinically significant acid GOR in preterm infants. A total of 23 infants with suspected GOR were studied with 24 h lower-oesophageal pH monitoring and during this period the OPS were tested for acid with litmus paper at 6 hourly intervals. Median (range) gestation was 28 weeks (24–31), birth weight 1023 g (480–1750) and age at study 34 days (11–76). Significant GOR was defined as a reflux index > 5%. Of the investigated infants, 18 subjects (78%) had significant GOR. Of this group, 16 infants had acid in the OPS on at least one occasion. Five infants did not demonstrate significant GOR and in four of these acid was not detected in the OPS. Our data indicate that as a predictor for significant GOR, litmus-testing OPS for acid has a sensitivity of 89%, specificity of 80%, positive predictive value of 94% and a negative predictive value of 67%. The difference in the incidence of acid OPS between the GOR and the No GOR group was significant ( $P < 0.03$ ).

**Conclusion** The presence of acid in the oropharyngeal secretions may help in the prediction of acid gastro-oesophageal reflux in preterm infants. The method is simple, inexpensive cheap and involves minimal disturbance. We suggest that it could aid clinical diagnosis and indicate a need for further investigation of gastro-oesophageal reflux.

**Key words** Gastro-oesophageal reflux · Preterm infants

**Abbreviations** GOR gastro-oesophageal reflux · OPS oro-pharyngeal secretions

### Introduction

Acid gastro-oesophageal reflux (GOR) is common in preterm infants [3, 8] and may cause serious problems including apnoea [8] and aspiration pneumonia [12]. Reflux may delay or prevent successful enteral feeding and this in turn may have adverse effects on growth and subsequent neurodevelopmental outcome [5].

There are a number of techniques used for diagnosing GOR including barium swallow [7] and scintigraphy [4], however, barium examination is an insensitive test [1] and scintigraphy is not practicable in preterm infants. The commonest and most informative method of investigation of GOR in this group is 24 h lower-oesophageal pH monitoring [11]. This investigation is accurate but time consuming, moderately invasive and requires specialist equipment which is not always readily

available. A more simple 'cotside' test to establish the presence of GOR in the preterm infant could therefore aid diagnosis. We tested the hypothesis that the detection of acid in the oro-pharyngeal secretions (OPS) of preterm infants is a valid indicator of clinically significant GOR. To our knowledge this has not previously been examined in preterm infants.

## Subjects and methods

### Subjects

The study was undertaken at the Regional Neonatal Intensive Care Unit at Birmingham Women's Hospital. Infants were enrolled into the study if the clinician caring for them suspected GOR. Symptoms of GOR included possetting, ruminating and xanthine-resistant apnoeas where infection had been excluded to the satisfaction of the clinical team. All subjects were over 7 days of age and receiving full enteral feeds at a minimum of 150 ml/kg per day.

A total of 27 consecutive subjects, (16 males and 11 females), fulfilled the criteria and were enrolled into the study. In four infants feeds were discontinued prior to completion of the study because of clinical deterioration (apnoeas and bradycardias). These infants were excluded from further analysis. The remaining 23 infants (14 males and 9 females) completed the study. The median (range) gestational age of this group was 28 weeks (24–31), birth weight 1023 g (480–1750) and age at study 34 days (11–76). Fourteen infants were receiving expressed maternal breast milk, six preterm formula (Cow and Gate Low Birth weight Formula), one term formula (Cow and Gate Premium), and two were receiving Pregestimil (Bristol Myers). One infant was receiving continuous feeds. The remainder were fed by bolus feed via a naso-gastric tube; 16 infants were fed at hourly intervals, three infants were fed 2 hourly and three infants were fed 3 hourly.

In addition to routine vitamins and minerals six infants were receiving cisapride (0.3 mg/kg tds), nine infants were receiving caffeine (6 mg/kg/day maintenance dose after 25 mg/kg loading dose), six infants were receiving lactulose (0.5 ml/kg/day) and two infants were receiving dexamethasone (0.05 mg b.d.). Three infants were receiving both caffeine and cisapride.

A further group of 27 infants with no symptoms of GOR were also tested for the presence of acid in the OPS. These infants did not undergo pH monitoring because it was considered unethical to subject asymptomatic infants to X-ray exposure. The reason for testing was to establish the prevalence of acid in the OPS of asymptomatic preterm infants. Median (range) gestation for this group was 29 weeks (26–36) birth weight 1210 g (620–3440) and age at study 30 days (7–106).

### Methods

A well validated intra-oesophageal pH monitoring system utilising a 1.5 mm diameter mono-crystalline antimony pH electrode and solid state recorder (Digitrapper MkIII, Synectics Medical, Sweden) was used to perform lower-oesophageal pH analysis during the study.

The tip of the pH electrode was placed 7/8 of the distance from the nares to the lower oesophageal sphincter. This distance was estimated by measuring the distance from the shoulder tip to the umbilicus. Position of the probe was confirmed by chest X-ray and was considered satisfactory if it was approximately 1 cm above the diaphragm. Minimal adjustment of position was necessary in a minority of cases. Data from the recorder were examined using the EsopHogram software programme (Synectics Medical, Sweden).

During the 24 h study period the nurses caring for the infant kept a hand written diary of significant events such as episodes of handling, feed times, apnoeas and bradycardias and the infants'

position. During the study period, specimens of OPS were aspirated from the mouth by gentle suction at 6 hourly intervals. Specimens were not taken in the 15 min period following feeding or after episodes of handling or disturbance. Nurses took great care not to induce reflux by eliciting a gag reflex during sampling. If this did occur the specimen was discarded. The OPS specimens were tested for acid with blue litmus paper and the result (positive or negative) was recorded in the event diary. A positive result was defined as any red discolouration of the litmus paper. Nursing and medical care was otherwise unaltered.

Significant GOR was defined as a reflux index greater than 5%. Reflux index was defined as the percentage of the 24 h study period during which the lower-oesophageal pH was below 4. Calibration of the pH probe was performed before and after each study using standard buffer solutions pH 1 and pH 7 (Synectics Medical). Informed parental consent was obtained in each case and the protocol was approved by the local research ethics committee.

## Results

Our study confirmed that reflux was common in this population. Of the 23 subjects, 18 (78%) had significant GOR with a reflux index > 5% (GOR group). The median (range) reflux index in this group was 15% (5.8–51.5). Five infants did not have significant GOR and had a reflux index < 5% (No GOR group). The median (range) reflux index in this group was 1.2% (0.1–3.8). There was no difference in the demographic data between the two groups although the number of babies in the No GOR group was small (Table 1).

Of the 18 subjects in the GOR group, 16 had acid in the OPS on at least one occasion during the study period. The two infants in this group with no acid detected in the OPS had acid present on subsequent testing outside the study period. Of the five subjects in the No GOR group, four had OPS which were consistently negative to acid during the study period. The infant in this group who had acid in the OPS had a reflux index of 3.8% which was the highest reflux index in this group. Importantly the infants in this group with no acid detected during the study continued to demonstrate consistently negative OPS outside the study period.

Analysis of the data from the symptomatic infants indicated that testing OPS in preterm infants for the presence of acid as a predictor of clinically significant GOR had a sensitivity of 88%, a specificity of 80%, a positive predictive value of 94% and a negative predictive value of 67%.

There was a significant difference in the incidence of acid OPS between the GOR and the No GOR group (Fisher's exact test,  $P < 0.03$ ).

The No GOR group included three of the nine infants receiving caffeine, one of the six infants receiving cisa-

**Table 1** Clinical data from the symptomatic patients. All data expressed as median (range)

	GOR ( $n = 18$ )	No GOR ( $n = 5$ )
Birth weight (g)	972 (480–1750)	940 (660–1240)
Age at study (d)	27 (11–76)	32 (26–47)
Reflux index (%)	15 (5.8–51.5)	1.2 (0.1–3.8)

pride and one of the two infants receiving dexamethasone. The median (range) reflux index of the nine infants receiving caffeine was 14.8 (1.2–40.4) and 9.0 (0.1–51.5) for the 14 infants who were not receiving caffeine. Of the 27 infants with no symptoms of GOR whose OPS were tested for the presence of acid in order to establish the prevalence of acidic secretions, 9 (33%) had acid in the OPS.

## Discussion

Our data confirm that GOR is common in this population. Because of potentially serious sequelae, early diagnosis and subsequent treatment of GOR in this vulnerable population is extremely important. A study investigating methods of diagnosing this condition is therefore meaningful.

We postulated that severe reflux, sufficient for gastric contents to be regurgitated into the pharynx may lead to the persisting presence of acid in the mouth. This could be potentiated in this group because of immature swallowing [6] and poor oesophageal clearance of refluxed material [9]. Our data show that acid can be detected in the mouth and this can be used as a method of detecting GOR.

Most infants with significant GOR had acid OPS on two or more occasions in a 24 h period and all these infants had acid in the OPS either during or after the study.

However, further analysis of the number of positive OPS compared with increasing reflux index (Table 2) showed that although the presence of acid was a sensitive indicator of significant reflux, the total number of positive OPS was not a sensitive predictor of reflux severity per se. We hypothesised that the presence of acid in the oro-pharynx occurred as a result of prolonged reflux episodes and therefore examined the mean number of reflux episodes greater than 5 min duration and compared these figures with the number of positive OPS (Table 3). Once again, it can be seen that the total number of positive OPS does not accurately predict the number of prolonged reflux episodes, but the absence of positive OPS is clearly associated with fewer prolonged episodes.

In this study, only a few infants had insignificant GOR. This is because we studied only those who were having symptoms which were suggestive of reflux and

**Table 2** Number of positive oro-pharyngeal secretions (OPS) according to reflux severity (reflux indices from individual patients with significant gastro-oesophageal reflux have been grouped together)

Reflux index (%)	Mean no. of positive OPS/24 h
5–10 ( <i>n</i> = 6)	3
10.1–15 ( <i>n</i> = 3)	1
15.1–20 ( <i>n</i> = 3)	2
20.1–30 ( <i>n</i> = 3)	3
30+ ( <i>n</i> = 3)	2

**Table 3** Number of positive OPS according to frequency of reflux episodes greater than 5 min

No of positive OPS/24 h	Mean RE > 5 mins/24 h
0	3.2
1	9.0
2	14.0
3	10.4
4	8.7

not surprisingly the majority of infants enrolled did have significant GOR. However, our method accurately identified four out of five infants who did not have GOR.

The study of asymptomatic infants shows that the majority of this group do not have acid in the OPS. The 33% of asymptomatic infants who did have acid detected may well have asymptomatic GOR and the data from the symptomatic group would support this. The phenomenon of asymptomatic reflux has been previously shown to be common in preterm infants [3, 8] and our findings are consistent with this. Whether infants with asymptomatic reflux should receive treatment is a subject for debate.

The feed frequency did not appear to affect the incidence of GOR. Although intuitively one may expect that the buffering effect of milk given at an hourly rate or by continuous infusion may reduce acid reflux, this was not noted in the symptomatic infants. The 16 infants on hourly feeds had a median (range) reflux index of 12.6% (0.1–50.5) and the infant on continuous feeds had a reflux index of 14.9%.

Several subjects in the study group were receiving drugs which have been reported as having an effect on GOR. Six infants were receiving cisapride which has been shown to increase LOS pressure and improve oesophageal motility [2]. Interestingly, the majority of infants receiving cisapride in our study demonstrated significant reflux. Of course, the degree of reflux in these infants prior to commencing cisapride is unknown and may well have been much higher than that documented while receiving the drug. The use of cisapride did not appear to affect the accuracy of our test. Likewise caffeine has been shown to increase gastric acid secretions and GOR in infants [10]. However this effect was not obvious in our study as although the median reflux index was higher in the infants on caffeine (14.7% compared with 9% in those symptomatic infants who were not receiving this drug), three out of the five infants in the No GOR group were receiving caffeine. These observations are interesting but our study was not designed to examine these effects.

Our data show that acid is present in the OPS in the majority of preterm infants with significant GOR and that this is simple to demonstrate. The presence of a single positive OPS was as clinically significant as two or greater in our study group. Consistent absence of acid in the oro-pharynx is a reasonably reliable method of excluding significant GOR.

The testing of OPS for the presence of acid is inexpensive, easily undertaken and involves minimal disturbance to the infant. However, it does not provide the detailed information which can be obtained through 24 h lower-oesophageal pH monitoring, such as the severity of significant reflux and frequency and duration of reflux episodes. Therefore if persistent acid OPS are noted, further investigation of GOR is warranted.

Our data indicate that testing of OPS for acid gives some indication of significant GOR and may be useful both in the initial diagnosis and subsequent monitoring of response to treatment.

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