Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children

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SUMMARY

Background

Extra-oesophageal symptoms are thought to be common, atypical symptoms of gastro-oesophageal reflux disease (GERD) in children.

Aim

To investigate the prevalence of GERD in children with extra-oesophageal symptoms or of extra-oesophageal symptoms in children with GERD, and the effect of GERD therapies on extra-oesophageal symptoms.

Methods

A systematic review of articles in PubMed and EMBASE.

Results

We identified 18 relevant articles. The pooled weighted average prevalence of GERD in asthmatic children was 23%, compared with 4% in healthy controls from the same five studies. The majority of studies evaluating the relationship between apparent life-threatening event (ALTE) and GERD did not suggest a causal relationship. Seven studies reported that respiratory symptoms, sinusitis and dental erosion were significantly more prevalent in children with GERD than in controls. Data from pharmacotherapeutic trials were inconclusive and provided no support for a causal relationship between GERD and extra-oesophageal symptoms.

Conclusions

Possible associations exist between GERD and asthma, pneumonia, bronchiectasis, ALTE, laryngotracheitis, sinusitis and dental erosion, but causality or temporal association were not established. Moreover, the paucity of studies, small sample sizes and varying disease definitions did not allow firm conclusions to be drawn. Most trials of GERD therapies showed no improvement in extra-oesophageal symptoms in children.

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) in adults develops when reflux of the stomach contents into the oesophagus causes troublesome symptoms such as heartburn or acid regurgitation, and/or complications such as oesophagitis.[1] However, there are less recognizable, extra-oesophageal symptoms of GERD, which affect various tissues and organ systems beyond the oesophagus.[2] The recent Montreal Definition of GERD described established associations, although not necessarily causal, between adult GERD and cough, laryngitis, asthma and dental erosion.[1] Associations with pharyngitis, sinusitis, idiopathic pulmonary fibrosis and recurrent otitis media have also been proposed in adults, but more data are needed to confirm a link with GERD.[1]

Extra-oesophageal symptoms occur in a third of adult patients with GERD, whether or not reflux oesophagitis is present.[3] Three large studies have shown that patients with GERD and individuals with GERD in the general population are up to three times more likely to have laryngeal or pulmonary conditions than those without GERD.[4-6] Extra-oesophageal symptoms such as these are hypothesized to be caused by refluxate from the stomach reaching the respiratory tract or via stimulation of the oesophagobronchial reflex.[7] It is also possible that symptoms such as cough and wheezing may cause reflux through an increase in intra-abdominal pressure.[8]

A recent systematic review reported a significant association between GERD and asthma in adults, although a temporal sequence could not be determined.[9] Fewer prevalence studies have been performed in the paediatric population. Only one systematic review of the association between extra-oesophageal symptoms and GERD in children has been published and this looked only at upper airway symptoms.[10]

This systematic review aims to evaluate the presence and magnitude of the association between GERD in children and a range of extra-oesophageal symptoms, including those highlighted in the Montreal Definition, the systematic review by Rosbe et al. and the recently published Paediatric Definition of GERD,[1, 10, 11] by assessing articles reporting the prevalence of GERD in children with extra-oesophageal symptoms or of extra-oesophageal symptoms in children with GERD, and studies assessing the effect of GERD therapies on extra-oesophageal symptoms.

METHODS

Search strategy and study selection

Studies were identified via systematic searches of Pub-Med and EMBASE using the search terms detailed in Figure 1. Searches were limited to journal articles reporting studies in humans aged 0–18 years.
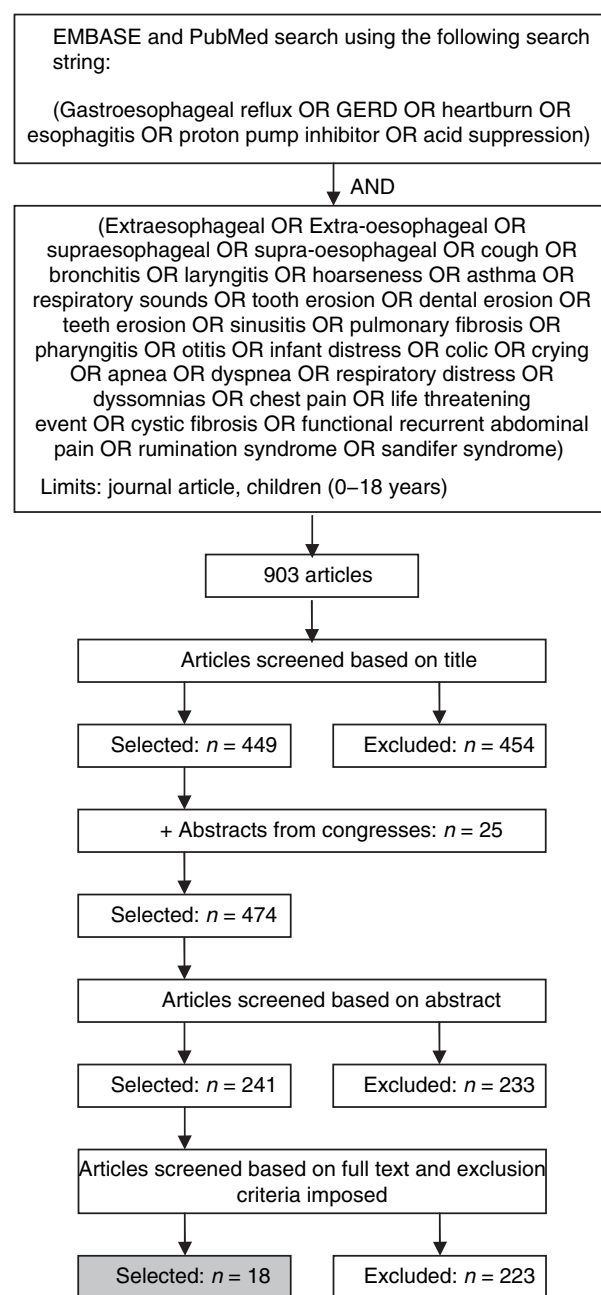

Figure 1. Flow diagram showing selection of articles.

Editorials, letters, practice guidelines, reviews, case reports, comments and *in vitro* articles were excluded. Relevant studies presented at the World Congress of Paediatric Gastroenterology, Hepatology and Nutrition (WCPGHAN), United European Gastroenterology Week (UEGW), North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and Digestive Disease Week (DDW) within the past 4 years were also identified from abstract titles.

Relevant studies were selected first on the basis of the title and then on the abstract, as outlined in Figure 1. Articles were then screened based on the full text; those that explored the association of GERD and extra-oesophageal symptoms in children and infants and those that studied the effect of anti-reflux medications on extra-oesophageal symptoms were selected. Studies presented at congresses were selected on the basis of the abstract text if enough information was included. Studies that did not have a control population and those not published in English were excluded.

The extra-oesophageal symptoms evaluated by our review process comprised: (i) respiratory conditions or symptoms: asthma, wheezing, cough, apnoea, bronchitis, pneumonia, bronchiectasis and apparent life-threatening events (ALTE); (ii) conditions affecting the ear, nose and throat (ENT), such as sinusitis, otitis media and laryngotracheitis; (iii) dental erosion.

Tabulation of results and analysis

The full papers (or abstracts only for the articles from congresses) from the studies selected based on the content of their abstracts were analysed. For the studies exploring the association of gastro-oesophageal reflux and extra-oesophageal symptoms in children, the following data were collected: sample size, study design, method of data collection, definition of reflux symptoms, definition of extra-oesophageal symptoms and the reported prevalence estimate. Where enough data were available, we determined overall prevalence estimates by pooling values from studies meeting the selection criteria and calculating average values weighted by sample size. For the studies evaluating the impact of GERD therapies on extra-oesophageal symptoms, the following data were collected: sample size, study design, definition of reflux symptoms, definition of extra-oesophageal symptoms, drug administered, dosage and length of treatment period, and the study outcome.

RESULTS

The PubMed and EMBASE searches identified 903 articles, and a further 25 potential abstracts were selected from recent conferences. Of these, 241 relevant articles were selected. Those studies with no control population and those not published in English were then excluded, resulting in 18 that were evaluated in our review. The majority of articles were excluded because of the lack of a healthy control population.

Prevalence of extra-oesophageal symptoms and GERD in children

We identified 15 studies satisfying our criteria that reported the prevalence of GERD and extra-oesophageal symptoms in children (Tables 1 and 2). Of these, six examined the prevalence of extra-oesophageal symptoms in children with GERD (Figure 2), while nine focussed on the prevalence of GERD in children with extra-oesophageal symptoms (Figure 3).

Respiratory symptoms were the most commonly studied extra-oesophageal symptom. Most articles focussed on a particular symptom or diagnosis such as asthma (six articles), ALTE (five articles), pneumonia (one article), bronchiectasis (one article) or general or multiple respiratory symptoms (two articles). ENT symptoms were the focus of three articles, and a further two articles evaluated dental erosion.

Asthma. Only one study meeting our inclusion criteria evaluated asthma in children with GERD, a large study by El-Serag and colleagues that used the administrative database at Texas Children's Hospital.[12] However, the data were based on the diagnoses made by several physicians and did not use a standardized definition of GERD or asthma, so caution is required in the interpretation of data from this study. The authors analysed retrospective data regarding medical diagnoses made in all patients with GERD (except those with cerebral palsy, mental retardation, tracheo-oesophageal congenital anomalies or congenital oesophageal stenosis) between 1996 and 2000. They examined records from 1980 children (older than 2 years; mean age 9.16 years) with a diagnosis of GERD and 7920 controls (children older than 2 years; mean age 8.64 years) without. The prevalence of diagnosed asthma in children with GERD

Table 1. Prevalence of extra-oesophageal symptoms in children with GERD

Symptom		Reference	Population size	Study design	Method of data collection	Definition of reflux symptoms	Definition of extra-oesophageal symptom	Prevalence of extra-oesophageal symptom in children with GERD
Respiratory symptoms	Asthma Pneumonia Bronchiectasis	El-Serag et al.[12]	1980 with GERD + 7980 controls	Association case-controlled study	Database	Physician diagnosis	Physician diagnosis	13.2% vs. 6.8% of controls (P < 0.0001) 6.3% vs. 2.3% of controls (P < 0.0001) 1% vs. 0.1% of controls (P < 0.0001)
	ALTE General respiratory symptoms	Tolia et al.[20]	173 with GERD + 169 controls	Association case-controlled study	Database	Physician diagnosis	Physician diagnosis	20% vs. 31% of controls (P < 0.12) 49% vs. 63% of controls (P < 0.01)
	General respiratory symptoms	Khalaf et al.[25]	42 with severe RI + 66 controls	Cross-sectional controlled study	Continuous recording of respiratory rate, heart rate, nasal air flow	RI > 6, presence of feeding problems and response to anti-reflux measures	Respiratory distress syndrome defined by clinical features and positive chest radiograph	62% vs. 36% of controls (P = 0.02)
ENT symptoms	Sinusitis Otitis media	El-Serag et al.[12]	1980 with GERD + 7980 controls	Association case-controlled study	Database	Physician diagnosis	Physician diagnosis	4.2% vs. 1.4% of controls (P < 0.0001) 2.1% vs. 4.6% of controls (P < 0.0001)
Dental symptoms	Dental erosion	Linnett et al.[28]	52 with GERD + 52 healthy controls	Prospective controlled study	Dental examination/ medical/dental records	Physician diagnosis	WHO criteria for caries	14% had erosion vs. 10% of controls (P < 0.05)
	Dental erosion	Ersin et al.[27]	38 with GERD + 42 healthy controls	Cross-sectional controlled study	Questionnaire/ dental exam	Physician diagnosis	WHO criteria for caries Eccles & Jenkins index for erosion by GERD	76% had erosion vs. 10% of controls (P < 0.0001) 37% had severe erosion vs. 1% of controls (P < 0.05)

ALTE, apparent life-threatening event; ENT, ear, nose and throat; GERD, gastro-oesophageal reflux disease; RI, reflux index (% of total time when pH < 4); WHO, World Health Organization.

Table 2. Prevalence of GERD in children with extra-oesophageal symptoms

Symptom	Reference	Population size	Study design	Method of data collection	Definition of extra-oesophageal symptoms	Diagnosis of reflux symptom	Prevalence of GERD in-patients with extra-oesophageal symptoms
Respiratory symptoms							
Asthma	Stordal et al.[14]	872 asthmatics + 264 controls	Cross-sectional controlled study	Questionnaire	GINA classification[66]	GERD questionnaire[13]	19.7% of asthmatics had a positive GERD symptom score vs. 8.5% of controls (odds ratio, 2.6, $P < 0.001$)
Asthma	Barakat et al.[16]	75 asthmatics + 25 controls	Cross-sectional controlled study	Medical history/ examination	Physician diagnosis	Endoscopy/ ultrasound	GI symptoms in 65% of those with asthma vs. 16% of controls ($P < 0.001$)
Asthma	Chopra et al.[17]	80 asthmatics + 10 controls	Cross-sectional controlled study	Medical examination	≥3 episodes of reversible bronchospasm that lessen after therapy	Presence of sciatica tracer in oesophagus in more than two frames	39% of asthmatics demonstrated reflux on scintiscanning, vs. 0% of controls ($P < 0.05$)
Asthma	Hughes et al.[18]	9 asthmatics + 7 controls	Cross-sectional controlled study	Medical examination	ATS criteria for reversible obstructive airway disease	Oesophageal pH monitoring; reflux defined as a decrease in pH to < 4 for at least 15 s	Gastro-oesophageal reflux occurred in 33% of asthmatics vs. 57% of controls No significant difference between the two groups in number or duration of reflux episodes or % of time pH < 4

Table 2. (Continued)

Symptom	Reference	Population size	Study design	Method of data collection	Definition of extra-oesophageal symptoms	Diagnosis of reflux symptom	Prevalence of GERD in-patients with extra-oesophageal symptoms
Asthma	Debley et al.[15]	296 asthmatics + 1510 controls	Population-based, cross-sectional controlled study	Questionnaire	Physician diagnosed or a positive response to selected questions on the ISAAC questionnaire[67, 68]	Positive response to selected questionnaire questions	19.3% of adolescents with current asthma had GERD symptoms vs. 2.5% of adolescents without asthma ($P < 0.001$)
ALTE	Gorrotxategi et al.[21]	14 infants with ALTE + 10 controls	Cross-sectional controlled study	Medical examination	Defined using guidelines from NIH Consensus Development Conference on infant apnoea	24-h pH monitoring	RI = 5.614 in ALTE patients vs. 2.01 in controls (not significant)
ALTE	Kahn et al.[22]	20 infants admitted for ALTE + 10 controls	Cross-sectional controlled study	Medical examination	Physician diagnosis	Oesophageal pH monitoring	No significant difference between the two groups in terms of pH falls or duration
ALTE	Kahn et al.[23]	50 infants admitted for ALTE + 50 controls	Cross-sectional controlled study	Medical examination	Physician diagnosis	pH < 4 for ≥30 sec	No significant difference between the two groups in terms of pH falls
ALTE	Sacre and Vandenplas[24]	62 infants with ALTE + 378 controls	Cross-sectional controlled study	Medical examination	Physician diagnosis	24-h pH monitoring	42% of infants with ALTE had gastro-oesophageal reflux vs. 8.5% of controls
ENT symptoms							
Laryngotracheitis	Contencin and Narcy[26]	8 patients consulting for laryngotracheitis + 6 controls	Cross-sectional controlled study	Medical examination	Physician diagnosis	Dual-channel pH monitoring. Pathological gastro-oesophageal reflux defined as RI > 5.2%	62.5% of patients had pathological gastro-oesophageal reflux vs. 16.6% of controls

ALTE, apparent life-threatening event; ATS, American Thoracic Society; ENT, ear, nose and throat; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; GINA, Global Initiative for Asthma; ISAAC, International Study of Asthma and Allergies in Childhood; NIH, National Institutes of Health; RI, reflux index.
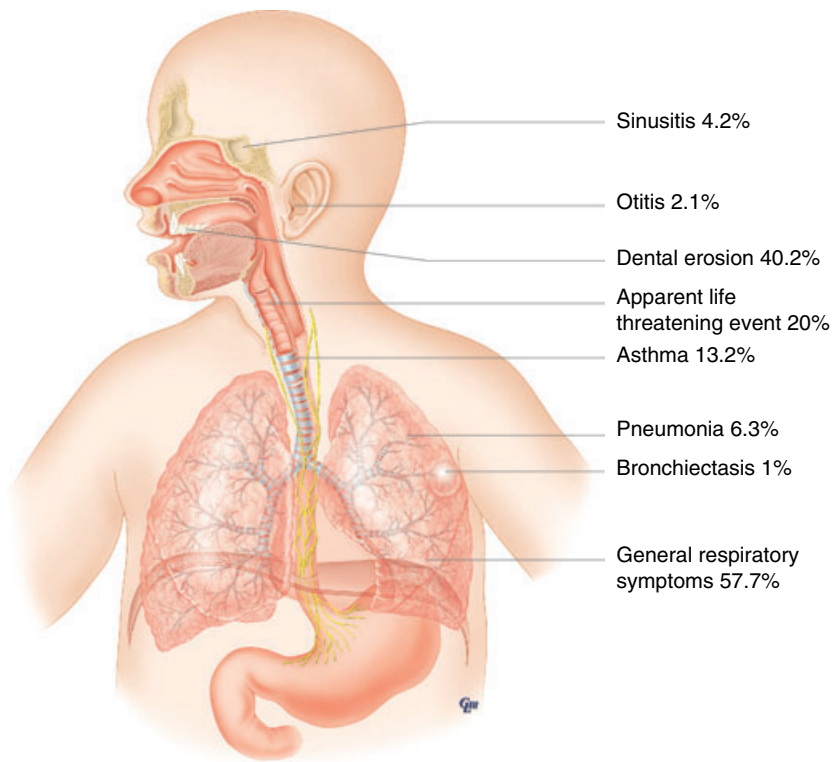
Figure 2. Estimated prevalence of extra-oesophageal symptoms in children with gastro-oesophageal reflux disease, based on five studies.

was twice that in controls (13.2% vs. 6.8%; $P < 0.0001$).[12]

Five studies evaluated the presence of GERD in children with asthma. Four of the studies reported a higher prevalence of GERD in children with asthma compared with healthy controls. A study in paediatric outpatient clinics evaluated 872 children (aged 7–16 years) with asthma (according to the Global Initiative for Asthma classification) and 264 healthy controls. Using the GERD Questionnaire developed by Nelson and colleagues,[13] the study showed that 19.7% of children with asthma had a positive GERD symptom score compared with 8.5% of controls (odds ratio 2.6, $P < 0.001$).[14] The questionnaire was completed regardless of current asthma symptoms. A further questionnaire-based study showed that among 13 and 14-year-olds with asthma, 19.3% had symptoms of GERD, compared with 2.5% of those without asthma ($P < 0.001$).[15] Another study showed the prevalence of gastrointestinal symptoms (investigated by endoscopy and abdominal ultrasonography) to be 65% in children with a diagnosis of asthma and 16% in healthy controls ($P < 0.001$).[16] A scintiscan study of 80 children (age range 9 months–12 years) with asthma (defined as three or more episodes of reversible bronchospasm) and a small control population of just 10 healthy controls

showed that 39% of the children with asthma but none of the controls had reflux symptoms.[17] However, this study evaluated just a single episode of postprandial reflux and therefore may not be a true indication of GERD. The smallest of the five studies investigated just nine children (mean age 15.2 years) with asthma according to the American Thoracic Society guidelines.[18] Oesophageal pH monitoring revealed that three of the nine children with asthma (33%) experienced reflux, compared with 4 of 7 healthy controls (57%).

Estimates of the prevalence of GERD in children with asthma varied between 19.3% and 65%, giving a pooled sample-size-weighted average prevalence of 23.4%. Estimates in controls varied between 0% and 57%, giving a pooled sample-size-weighted average prevalence of 3.8%. The variation in the results is most probably related to the methodology used to identify GERD. The studies using an oesophageal pH probe or endoscope reported relatively high prevalence estimates (33–65%),[16, 18] as did the study using scintigraphy (39%),[17] whereas the studies that used a questionnaire to assess GERD symptoms reported the lowest prevalence estimates (19.3% and 19.7%).[15, 19] Alternative sources of variation in the data include the small sample sizes, the lack of standardized definitions for reflux and asthma symptoms, the
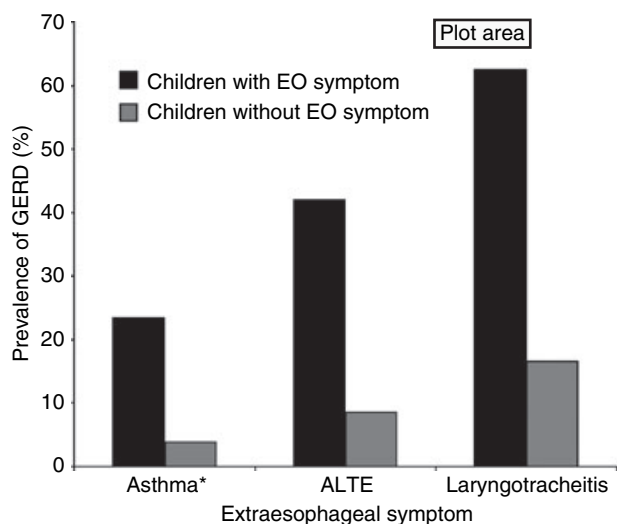
Figure 3. Reported prevalence estimates for gastro-oesophageal reflux disease (GERD) in children with extra-oesophageal symptoms. ALTE: apparent life-threatening event; EE: extra-oesophageal. *Represents the pooled sample-size-weighted average calculated from the prevalence estimates reported by four studies.

timing of the study in relation to the patients' symptoms, and the variation in age groups between the studies.

Pneumonia. Only one study meeting our inclusion criteria evaluated the prevalence of pneumonia in children with GERD. In the Texan study by El-Serag and colleagues described above, the prevalence of pneumonia in 1980 children with GERD was 6.3%, compared with 2.3% in a healthy control population of 7920 children ($P < 0.0001$).[12] Again, standardized definitions were not used for the symptoms, and the temporal relation between the onset of pneumonia and GERD symptoms was not noted; it is therefore hard to draw firm conclusions from these data alone.

Apparent life-threatening event. A large study reported the prevalence of ALTE (an episode characterized by some combination of apnoea, colour change, marked change in muscle tone, choking or gagging, that is frightening to the observer) to be 20% in a sample of 173 infants (under 1 year of age) with GERD (diagnosed as a reflux index greater than 5% on extended pH monitoring). This was less

than the prevalence among the 169 healthy controls (31%; $P < 0.12$).[20] As this study was retrospective, it did not document the rate of ALTEs that occurred during reflux. A further four smaller studies reported the occurrence of GERD in infants (less than 1 year of age) presenting with ALTE, although no study established a temporal link. Three of these studies reported no significant difference in terms of reflux symptoms between infants who had experienced an ALTE and controls.[21-23] However, the largest of the four studies evaluated 62 infants with episodes of paleness possibly suggestive of an ALTE.[24] The results of the study showed that 42% of the 62 infants had abnormal pH-metry results, compared with 8.5% of the 378 control infants.

Bronchiectasis. The retrospective study by El-Serag *et al.* described above showed that the prevalence of bronchiectasis was 10-fold higher in children with GERD than in healthy controls (1% vs. 0.1%; $P < 0.0001$).[12] It is hard to draw firm conclusions from these data alone, given the limitations of the study described above.

General respiratory symptoms. The two studies that investigated general or multiple respiratory symptoms in infants with GERD reported contradictory results. One database study showed that significantly fewer of the 173 infants (mean age 3.3 months) with GERD had respiratory symptoms (including wheezing, apnoea, aspiration, pneumonia, ALTE, and/or cyanotic episodes) than did the 169 controls (49% vs. 63%; $P < 0.01$).[20] A smaller cross-sectional study of 42 patients with GERD and 66 healthy controls showed a prevalence of up to 62% for general respiratory symptoms in infants with GERD, which was significantly higher than that in healthy children ($P < 0.02$).[25]

Ear, nose and throat symptoms. In the retrospective study described above, sinusitis was present in 4% of children with GERD compared with only 1% of controls ($P < 0.0001$).[12] Moreover, the prevalence of otitis media was significantly lower in children with GERD (2.1%) than in controls (4.6%; $P < 0.0001$) in the same study. No further data were found that confirmed this finding. A small prospective study of children (aged 2 months–7.5 years) being

evaluated for laryngotracheitis showed that 62% had pathological reflux, compared with 16.6% of controls.[26]

Dental erosion.   Two studies reported considerably different values for the prevalence of dental erosion in children with GERD (14% and 76%). Both showed that the prevalence was higher in children with GERD than in healthy controls ($P < 0.05$).[27, 28]

Other symptoms.   There were no studies meeting our inclusion criteria that evaluated the putative relationship between GERD in children and apnoea, cough, bronchitis, laryngitis, pharyngitis, functional recurrent abdominal pain, colic, rumination syndrome, cystic fibrosis or Sandifer's syndrome.

Pharmacotherapy of extra-oesophageal symptoms

The impact of pharmacotherapy of GERD on extra-oesophageal symptoms was evaluated in three studies in children (Table 3). A short-term (4-week) study considering the effect of the prokinetic agent cisapride (in the presence of the histamine-2 antagonist ranitidine) on persistent crying in infants aged 0.5–8.2 months showed no advantage over placebo.[29]

A 12-week study also failed to show improvement in asthma symptoms following treatment with a proton pump inhibitor (PPI).[19] However, a longer-term (6-month) study reported significant improvements in asthma symptoms in-patients receiving a PPI compared with control groups.[30]

DISCUSSION

Summary of results

Data from well-selected retrospective and prospective observational studies may suggest an association between GERD and asthma in children, and further possible associations with pneumonia, bronchiectasis, ALTE, laryngotracheitis, sinusitis and dental erosion. However, the paucity of large well-conducted controlled studies, the varying definitions of diseases used and the wide range of investigative techniques make it difficult to draw firm conclusions.

The impact on extra-oesophageal symptoms of treating GERD by pharmacological approaches varied between studies. PPIs may be beneficial in the control of childhood asthma, but further studies are needed to confirm this.

Results in context

Prevalence of GERD in children with extra-oesophageal symptoms.   The reported prevalence of GERD in children with asthma ranged from 19.3% to 65%. This wide variation in prevalence estimates most likely reflects the small sample sizes, the differing definitions of asthma and GERD used in studies, the fact whether or not asthma symptoms were present during the investigations, the variety of age groups studied, and the differing techniques used to make a diagnosis. None of the included studies differentiated patients with allergic asthma; the impact of the proposed link between GERD and atopic conditions (discussed below) on the results was therefore not apparent. The calculated pooled sample-size-weighted average for these prevalence data (23.4%) is higher than that for the control data from the same studies (3.8%). In adults, the prevalence of GERD symptoms in-patients with asthma appears to be higher (59.2%) than that found for children in our analysis.[9]

Data included in this review suggest a possible association between laryngotracheitis and GERD in children. The prevalence of pathological reflux (defined as a reflux index greater than 5.2%) in children with laryngotracheitis (62.5%) is substantially higher than previous estimates determining that 4–10% of adults with laryngeal disease have concomitant GERD.[31]

Previously reported estimates of the prevalence of GERD in the general paediatric population varied from approximately 2% to 25% depending on the symptoms evaluated.[13] A population-based retrospective study estimated the prevalence of GERD in children under 5 years of age (mean age at diagnosis, 7.3 months) to be 0.91 per 1000 person-years.[32] The broad range of reported prevalence estimates may be attributable to the lack of a uniform definition of symptoms and the methods of data collection. In the general adult population, a prevalence of 10–20% has been reported.[33] Only one of the four studies included in our analysis that investigated GERD in children who had symptoms suggestive of an ALTE reported a prevalence value.[24] The prevalence reported in this study (42%) is slightly higher than the figures reported by Nelson *et al.* and Dent *et al.*,[13, 33] possibly suggesting that ALTE is associated with an increased prevalence of GERD;

Table 3. Outcomes of GERD drug therapy on extra-oesophageal symptoms

Reference	Population size	Study design	Definition of reflux symptoms	Definition of extra-oesophageal symptom	Drug and dosage	Outcome
Khoshoo and Haydel[30]	44	Investigator-blinded prospective trial	24-h pH monitoring pH < 4 for >5% of the time	Asthma ≥ 3 episodes per year despite optimal treatment	Group A: esomeprazole (40 mg/day)/metoclopramide Group B: ranitidine (150 mg 3 times daily) Group C: control (fundoplication) All had previously had PPI/prokinetic for 1 year	Following 6 months' treatment, group B had significantly more exacerbations than groups A and C
Jordan et al.[29]	34	Randomized placebo-controlled trial	Oesophageal 24-h pH monitoring	Physician diagnosis of persistent crying	4 weeks treatment with ranitidine (3 mg/kg, 3 times daily) plus cisapride (0.2 mg/kg, 4 times daily)	Anti-reflux medications were not superior to placebo in treating infants with persistent crying
Stordal et al.[19]	38 with asthma	Randomized placebo-controlled trial	Questionnaire/RI ≥ 5 on 24-h pH monitoring	Physician-diagnosed asthma	Omeprazole 20 mg once daily or placebo for 12 weeks	Asthma symptoms scored by two questionnaires did not differ significantly between groups following treatment

PPI, proton pump inhibitor; RI, reflux index.

however, further large controlled studies using a standardized definition are required to confirm this.

A recent study in adults showed a positive association between cough and acid reflux in a significant subgroup of patients with chronic cough.[34] We did not identify any controlled studies that evaluated the association between GERD and cough in children. Nor did we identify any studies meeting our inclusion criteria that evaluated the putative relationship between GERD in children and apnoea, bronchitis, laryngitis, pharyngitis, functional recurrent abdominal pain, colic, rumination syndrome, cystic fibrosis or Sandifer's syndrome, mainly because of the lack of a control group.

Prevalence of extra-oesophageal symptoms in children with GERD. The single study of asthma in children with GERD showed asthma to be more prevalent in these children than in healthy controls. However, as discussed above, there are several limitations to this study and so more studies are required to confirm this finding. Similarly, evidence from a systematic review of adult data and a prospective multicentre open cohort study show that the prevalence of asthma is higher in adults with GERD than in the general population, but it appears to be lower than in the study in children described in our review.[3, 9] We found that pneumonia was more prevalent in children with GERD (6.3%) than has been previously found in a large population-based trial (2%).[35] The single study reporting the prevalence of ALTE in infants with GERD showed it to be lower than in controls. This suggests a lack of correlation between GERD and ALTE. Further large controlled prospective studies are required to confirm this result, but the findings are in agreement with previous data.[36] Respiratory symptoms such as cough, wheezing and asthma have been reported to be more common in children with an inlet patch (a distinct area of ectopic gastric mucosa located in the proximal oesophagus) than in controls.[37]

The large database study[12] that found an association between GERD in children and sinusitis is supported by data from a systematic review of adult patients that showed a positive association between GERD and both sinusitis and laryngeal malignancy.[38] The database study by El-Serag and colleagues[12] also showed that otitis media was significantly less prevalent in children with GERD than in controls. There is no evidence in the literature for a protective mechanism, so it seems unlikely that GERD is protective against otitis. This result may therefore be a consequence of the weaknesses of this study, as highlighted above. Data from two studies that did not meet the inclusion criteria for our review because of the lack of a control group reported an association between acid reflux and otitis media in children.[39, 40]

Despite few studies meeting the inclusion criteria for our review because of their lack of control group, we found some support for the hypothesis that children with GERD have a significantly higher prevalence of dental erosion than healthy controls. The acidic nature of gastric reflux is thought to cause characteristic dental erosion, although both GERD and dental erosion have been associated with common modifiable risk factors such as consumption of sugary carbonated soft drinks, and not brushing teeth after every meal.[41–43] A recent systematic review[44] showed a strong association between the prevalence of GERD and dental erosion. The median prevalence of GERD in adults with dental erosions was 32.5%, while in paediatric patients with dental erosions it was 17%. However, a study in young adults (19–22 years old) reported that there was no association between dental erosions and GERD.[45]

Pharmacotherapeutic data. We found possible support for an association between GERD and asthma in children from one long-term (6-month) pharmacotherapeutic trial of a PPI (esomeprazole, given in combination with metoclopramide),[30] although two shorter term studies (including one randomized blinded trial) failed to show a significant improvement in asthma symptoms over placebo of either omeprazole, or ranitidine in combination with cisapride.[19, 29] In their study, Khoshoo and Haydel selected only patients with pathological reflux and not those with weakly acid reflux, which may have favoured a positive effect of the PPI. The variation in the recorded outcomes may be a result of the anti-reflux therapy chosen; the superior control of extra-oesophageal symptoms with PPIs compared with cisapride may correspond with a greater effectiveness of PPIs in providing relief from GERD.[46, 47] Alternative reasons for the variation in the results could include the symptoms studied, the disease definitions and methodology used, the dosing regimen, the length of study and the small sample sizes.

A large controlled trial in adults showed that acid inhibition led to only a small improvement in asthma

symptoms in adults with gastro-oesophageal reflux who had nocturnal episodes of asthma.[48] In contrast, two recent meta-analyses found that PPIs failed to have a significant effect on chronic laryngeal symptoms that had been attributed to GERD in adult patients.[49, 50] Furthermore, a Cochrane systematic review of randomized controlled trials identified from the Cochrane Airways Group trial register evaluated the effects of GERD treatment on asthma.[51] The majority of the studies focussed on adult patients but one looked at the effects of GERD treatment in adolescent patients. In agreement with our findings, the authors of the Cochrane review found that the interventions used and outcomes assessed were inconsistent between the 12 studies they reviewed. The authors concluded that in-patients with both asthma and GERD, treatment for GERD did not produce consistent improvement in asthma symptoms. A more recent Cochrane review reported that there was insufficient evidence to conclude that PPI treatment is beneficial for cough associated with GERD in adults and children.[52]

Clinical implications

The lack of studies investigating the temporal relationship between GERD and extra-oesophageal symptoms makes it difficult to determine a causal relationship. Gastro-oesophageal reflux has previously been suggested to be a symptom of atopic disease.[53] It is therefore possible that GERD may be secondary to atopic conditions such as asthma. Allergic exacerbation may cause wheezing, which in turn induces reflux through an increase in intra-abdominal pressure. A further consideration is that reflux could cause respiratory symptoms. The reflex theory postulates that the presence of acid in the oesophagus stimulates a vagally mediated bronchoconstriction.[7] A large longitudinal study, conducted using the UK General Practice Research Database, showed that patients with asthma had an increased risk of developing GERD, but that patients with GERD did not have an increased risk of developing asthma.[54] Future longitudinal studies would help in clarifying any possible causal relationship.

Our results suggest that the prevalence of GERD may vary according to the methodology used to diagnose it. Further to clinical diagnoses, the most commonly used technique was pH-metry. However, it has the limitation of being unable to detect non-acid reflux and this is one reason why several other

techniques have been used to investigate GERD. Simultaneous dual channel oesophageal pH monitoring has been shown to identify reflux in a further 46% of children who would otherwise have been falsely presumed to have normal reflux parameters.[55] Multichannel intraluminal impedance is of use in the detection of non-acid or weakly acid reflux events.[56, 57] Radionuclide scanning can be used to detect episodes of gastro-oesophageal reflux and pulmonary aspiration occurring during or shortly after meals. Its reported sensitivity for micro-aspiration is relatively low, but the infrequency of aspiration events may explain a negative test.[58–60] Nuclear scintigraphy is not recommended in the routine diagnosis and management of GERD in infants and children but may be of use for detecting non-acid reflux events.[61] Oesophageal ultrasonography is a favourable option in children because of its non-invasive nature,[62–65] but at present its use as a diagnostic tool for GERD is limited. It is therefore necessary for physicians to consider the variability between techniques when evaluating extra-oesophageal manifestations of GERD in the paediatric population.

Further research is required to confirm the data reviewed in this study that suggest an association between GERD and several extra-oesophageal symptoms in children. GERD may be a possible underlying cause or aggravating factor in children with asthma and other respiratory symptoms. PPIs have been used for both the diagnosis and treatment of extra-oesophageal manifestations of GERD in adults, with varying success.[1] Despite a high proportion of studies showing abnormal reflux in-patients with asthma, empiric PPI therapy is unlikely to be an effective approach. Instead, long-term anti-reflux therapy should be used only for those with persistent refractory asthma. Today, there is no evidence to recommend the use of anti-reflux medication in-patients presenting only with respiratory symptoms and without an objective diagnosis of GERD or evidence of temporal relationship between reflux and the respiratory event. Further data are required to confirm the usefulness of anti-reflux therapies for managing extra-oesophageal symptoms in GERD in the paediatric population.

Strengths and limitations

Only one other systematic review has assessed the prevalence of extra-oesophageal symptoms and their

relationship with GERD in infants and children. Our review is the first systematic review to explore the relationship between a broad range of extra-oesophageal symptoms and GERD in children. There were a number of limitations to our analysis. Very few available studies included a healthy control cohort, which limited the number of studies that could be included in our review. To gain a better understanding of whether extra-oesophageal symptoms are more prevalent in-patients with GERD, and vice versa, we have made some comparisons with prevalence estimates from the general population. However, it is not ideal to draw comparisons between different population groups. Several studies did not explain how the GERD or extra-oesophageal conditions were diagnosed. As a result, there is likely to be variation in the definitions used and in the severity of illness, which makes direct comparisons of results difficult. Moreover, the lack of a consistent definition of GERD may have caused some patients to be falsely presumed to have GERD, resulting in inaccurate estimations of prevalence. The broad range in reported prevalence is probably the result of referral bias to centres with specialized interest, the sample size, or the technique used to make the diagnosis. A further consideration is that, because of the small number of studies that met our inclusion criteria, a substantial proportion of our data came from a single study that investigated multiple symptoms in children with GERD.[12] Therefore, the limitations of the study by El-Serag and colleagues described above may have skewed the results of this review. Variations between the studies are also likely to have had an impact on the results from the pharmacotherapeutic trials; the studies varied in terms of the combinations of drugs used, the dosing regimens, the length of treatment and the symptoms studied.

Conclusions and future work

This review presents retrospective evidence from the literature that many children and infants with reflux symptoms may also have extra-oesophageal symptoms. It highlights the need for further well-designed case-controlled trials, using standardized techniques of investigation, a standardized definition of GERD (such as the Montreal Definition or the new paediatric definition of GERD[1, 11]) and standardized definitions of the extra-oesophageal symptoms. Future trials of anti-reflux therapies should be randomized controlled trials with appropriate control groups and make use of newer techniques such as Multichannel impedance pH monitoring so that clinically useful conclusions may be drawn. Longitudinal studies assessing the temporal relationship between GERD and extra-oesophageal symptoms in children are also needed.

REFERENCES

1 Vakil N, Veldhuyzen van Zanten S, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastro-esophageal reflux disease (GERD) – a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**: 1900–20.

2 Hungin AP, Raghunath A, Wiklund I. Beyond heartburn: a review of the spectrum of reflux-induced disease. *Fam Pract* 2005; **22**: 591–603.

3 Jaspersen D, Kulig M, Labenz J, *et al.* Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. *Aliment Pharmacol Ther* 2003; **17**: 1515–20.

4 Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. *Gastroenterology* 1997; **112**: 1448–56.

5 El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. *Gastroenterology* 1997; **113**: 755–60.

6 Gislason T, Janson C, Vermeire P, *et al.* Respiratory symptoms and nocturnal gastroesophageal reflux: a population-based study of young adults in three European countries. *Chest* 2002; **121**: 158–63.

7 Paterson WG. Extraesophageal complications of gastroesophageal reflux disease.

Can J Gastroenterol 1997; 11(Suppl B): 45B–50B.

8 Avidan B, Sonnenberg A, Schnell TG, Sontag SJ. Temporal associations between coughing or wheezing and acid reflux in asthmatics. *Gut* 2001; 49: 767–72.

9 Havemann B, Henderson CA, El-Serag HB. The association between gastro-esophageal reflux disease and asthma: a systematic review. *Gut* 2007; 56: 1654–64.

10 Rosbe KW, Kenna MA, Auerbach AD. Extraesophageal reflux in pediatric patients with upper respiratory symptoms. *Arch Otolaryngol Head Neck Surg* 2003; 129: 1213–20.

11 Sherman P. *A Global, Evidence-Based Consensus on the Defintion of Pediatric Gastroesophageal Reflux Disease (GERD) WCPGHAN-3 Congress*. 2008.

12 El-Serag HB, Gilger M, Kuebeler M, Rabeneck L. Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects. *Gastroenterology* 2001; 121: 1294–9.

13 Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med* 2000; 154: 150–4.

14 Stordal K, Johannesdottir GB, Bentsen BS, Carlsen KC, Sandvik L. Asthma and overweight are associated with symptoms of gastro-oesophageal reflux. *Acta Paediatr* 2006; 95: 1197–201.

15 Debley JS, Carter ER, Redding GJ. Prevalence and impact of gastroesophageal reflux in adolescents with asthma: a population-based study. *Pediatr Pulmonol* 2006; 41: 475–81.

16 Barakat M, Sherit AH, El-Kady ZM, Hasanean MH. Patterns of Gastrointestinal symptoms in children with wheezy chest. *Gut* 2006; 55(Suppl 5): G-403.

17 Chopra K, Matta SK, Madan N, Iyer S. Association of gastroesophageal reflux (GER) with bronchial asthma. *Indian Pediatr* 1995; 32: 1083–6.

18 Hughes DM, Spier S, Rivlin J, Levison H. Gastroesophageal reflux during sleep in asthmatic patients. *J Pediatr* 1983; 102: 666–72.

19 Stordal K, Johannesdottir GB, Bentsen BS, *et al.* Acid suppression does not change respiratory symptoms in children with asthma and gastro-oesophageal reflux disease. *Arch Dis Child* 2005; 90: 956–60.

20 Tolia V, Wuerth A, Thomas R. Gastroesophageal reflux disease: review of presenting symptoms, evaluation, management, and outcome in infants. *Dig Dis Sci* 2003; 48: 1723–9.

21 Gorrotxategi P, Eizaguirre I, Saenz de Ugarte A, *et al.* Characteristics of continuous esophageal pH-metering in infants with gastroesophageal reflux and apparent life-threatening events. *Eur J Pediatr Surg* 1995; 5: 136–8.

22 Kahn A, Rebuffat E, Sottiaux M, Blum D, Yasik EA. Sleep apneas and acid esophageal reflux in control infants and in infants with an apparent life-threatening event. *Biol Neonate* 1990; 57: 144–9.

23 Kahn A, Rebuffat E, Sottiaux M, Dufour D, Cadranel S, Reiterer F. Lack of temporal relation between acid reflux in the proximal oesophagus and cardiorespiratory events in sleeping infants. *Eur J Pediatr* 1992; 151: 208–12.

24 Sacre L, Vandenplas Y. Gastroesophageal reflux associated with respiratory abnormalities during sleep. *J Pediatr Gastroenterol Nutr* 1989; 9: 28–33.

25 Khalaf MN, Porat R, Brodsky NL, Bhandari V. Clinical correlations in infants in the neonatal intensive care unit with varying severity of gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 2001; 32: 45–9.

26 Contencin P, Narcy P. Gastropharyngeal reflux in infants and children. A pharyngeal pH monitoring study. *Arch Otolaryngol Head Neck Surg* 1992; 118: 1028–30.

27 Ersin NK, Oncag O, Tumgor G, Aydogdu S, Hilmioglu S. Oral and dental manifestations of gastroesophageal reflux disease in children: a preliminary study. *Pediatr Dent* 2006; 28: 279–84.

28 Linnett V, Seow WK, Connor F, Shepherd R. Oral health of children with gastroesophageal reflux disease: a controlled study. *Aust Dent J* 2002; 47: 156–62.

29 Jordan B, Heine RG, Meehan M, Catto-Smith AG, Lubitz L. Effect of antireflux medication, placebo and infant mental health intervention on persistent crying: a randomized clinical trial. *J Paediatr Child Health* 2006; 42: 49–58.

30 Khoshoo V, Haydel R Jr. Effect of antireflux treatment on asthma exacerbations in nonatopic children. *J Pediatr Gastroenterol Nutr* 2007; 44: 331–5.

31 Gilger MA. Pediatric otolaryngologic manifestations of gastroesophageal reflux disease. *Curr Gastroenterol Rep* 2003; 5: 247–52.

32 Chitkara DK, Talley N, Weaver AL, *et al.* Incidence of presentation of common functional gastrointestinal disorders in children from birth to 5 years: a cohort study. *Clin Gastroenterol Hepatol* 2007; 5: 186–91.

33 Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; 54: 710–7.

34 Blondeau K, Dupont LJ, Mertens V, Tack J, Sifrim D. Improved diagnosis of gastro-oesophageal reflux in patients with unexplained chronic cough. *Aliment Pharmacol Ther* 2007; 25: 723–32.

35 Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's respiratory study. II. Lower respiratory tract illness in the first year of life. *Am J Epidemiol* 1989; 129: 1232–46.

36 Ariagno RL, Guilleminault C, Baldwin R, Owen-Boeddiker M. Movement and gastroesophageal reflux in awake term infants with "near miss" SIDS, unrelated to apnea. *J Pediatr* 1982; 100: 894–7.

37 Macha S, Reddy S, Rabah R, Thomas R, Tolia V. Inlet patch: heterotopic gastric mucosa – another contributor to supra-esophageal symptoms? *J Pediatr* 2005; 147: 379–82.

38 Weaver EM. Association between gastroesophageal reflux and sinusitis, otitis media, and laryngeal malignancy: a systematic review of the evidence. *Am J Med* 2003; 115(Suppl 3A): 81S–9S.

39 Crapko M, Kerschner JE, Syring M, Johnston N. Role of extra-esophageal reflux in chronic otitis media with effusion. *Laryngoscope* 2007; 117: 1419–23.

40 Tasker A, Dettmar PW, Panetti M, Koufman JA, J PB, Pearson JP. Is gastric reflux a cause of otitis media with effusion in children? *Laryngoscope* 2002; 112: 1930–4.

41 Mayne ST, Risch HA, Dubrow R, *et al.* Carbonated soft drink consumption and risk of esophageal adenocarcinoma. *J Natl Cancer Inst* 2006; 98: 72–5.

42 Larsen MJ, Nyvad B. Enamel erosion by some soft drinks and orange juices relative to their pH, buffering effect and contents of calcium phosphate. *Caries Res* 1999; 33: 81–7.

43 Dahshan A, Patel H, Delaney J, Wuerth A, Thomas R, Tolia V. Gastroesophageal reflux disease and dental erosion in children. *J Pediatr* 2002; 140: 474–8.

44 Pace F, Pallotta S, Tonini M, Vakil N, Bianchi Porro G. Systematic review: gastro-oesophageal reflux disease and dental lesions. *Aliment Pharmacol Ther* 2008; 27: 1179–86.

45 Jensdottir T, Arnadottir IB, Thorsdottir I, *et al.* Relationship between dental erosion, soft drink consumption, and

gastroesophageal reflux among Icelanders. *Clin Oral Investig* 2004; **8**: 91–6.

46 Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. *Cochrane Database Syst Rev* 2007; (2): CD003244.

47 van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* 2006; **3**: CD002095.

48 Kiljander TO, Harding SM, Field SK, *et al.* Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006; **173**: 1091–7.

49 Gatta L, Vaira D, Sorrenti G, Zucchini S, Sama C, Vakil N. Meta-analysis: the efficacy of proton pump inhibitors for laryngeal symptoms attributed to gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007; **25**: 385–92.

50 Qadeer MA, Phillips CO, Lopez AR, *et al.* Proton pump inhibitor therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2006; **101**: 2646–54.

51 Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. *Cochrane Database Syst Rev* 2003; (2): CD001496.

52 Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev* 2006; (4): CD004823.

53 Iacono G, Carroccio A, Cavataio F, *et al.* Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. *J Allergy Clin Immunol* 1996; **97**: 822–7.

54 Ruigomez A, Garcia Rodriguez LA, Wallander MA, Johansson S, Thomas M, Price D. Gastroesophageal reflux disease and asthma: a longitudinal study in UK general practice. *Chest* 2005; **128**: 85–93.

55 Little JP, Matthews BL, Glock MS, *et al.* Extraesophageal pediatric reflux: 24-hour double-probe pH monitoring of 222 children. *Ann Otol Rhinol Laryngol Suppl* 1997; **169**: 1–16.

56 Castell DO, Vela M. Combined multichannel intraluminal impedance and pH-metry: an evolving technique to measure type and proximal extent of gastroesophageal reflux. *Am J Med* 2001; **111**(Suppl 8A): 157S–9S.

57 Shay SS, Johnson LF, Richter JE. Acid rereflux: a review, emphasizing detection by impedance, manometry, and scintigraphy, and the impact on acid clearing pathophysiology as well as interpreting the pH record. *Dig Dis Sci* 2003; **48**: 1–9.

58 McVeagh P, Howman-Giles R, Kemp A. Pulmonary aspiration studied by radionuclide milk scanning and barium swallow roentgenography. *Am J Dis Child* 1987; **141**: 917–21.

59 Ravelli AM, Panarotto MB, Verdoni L, Consolati V, Bolognini S. Pulmonary aspiration shown by scintigraphy in gastroesophageal reflux-related respiratory disease. *Chest* 2006; **130**: 1520–6.

60 Fawcett HD, Hayden CK, Adams JC, Swischuk LE. How useful is gastroesophageal reflux scintigraphy in suspected childhood aspiration? *Pediatr Radiol* 1988; **18**: 311–3.

61 Vandenplas Y, Ashkenazi A, Belli D, *et al.* A proposition for the diagnosis and treatment of gastro-oesophageal reflux disease in children: a report from a working group on gastro-oesophageal reflux disease. Working group of the European Society of Paediatric Gastro-enterology and Nutrition (ESPGAN). *Eur J Pediatr* 1993; **152**: 704–11.

62 Di Ciaula A, Portincasa P, Di Terlizzi L, Paternostro D, Palasciano G. Ultrasonographic study of postcibal gastro-esophageal reflux and gastric emptying in infants with recurrent respiratory disease. *World J Gastroenterol* 2005; **11**: 7296–301.

63 Naik DR, Bolia A, Moore DJ. Comparison of barium swallow and ultrasound in diagnosis of gastro-oesophageal reflux in children. *Br Med J (Clin Res Ed)* 1985; **290**: 1943–5.

64 Westra SJ, Wolf BH, Staalman CR. Ultrasound diagnosis of gastroesophageal reflux and hiatal hernia in infants and young children. *J Clin Ultrasound* 1990; **18**: 477–85.

65 Riccabona M, Maurer U, Lackner H, Uray E, Ring E. The role of sonography in the evaluation of gastro-oesophageal reflux – correlation to pH-metry. *Eur J Pediatr* 1992; **151**: 655–7.

66 Von Mutius E. Presentation of new GINA guidelines for paediatrics. The global initiative on asthma. *Clin Exp Allergy* 2000; **30**(Suppl 1): 6–10.

67 Gibson PG, Henry R, Shah S, *et al.* Validation of the ISAAC video questionnaire (AVQ3.0) in adolescents from a mixed ethnic background. *Clin Exp Allergy* 2000; **30**: 1181–7.

68 Asher MI, Keil U, Anderson HR, *et al.* International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; **8**: 483–91.