Multidisciplinary Respiratory Medicine 2022; volume 17:832

ORIGINAL RESEARCH ARTICLE

A putative link between pertussis and new onset of gastroesophageal reflux an observational study

Leticia Burton,[1] Daminda P. Weerasinghe,[1] David Joffe,[2] Jennifer Saunders-[3] Gregory L. Falk,[4] Hans Van der Wall[1]

[1]CNI Molecular Imaging and University of Notre Dame, Sydney
[2]Department of Respiratory Medicine, Royal North Shore Hospital, Sydney
[3]Spine & Sports Medicine and University of Notre Dame, Sydney
[4]Sydney Heartburn Clinic, Concord Hospital; University of Sydney, Australia

ABSTRACT

Background: Pertussis is an infectious disease of the respiratory tract with a changing epidemiology. An increasing incidence has been found in the adult population with recurrent infections possibly related to changes in the current vaccine. Is there an association between pertussis infection, refractory cough and atypical gastro-oesophageal reflux (GORD)? Does this magnify and compound respiratory complications?

Methods: Observational study which compares post-pertussis (n=103) with non-pertussis patients (n=105) with established GORD. Patients were assessed for laryngopharyngeal reflux and aspiration of refluxate by a novel scintigraphic study.

Results: Both groups showed severe GORD in association with high rates of laryngopharyngeal reflux (LPR) and pulmonary aspiration and lung disease. High rates of hiatus hernia and clinical diagnosis of "atypical" asthma showed correlations with pulmonary aspiration.

Conclusions: A high level of new onset LPR and lung aspiration has been shown in patients with chronic cough after recent pertussis infection by a novel scintigraphic technique with fused hybrid x-ray computed tomography (SPECT/CT).

Key words: GORD; scintigraphy; laryngopharyngeal; aspiration; hiatus hernia; asthma.

Correspondence: Leticia Burton, CNI Molecular Imaging, Suite 101/5 Bay Dr, Meadowbank, NSW 2114, Australia.
Tel. +61.2.97361040 - Fax: +61.2.97362095. E-mail: leticia.burton@gmail.com

Contributions: LB, DJ, concept; LB, HVW, DW, writing; DJ, JS, GLF, editing; DW, HVW, statistics; LB, DW, JS, HVW, design. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Availability of data and materials: The datasets used and/or analysed during the study are available from corresponding author on reasonable request.

Ethics approval: The study was approved by the Institutional Ethics Committee of the University of Notre Dame (Reference number 015149S). All patients provided written and informed consent.

Introduction

Pertussis commonly known as "whooping cough" is an infectious disease of the respiratory tract caused by *Bordetella pertussis* or *Bortedella parapertussis* [1]. The disease primarily affected young children, with a high associated mortality rate [1-3]. The introduction of vaccination in the late 1940s led to a significant reduction in cases globally. A brief resurgence in the disease was seen in the 1970s and 1980s in the United Kingdom due to the disruption in the vaccination program. However, a significant increase has been observed in a period of the last 30 years in the adolescent and adult population in developed countries [1,2,4]. This change in epidemiology is demonstrated by the rate of pertussis infection in Australia, shown in Figure 1.

Multiple factors may have contributed to this resurgence but the most notable include i) waning immunity resulting from omission of a booster [5-8]; ii) increased screening due to greater accessibility and sensitivity for the diagnosis with nucleic acid testing and the polymerase chain reaction (PCR) [9]. There is also some evidence that the current acellular vaccine may be less effective than the older whole cell vaccine [5,10,11]. Complications observed in adults include encephalitis, pneumonia (4%), pneumothorax, sinusitis/otitis media (13%), transient urinary incontinence (4%), aspiration, hearing loss, rib fracture (2%), inguinal hernia and weight loss (3%) [2,4,12]. The symptom profile [13] indicates 97% reported cough (of >3 weeks duration), 73% had a paroxysmal cough, 89% reported apnoeic episodes and 65% vomiting [12]. Chronic persistent cough following appropriate diagnosis using serology and treatment, usually warrants further investigation [14,15].

This study was triggered by the disturbing observation of a common history in many patients who reported a temporal relationship between acute clinical pertussis infection and the onset of symptomatic reflux. This led to a putative hypothesis that the acute onset of gastro-oesophageal reflux in this group may have been linked to persistent explosive cough and changes in the thoraco-abdominal pressure gradients leading to symptomatic reflux, particularly laryngopharyngeal reflux (LPR) and pulmonary aspiration. To evaluate this hypothesis a large consecutive cohort of patients who presented with proven gastro-oesophageal reflux were divided into those i) with a history of recent clinical pertussis (IgA positive) associated with the initial onset of symptomatic reflux and ii) with no history of past or recent pertussis infection, and mostly with atypical symptom (rarely with heartburn/ regurgitation).

Methods

Study setting

The data was collected during specific referral for investigation of possible laryngopharyngeal reflux (LPR) or lung aspiration in individuals with established gastro-oesophageal reflux disease (GORD). Consecutive patients were prospectively entered into a database and divided by new-onset (<6 months) GORD/LPR following clinically established "whooping cough" and serologically confirmed recent pertussis infection (IgA+) or long-standing GORD/LPR without a history of pertussis infection (IgA-). All patients were investigated with standard pH/ impedance/manometry and/ or gastroscopy prior to referral for the scintigraphic test and confirmed as having gastroesophageal reflux disease.

Ethics approval

The study was approved by the Institutional Ethics Committee of the University of Notre Dame (Reference number 015149S). All patients provided written and informed consent.

All individuals completed standardised reflux questionnaires such as the Reflux Symptom Index (RSI) [16], the Cough Severity Index (CSI), Newcastle Laryngeal Hypersensitivity Questionnaire (LHQ) [17].

Study population

Patients were prospectively referred to a single centre for scintigraphic assessment of LPR symptoms and/or pulmonary aspiration. All patients fulfilling the diagnosis of GORD and LPR/ pulmonary aspiration were included. The only exclusion criteria were anti-reflux treatment prior to the initial pertussis infection or if immunocompromised. The patients with a recent clinical and serological diagnosis of pertussis were analysed as a comparative group against the remainder of the patients with no history of pertussis. Data was collected over an 18-month period and stored in a password protected secure central database. Patients were referred from a variety of sources that included otolaryngology, respiratory, gastroenterology, and general practice.

All individuals had an established diagnosis of GORD (gastroscopy/pH/impedance and manometry) with refractory symptoms. This was an important criterion for inclusion with the major aim of evaluating subjects for laryngopharyngeal contamination or lung aspiration of refluxate. The clinical diagnosis of pertussis was based on published guidelines of the American College of Chest Physicians (CHEST) [18]. Principal symptoms included paroxysmal cough, post-tussive vomiting, inspiratory whoop and absence of fever. IgA testing for pertussis was performed with an enzyme-linked immunosorbent assay to *Bordetella pertussis* toxin (ab247192, Abcam, Melbourne, Australia).

Scintigraphic method

The scintigraphic technique has been extensively described in previous publications [19-23]. Briefly, patients were fasted for 4 hours prior to the scan. A dose of 60-100MBq of Tc-99m Phytate (colloid) was administered in water. All images were acquired on a General Electric Hawkeye 4 Hybrid gamma camera (General

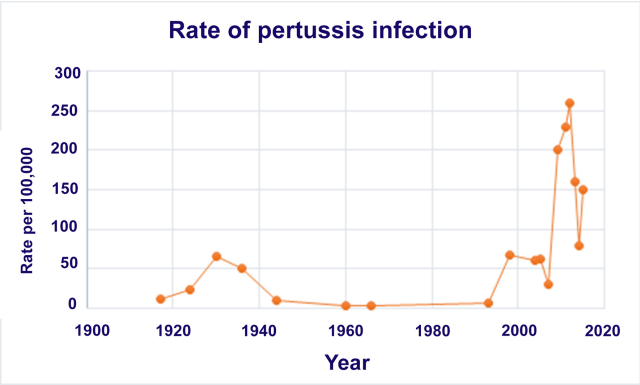

Figure 1. Graph showing rates of pertussis infection in Australia. A significant fall occurs in the early 1940s after institution of whole-cell vaccines. Following the change to the acellular vaccines in the 1970s, there is a progressive rise which peaks in 2012 and remains relatively high.

Electric, Milwaukee, WI, USA). Two consecutive dynamic studies were acquired from the mandible to the stomach i) a 2-min upright image; ii) 30-min supine image. A delayed single photon emission tomography/X-ray computed tomography (SPECT/CT) image of the head, neck and thoracic structures at 2 hours. Dynamic images were qualitatively and quantitatively evaluated. Liquid gastric emptying (LGE) was assessed using geometric mean analysis of the supine study. Analytic time-activity curves of the laryngopharyngeal region and oesophagus were generated and other parameters of oesophageal reflux derived. These results will be presented in a separate manuscript as a large amount of data resulted from the analysis.

Registered SPECT/CT images were qualitatively evaluated in 3 standard projections for evidence of refluxate in the head, neck and pulmonary structures. The diagnosis was binary, either showing LPR/ pulmonary aspiration or not.

Statistical analysis

The symptomatic profile of the patients was assessed using standardised questionnaires such as the cough severity index (CSI), reflux severity index (RSI) and Newcastle laryngeal hypersensitivity questionnaire score (LHQ). Chi square test was applied between aspiration and the following 2*2 categorical variables; known hiatus hernia, burping, fundoplication, bloating, respiratory function test, asthma, chest infection, pneumonia, and pulmonary disease. The variables with multiple criteria; body mass index (BMI) (kg/m^2) and reflux frequency were assessed with the analysis of variance (ANOVA).

The following were assessed as continuous variables; patients age (years from the date of assessment), area under the curve (AUC) for pharynx to background and amplitude of reflux and these were reported as medians with interquartile ranges (IQR).

The dependent variable aspiration and several independent variables; hiatus hernia, gender, burping, bloating, RFT, asthma, pneumonia, and pulmonary disease were set as dichotomous variables. The other selected independent predictors were categorised with appropriate cut-off points. CSI was grouped as ≤3 and >3, and ≤3 as control [17]. LHQ was grouped as ≤17.1 and >17.1, and ≤17.1 as the control [24]. Gastric emptying time (GE) (in min) was grouped as <19 min and ≥19, and <19 min as the control. BMI was grouped as underweight, healthy weight, overweight and obese, and healthy weight as the control.

The strength of linear relationships was determined using Spearman correlation coefficients. Covariates with a p≤0.25 were entered into the multivariate logistic regression model. In the multivariate model, variables were selected with stepwise, backward elimination. Significance was defined as a p<0.05. Logistic models were validated with c and the Hosmer-Lemeshow statistics [25]. Statistical analyses were conducted with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 208 patients were included in the study, 103 patients with recent clinical pertussis and supportive IgA serology and 105 with no history of pertussis infection. The age range of the patients in the two groups was 16.0 to 85.0 years. In the pertussis group the distribution of males and females was 70% females and 30% males,

Table 1. **Spearman correlation coefficients and bivariate association of patient characteristics for patients with and without pertussis.**

Patient characteristics	With pertussis (n=103)		No pertussis (n=105)			Spearman correlation	
Continuous variables	Median	IQR	Median	IQR	p	For pertussis	p
Age at screening (years)	61.2	23.1	55.8	20.3	0.025	0.180	0.003
BMI (kg/m^2)	27.9	8.1	27.6	8.5	0.563	-0.184	0.005
Amplitude	2.4	1.6	2.2	1.3	0.068	0.138	0.023
Reflux symptom index	23	14	20	14	0.104	0.077	0.330
Cough severity index	11	22	6	17	0.018	0.148	0.059
LHQ	14.5	5.4	14.1	6.0	0.458	0.164	0.036
Area under the curve	1.2	1.3	1.1	0.8	0.035	0.151	0.013
Frequency of reflux	3	4	3	2	0.933	-0.031	0.614
GE (minutes)	18.6	23.9	23.4	32.8	0.436	-0.108	0.077
Categorical variables	**n**	**%**	**n**	**%**	**p**		
Gender (male)	30	29.1	40	38.1	0.171	0.008	0.919
Known hiatus hernia	32	31.1	28	26.7	0.484	-0.005	0.954
Aspiration	30	29.1	42	40.0	0.099	-0.060	0.446
Burping	52	50.5	57	54.3	0.583	-0.113	0.152
Fundoplication	3	2.9	3	2.8	0.981	0.013	0.872
Bloating	60	58.2	59	56.2	0.764	-0.039	0.620
Respiratory function test	52	50.5	44	41.9	0.215	0.046	0.557
Asthma	36	34.9	30	28.6	0.323	0.027	0.737
Chest infection	53	51.5	46	43.8	0.270	0.003	0.973
Pneumonia	33	32.0	26	24.7	0.244	0.063	0.423
Pulmonary fibrosis	6	5.8	7	6.7	0.802	0.046	0.557

BMI, Body mass index; LHQ, Newcastle laryngeal hypersensitivity questionnaire; GE, gastric emptying time.

with an age range from 16.6 to 85.5years and mean 60.2 (median 61.2) years. The group without a history of pertussis comprised 62% females and 38% males. The age range for the non-pertussis group was 18.6 to 84.9 years with a mean age of 55.5 (median 55.8) years. There was no significant difference between the two groups by gender ($p<0.05$), but a significant difference for mean age ($p=0.02$). The age distribution of the pertussis group was skewed to an older age cohort and the non-pertussis group was normally distributed. The body mass index (BMI) scores were not significantly different ($p<0.05$) at 28.2 (median 27.9) (overweight) for the pertussis group and 27.6 (median 27.4) for the non-pertussis group. BMI was >30 (obese) in 51% of the pertussis group and 47% of the non- pertussis group. Hiatus hernias were shown in 31% with pertussis and 27% without ($p<0.05$). High resolution x-ray computed tomography (HRCT) of the lungs was reported as abnormal in 94.1% pertussis group and 93.4% in the non-pertussis group ($p<0.05$) being a mixture of fibrotic changes and bronchiectasis (Figure 2). Summarised results and correlations are shown in Table 1.

Symptom profiling

The principal symptoms reported were chronic cough (90%), throat clearing (85%), sore throat (70%), bloating (45%), burping (30%), episodic choking (8%), recurrent chest infections and dyspnoea (20%). Cough was reported more frequently in the group with pertussis infection (96%). Heartburn was reported in few patients (<5%). A label of "atypical" asthma had been clinically applied in 66% of patients with pertussis and 74% without, prior to referral by the referring doctors ($p<0.05$). The patients arrived for their study with this diagnosis already made by the managing clinician. There was no supportive clinical evidence of reversible airways disease or lung function testing to support this diagnosis. Respiratory function tests (RFTs) showed non-specific abnormalities in many of these patients.

The mean RSI scores between the two groups were not significant ($p<0.05$) at 23 (pertussis) *versus* 20 (non-pertussis), although in the abnormal range (>13). The CSI of the two groups was different with a median of 11 for the pertussis group and 6 in the non-pertussis groups ($p=0.02$). However, the Newcastle LHQ scores between the two groups was not different ($p<0.05$) at 14.5 and 14.1 respectively, although abnormal (<17) (Table 1). Asthma was diagnosed clinically in 35% with pertussis and in 29% without, a non-significant difference ($p<0.05$).

Scintigraphic findings

Scintigraphic evidence of gastro-oesophageal reflux disease was confirmed in all patients on dynamic planar imaging in the upright and supine positions. Delayed SPECT/CT imaging of the head, neck and lungs demonstrated LPR events (Figure 3) and pulmonary aspiration (Figures 2 and 4) in 29% of the pertussis group and 40% of the non-pertussis group ($p<0.05$). Events without involvement of the laryngopharynx or pulmonary aspiration were diagnosed in 14% of pertussis and 21% of the non-pertussis group ($p<0.05$). No gender difference was found between patients with and without LPR ($p>0.05$). LGE studies were abnormal ($T_{1/2}$ >19 minutes) in 57% of the pertussis group (Mean=36.6 min) and 93% non- pertussis group (Mean 53.3 min) ($p<0.05$) (Figure 5). Correlations with LPR and pulmonary aspirations are shown in Table 1.

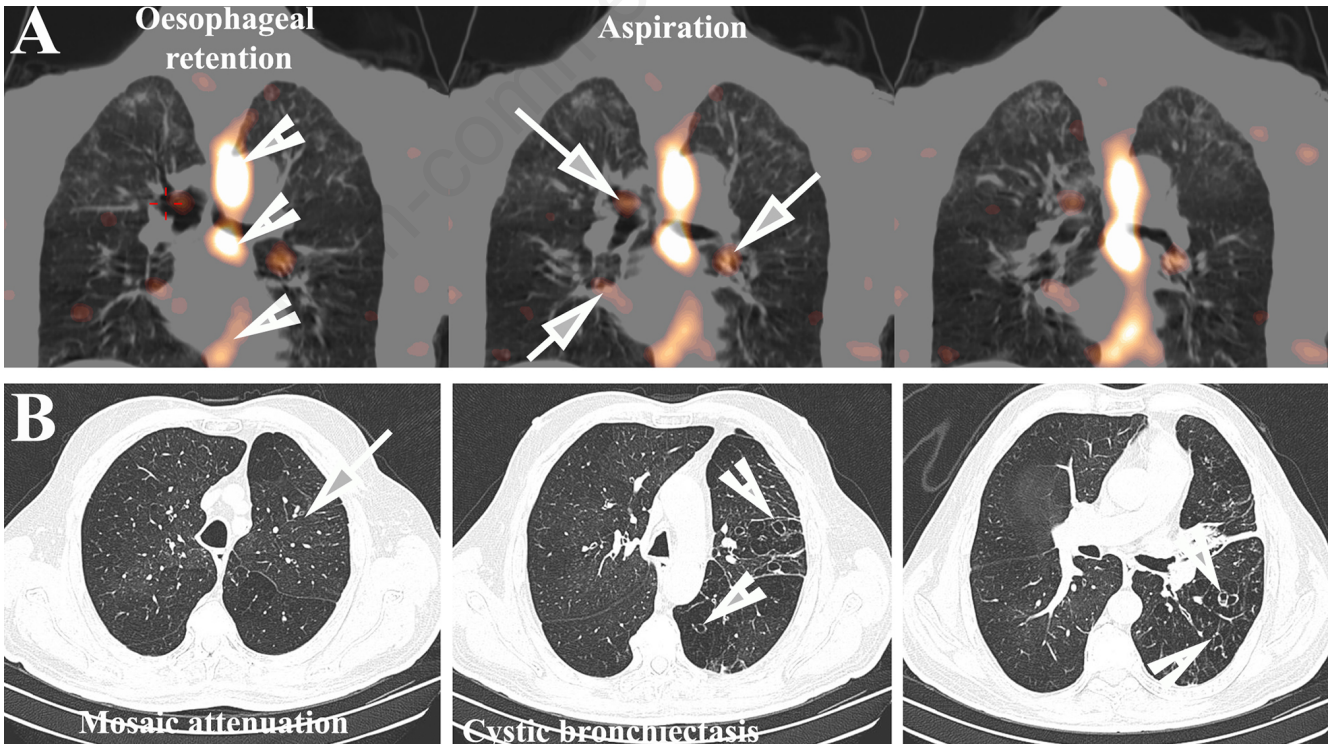

Figure 2. A) Coronal images from a low-dose SPECT/CT study of the lungs which shows significant retention of refluxate in the oesophagus (arrowheads) and refluxate located in the main bronchi (arrows). B) High-resolution transaxial CT images of the chest showing a combination of mosaic attenuation (arrows) and cystic bronchiectasis (arrowheads).

Bivariate association of patient characteristics with pulmonary aspiration

The only comorbid condition shown to have statistically significant association with aspiration was BMI. Half of the patients with healthy weight had aspiration, while only 21.8% of the obese patients had aspiration (Table 2). AUC and GE also show a statistically significant association with aspiration.

Predictors of pulmonary aspiration by multivariate analysis

Controlling for patients with LPR, the predictors of aspiration were assessed with a logistic regression model (Table 3). With backward elimination, 11 variables were retained in the final model. The logistic model has strong discriminatory properties. In terms of area under the receiver operating curve (ROC) analysis shown to be

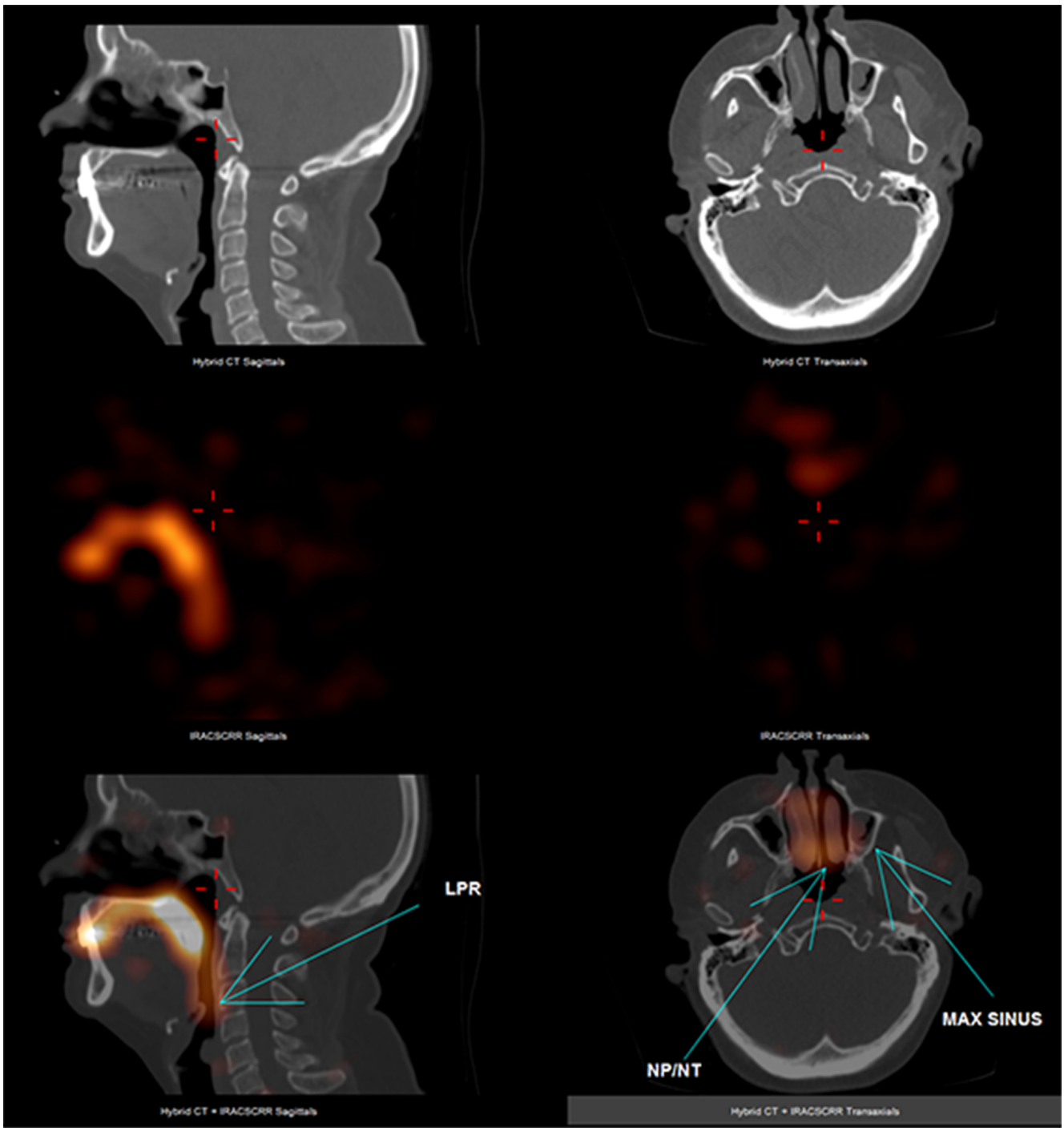

Figure 3. The low-dose SPECT/CT images of the head and neck in the sagittal and transaxial planes with fusion images show refluxate contaminating the laryngopharynx (LPR), nasopharynx (NP), nasal turbinates (NT) and the left maxillary sinus. Significant soft tissue thickening is apparent in the left maxillary sinus.

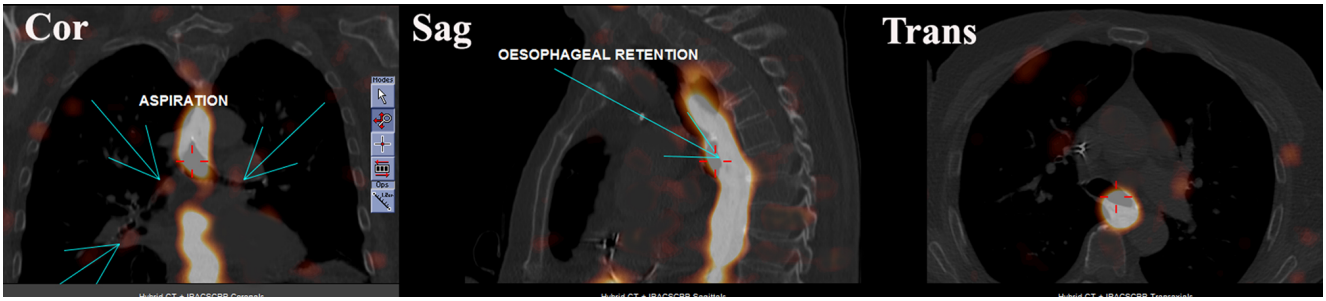

Figure 4. **Fused images from a low-dose SPECT/CT image of the head and neck demonstrates significant retention of refluxate in the oesophagus, consistent with ineffective clearance and contamination of the main bronchi in both lungs.**

0.805, which could be classified as a "good" [26] predictive model. Furthermore, the Hosmer-Lemeshow test (χ^2: 5.81, p>0.05) fails to reject the null hypothesis that there is lack of fit for the model. The multivariate model (Table 3) demonstrates that LPR patients with a higher BMI (overweight: OR=0.374, p=0.04 and obese: OR=0.161, p=0.0009) are less likely to aspirate than patients with a healthy weight. This effect was also demonstrated in the bivariate analysis; a higher proportion of healthy weight patients had aspiration compared to overweight and obese patients. Patients with abnormal RSI (RSI >13) are 3.3 (OR=3.277, p=0.02) times more likely to aspirate than patients with normal RSI (RSI >13). Known hiatus hernia patients are less likely to aspirate (OR=0.222, p=0.01) than patients with no known hiatus hernia. Out of pre-morbid conditions entered in the model, patients with a presumptive diagnosis of asthma are 3.3 (OR=3.267, p=0.02) times more likely to aspirate than non-asthma patients. Patients who have gastric emptying times over 19 minutes are 2.6 times (OR=2.594, p=0.03) more likely to aspirate. With a unit increase in area under the curve (AUC) for pharynx to background, LPR patients are 2.1 (OR= 2.139, p=0.0003) times more likely to aspirate.

Limitations

The analysis in this study was restricted to patients with severe and refractory GORD and pulmonary disease referred to a tertiary service for evaluation of GORD as a cause or contributor to respiratory disease. These are not standard community referrals but tertiary referrals from specialists, many already with a diagnostic label of "atypical" asthma.

Discussion

Currently pertussis and GORD are considered disparate diseases. This observational study challenges this assumption in a large cohort of patients. There is a clear temporal relationship between clinically significant pertussis infection and the acute onset of severe gastroesophageal reflux with a high prevalence of atypical symptoms and less than 5% complaining of heartburn. There is the strong implication that this is related to changed thoraco-abdominal pressure dynamics due to explosive coughing with the propensity to promote regurgitation. Many other symptoms may reflect this mechanism, such as vomiting, urinary incontinence, rib fracture and development of abdominal hernias. The patients in the current study noted a temporal connection between the clinical pertussis infection, persistent cough and the acute onset of symptomatic GORD/LPR. These patients had no prior history of symptomatic or treated symptoms of GORD/ LPR. The pertussis

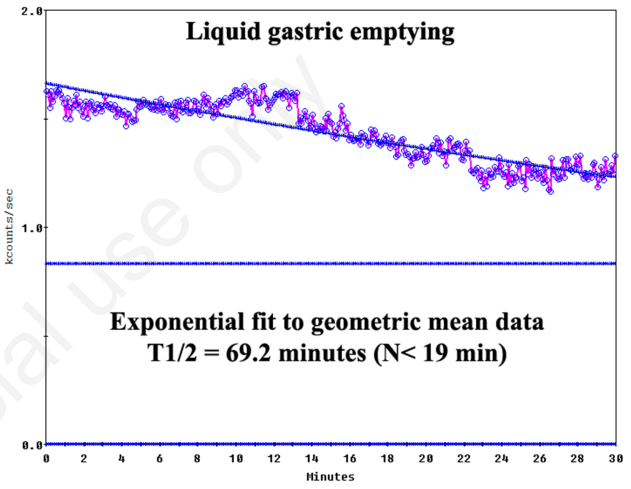

Figure 5. **Graphical analysis of liquid gastric emptying with data from the supine study showing significant prolongation in emptying with a time to half clearance of 69.2 minutes.**

infections were clinically obvious and characterised by explosive coughing, inspiratory "whooping" vomiting, *etc*. and serologically confirmed by the IgA response to the pertussis toxin. It is conceivable that pertussis may have transformed asymptomatic or low-grade GORD (± hiatus hernia) into more florid symptomatic disease due to the altered thoracoabdominal dynamics. The patients were referred for reflux scintigraphy to evaluate atypical symptoms that raised the possibility of laryngopharyngeal reflux (LPR) or pulmonary micro-aspiration of refluxate[19,22,27]. The scintigraphic test utilised in the study has been validated against the current standards of oesophageal pH/ impedance and multi-channel dent-sleeve manometry in the oesophagus[21,22,27,28]. It has also shown significant difference in scan pattern between GORD and LPR [28] and a strong correlation with resolution of symptoms of LPR/ pulmonary-micro-aspiration after fundoplication [22,28]. It is the first imaging test to physically demonstrate refluxate in the laryngopharynx, other head and neck structures and pulmonary micro-aspiration on fused SPECT/ CT imaging as shown in Figures 2-4. A scintigraphic study in normal volunteers [20] yielded similar findings to oesophageal pH/ impedance and manometry in asymptomatic subjects. Upright reflux which did not reach the oropharynx was shown in 34% and there was no evidence of supine reflux.

The principal aim of this study was to assess all patients for the presence of LPR and pulmonary micro-aspiration in an attempt to link and explain a variety of atypical symptoms for the diagnosis of reflux disease. Pulmonary micro-aspiration is strongly correlated with older age (p=0.007). The multivariate analysis yielded a strong association with area under the curve for the pharynx/laryngopharynx (OR 2.1), burping (OR 2.2), pre-test diagnosis of asthma (OR 3.3), reflux symptom index (OR 3.3) and liquid gastric emptying (OR 2.6). Negative associations for pulmonary micro-aspiration were with obesity (OR 0.2), known hiatus hernia (OR 0.2) and pertussis infection (OR 0.5).

In purely mechanical terms it implies that LPR and pulmonary micro-aspiration are more likely as the severity of reflux increases (RSI score) in association with a delay in liquid gastric emptying and poor clearance of refluxate from the pharynx/ laryngopharynx (area under the curve). It is also clear from this data that pulmonary micro-aspiration is often diagnosed as "atypical asthma", especially in the absence of typical reflux symptoms such as heartburn. The high prevalence of radiological lung disease also reflects this confusion. The failure to consider airways reflux as a potential cause of pulmonary disease has been recognised by others [29]. The combination of LPR and lung aspiration was visualised in the scintigraphic SPECT/ CT studies in 29% of patients with recent pertussis infection and 40% without.

What are the salient differences between the two groups in this study? As Table 1 shows, patients with recent pertussis infection had a higher median age (61.2 V 55.8 years), a significantly higher median cough severity index (11 V 6) and critically, an AUC value for the pharynx/laryngopharynx (p<0.05 for each). The AUC value is a marker of the delay in clearance of refluxate from the upper airway, increasing the risk of both LPR and pulmonary micro-aspiration. This has been reported as a key predictor of pulmonary micro-aspiration and was strongly associated with oesophageal dysmotility [30]. The higher rate of aspiration in the non-pertussis infected group (40% *versus* 29%) may be a reflection of the chronicity of the reflux disease and temporal progression in severity [31]. However, a significantly higher proportion of patients with pertussis infection had LPR, although without pulmonary micro-aspiration.

Chronic cough was the most distressing symptom in both groups and more severe in the patients with recent pertussis infection. A high proportion (>60%) of patients in both groups had been clinically labelled as "atypical" asthma by their managing clinicians, most likely based on a working diagnosis of cough-variant asthma [32]. The persistent stimulation of the cough reflex by pertussis infection is due to injury and destruction of the epithelial tis-

Table 2. Spearman correlation coefficients and bivariate association of patient characteristics with aspiration, for patients with laryngopharyngeal reflux disease.

Patient characteristics		With aspiration		No aspiration			Spearman correlation	
Continuous variables		Median	IQR	Median	IQR	p	For aspiration	p
Age at screening (years)		60.3	24.4	58.6	22.2	0.467	0.007	0.911
Amplitude		2.9	1.3	2.2	1.4	0.441	0.097	0.112
Area under the curve		1.3	1.3	1.1	1.0	0.003	0.181	0.003
Categorical variables			%		%	p		
Gender (male)			32.7		37.0	0.587	-0.043	0.590
BMI (kg/m²)	Healthy weight		50.9		26.9	0.002	-0.184	0.005
	Overweight		27.3		34.3	0.366		
	Obese		21.8		38.9	0.029		
Reflux symptom index ≤13			21.8		27.8	0.411	-0.044	0.470
Cough severity index ≤3			41.8		33.3	0.287	-0.039	0.528
LHQ ≤17.1			72.7		77.8	0.475	0.068	0.267
Known hiatus hernia			27.3		28.7	0.848	-0.015	0.849
Pertussis			41.8		48.2	0.443	-0.060	0.446
Burping			61.8		48.1	0.098	0.129	0.100
Fundoplication			0.0		3.7	0.148	-0.113	0.150
Bloating			63.6		59.3	0.588	0.042	0.591
Respiratory function test			47.3		42.6	0.569	0.045	0.572
Asthma			34.5		28.7	0.444	0.060	0.448
Chest infection			38.2		52.8	0.078	-0.138	0.079
Pneumonia			30.9		25.9	0.501	0.053	0.504
Pulmonary fibrosis			3.6		6.5	0.452	-0.059	0.455
GE (minutes)	<19		38.2		55.6	0.036	0.056	0.478
Frequency of reflux	1-2		23.6		36.1	0.106	0.095	0.119
	3		30.9		32.4	0.846		
	4+		45.5		31.5	0.079		

BMI, Body mass index; LHQ, Newcastle laryngeal hypersensitivity questionnaire; GE, gastric emptying time.

sues lining the larynx and tracheobronchial structures [33,34]. The CSI values were increased in both patient groups (>10) but significantly higher in the pertussis group with no significant difference in the LHQ scores between the two groups which were also abnormal [24]. This may reflect the additive effect of reflux-induced injury/ sensitisation of the upper airways.

There is some evidence that respiratory tract infections such as pertussis, viral, allergic or non-allergic irritants may trigger a range of sensory symptoms suggestive of upper airway and laryngeal neural dysfunction [34,35]. Liquid gastric emptying was abnormal in 93% of non-pertussis patients with a longer history of chronic cough, compared with 57% of patients with pertussis infection and a shorter history of coughing. The linkage between dysfunction of the parasympathetic nerve supply and abnormal oesophageal peristalsis and gastric emptying has previously been shown in patients with GORD/LPR [36].

The anti-reflux function of the normal LOS can be overcome or damaged by recurrent changes in intra-abdominal pressure. There is experimental evidence to show that reflux may occur when the inspiratory thoraco-abdominal pressure gradient exceeds the LOS pressure, even if the LOS is in the normal range [37,38]. Vigorous coughing may increase intrathoracic pressures by up to 300 mm Hg and result in expiratory flow rates that approach 800 km/h [39]. We hypothesise a number of mechanisms that could produce GORD/LPR based on these observations.

Vomiting is a common symptom reported in patients with pertussis infection. Recurrent vomiting has been reported to significantly injure the lower oesophageal sphincter in patients with bulimia and self-induced vomiting [40]. This may promote a high rate of induced GORD. When raised intra-abdominal pressures are added to this due to the vigorous nature of the coughing, it may increase the risk of hiatus hernia formation and so promote reflux disease. There is data to show that hiatus hernias are common and estimated to occur in approximately 10% of people under 40 years of age and up to 70% of people over 70 years of age [41]. Hiatus hernias interfere with the LOS function at the level of the oesophageal ampulla [42]. A similar incidence of hiatus hernias was observed in this study in the pertussis group (70%) and the non-pertussis group (69%).

Burping had a significant relationship with pulmonary micro-aspiration in this study. It is likely to be related to aerophagia which may occur during the process of recurrent and vigorous coughing, especially during the "whooping" inspiratory phase or any violent inspiration. The swallowed air leads to distension of the gastric fundus. This increases the frequency of transient lower oesophageal sphincter relaxations (TLOSR), leading to significant reflux of stomach contents into the oesophagus, even in the presence of a normal LOS mechanism [43].

Over 50% of patients in the pertussis group had an elevated BMI (>30), a fertile precondition for GORD, but not for pulmonary micro-aspiration, which was more common in cases of a healthy weight (Tables 2 and 3). This is a surprising finding and difficult to explain. A review of the evidence for the role of obesity in GORD showed a two-fold increased risk of GORD based on an analysis of 23 publications since 2005 [44]. Principal mechanisms were thought to be increased intragastric pressures, increased fre-

Table 3. Multivariate association with the dependent variable aspiration, controlling for patients with laryngopharyngeal reflux disease.

Independent variables		Association with aspiration OR	LCL	UCL	p
Body mass index	Healthy weight				
	Overweight	0.374	0.144	0.973	0.044
	Obese	0.164	0.057	0.476	0.0009
Age (years)		1.106	0.989	1.044	0.249
Reflux symptom index	>13	3.309	1.256	8.717	0.016
	13				
Known hiatus hernia	Yes	0.222	0.069	0.707	0.011
	No				
Pertussis	Yes	0.496	0.215	1.143	0.100
	No				
Burping	Yes	2.240	0.946	5.302	0.067
	No				
Respiratory function test	Yes	0.558	0.219	1.424	0.222
	No				
Asthma	Yes	3.267	1.219	8.760	0.019
	No				
Chest infection	Yes	0.449	0.191	1.056	0.067
	No				
Area under the curve*	<19	2.139	1.419	3.224	0.0003
Gastric emptying time (minutes)	19	2.594	1.118	6.020	0.026
-2 Log L	208.4				
Likelihood ratio χ^2 50.8	<0.0001	Wald χ^2	30.8	0.004	
R-square	0.371	c		0.805	
Hosmer-Lemeshow χ^2	5.814	Pr > χ^2		0.668	

*Area under the curve for pharynx to background; OR, odds ratio; LCL, lower confidence limit; UCL, upper confidence limit.

quency of TLOSRs, anatomical disruption of the LOS mechanisms and a higher incidence of hiatus hernias.

Conclusions

The epidemiology of pertussis has changed, particularly in the adult population for a number of reasons. The associated chronic cough may persist and lead to dynamic changes in thoracoabdominal pressures that predispose to GORD, hiatus hernia formation and LPR events and pulmonary micro-aspiration of refluxate that has been poorly recognised. A novel scintigraphic test has been developed that allows visualisation by SPECT/ CT of manifestations of airways reflux.

Abbreviations

BMI: body mass index;
CSI: cough severity index;
GE: gastric emptying time;
GORD: gastro-oesophageal reflux disease;
HRCT: high resolution X-ray computed tomography;
IQR: interquartile ranges;
LGE: liquid gastric emptying;
LHQ: laryngeal hypersensitivity questionnaire;
LOS: lower oesophageal sphincter;
LPR: laryngopharyngeal reflux;
MBq: megabecquerel (international system unit of radioactivity);
PCR: polymerase chain reaction;
pH: potential of hydrogen;
RFT: respiratory function tests;
ROC: receiver operating curve;
RSI: reflux symptom index;
SPECT/CT: single photon emission tomography/X-ray computed tomography;
Tc-99m: technetium-99m;
TLOSR: transient lower oesophageal sphincter relaxations.

References

1. Kent A, Heath PT. Pertussis. Medicine 2014;42:8-10.
2. Gabutti G, Azzari C, Bonanni P, Prato R, Tozzi AE, Zanetti A, et al. Pertussis. Hum Vaccin Immunother 2015;11:108-17.
3. Bhattacharyya S, Ferrari MJ, Bjørnstad ON. Species interactions may help explain the erratic periodicity of whooping cough dynamics. Epidemics 2018;23:64-70.
4. Gideon Informatics, Inc., Berger S. Pertussis: Global status. Los Angeles: Gideon Informatics, Inc.; 2018.
5. Klein NP, Bartlett J, Fireman B, Rowhani-Rahbar A, Baxter R. Comparative effectiveness of acellular versus whole-cell pertussis vaccines in teenagers. Pediatrics 2013;131:e1716-22.
6. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 2012;367:1012-9.
7. Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, Clark TA, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA 2012;308:2126-32.
8. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. Pediatrics 2014;133:e513-9.
9. Kaczmarek MC, Valenti L, Kelly HA, Ware RS, Britt HC, Lambert SB. Sevenfold rise in likelihood of pertussis test requests in a stable set of Australian general practice encounters, 2000-2011. Med J Aust 2013;198:624-8.
10. Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. Clin Infect Dis 2012;54:1730-5.
11. Baxter R, Bartlett J, Rowhani-Rahbar A, Fireman B, Klein NP. Effectiveness of pertussis vaccines for adolescents and adults: case-control study. BMJ 2013;347:f4249.
12. Cherry JD. Adult pertussis in the pre- and post-vaccine eras: lifelong vaccine-induced immunity? Expert Rev Vaccines 2014;13:1073-80.
13. De Serres G, Shadmani R, Duval B, Boulianne N, Dery P, Douville Fradet M, et al. Morbidity of pertussis in adolescents and adults. J Infect Dis 2000;182:174-9.
14. Smith JA, Aliverti A, Quaranta M, McGuinness K, Kelsall A, Earis J, et al. Chest wall dynamics during voluntary and induced cough in healthy volunteers. J Physiol 2012;590:563-74.
15. Polverino M, Polverino F, Fasolino M, Andò F, Alfieri A, De Blasio F. Anatomy and neuro-pathophysiology of the cough reflex arc. Multidiscip Respir Med 2012;7:5.
16. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16:274-7.
17. Shembel AC, Rosen CA, Zullo TG, Gartner-Schmidt JL. Development and validation of the cough severity index: a severity index for chronic cough related to the upper airway. Laryngoscope 2013;123:1931-6.
18. Moore A, Harnden A, Grant CC, Patel S, Irwin RS, Panel CEC. Clinically diagnosing pertussis-associated cough in adults and children: CHEST guideline and expert panel report. Chest 2019;155:147-54.
19. Burton L, Falk G, Baumgart K, Beattie J, Simpson S, Van der Wall H. Esophageal clearance in laryngopharyngeal reflux disease: Correlation of reflux scintigraphy and 24-hour impedance/pH in a cohort of refractory symptomatic patients. Mol Imaging Radionucl Ther 2020;29:7-16.
20. Burton L, Falk G, Beattie J, Novakovic D, Simpson S, Wall H. Findings from a novel scintigraphic gastroesophageal reflux study in asymptomatic volunteers. Am J Nucl Med Mol Imaging 2020;10:342-8.
21. Burton L, Falk GL, Parsons S, Cusi M, Van Der Wall H. Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. Mol Imaging Radionucl Ther 2018;27:113-20.
22. Falk G, Beattie J, Ing A, Falk S, Magee M, Burton L, et al. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: A definitive diagnostic test? World J Gastroenterol 2015;21:3619-27.
23. Falk GL, Vivian SJ. Laryngopharyngeal reflux: diagnosis, treatment and latest research. Eur Surg 2016;48:74-91.
24. Vertigan AE, Bone SL, Gibson PG. Development and validation of the Newcastle laryngeal hypersensitivity questionnaire. Cough 2014;10:1.
25. Hosmer DW, Lemeshow S. Applied logistic regression. New York: J. Wiley & Sons, Inc.; 1989.
26. Zhu W, Zeng N, Wang N. Sensitivity, specificity, accuracy, associated confidence interval and ROC analysis with practical SAS® implementations. NorthEast SAS users group, health care and life sciences [Internet]. 2010. Available from: https://www.lexjansen.com/nesug/nesug10/hl/hl07.pdf

27. Khoma O, Falk SE, Burton L, Van der Wall H, Falk GL. Gastro-Oesophageal reflux and aspiration: Does laparoscopic fundoplication significantly decrease pulmonary aspiration? Lung 2018;196:491-6.
28. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun 2015;36:625-30.
29. Morice AH. Airway reflux as a cause of respiratory disease. Breathe 2013;9:256.
30. Khoma O, Burton L, Falk MG, Van der Wall H, Falk GL. Predictors of reflux aspiration and laryngo-pharyngeal reflux. Esophagus 2020;17:355-62.
31. Kulig M, Nocon M, Vieth M, Leodolter A, Jaspersen D, Labenz J, et al. Risk factors of gastroesophageal reflux disease: methodology and first epidemiological results of the ProGERD study. J Clin Epidemiol 2004;57:580-9.
32. Paoletti G, Melone G, Ferri S, Puggioni F, Baiardini I, Racca F, et al. Gastroesophageal reflux and asthma: when, how, and why. Curr Opin Allergy Clin Immunol 2021;21:52-8.
33. Soane M, Jackson A, Maskell D, Allen A, Keig P, Dewar A, et al. Interactions of Bordetella pertussis with human respiratory mucosa in vitro. Resp Med 2000;94:791-9.
34. Zanasi A, Fontana GA, Mutolo D. Cough: Pathophysiology, diagnosis and treatment. Dordrecht: Springer; 2020.
35. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. Lancet Respir Med 2013;1:414-22.
36. Cunningham KM, Horowitz M, Riddell PS, Maddern GJ, Myers JC, Holloway RH, et al. Relations among autonomic nerve dysfunction, oesophageal motility, and gastric emptying in gastro-oesophageal reflux disease. Gut 1991;32:1436-40.
37. Ayazi S, DeMeester SR, Hsieh CC, Zehetner J, Sharma G, Grant KS, et al. Thoraco-abdominal pressure gradients during the phases of respiration contribute to gastroesophageal reflux disease. Dig Dis Sci 2011;56:1718-22
38. Turb Turbyville JC. Applying principles of physics to the airway to help explain the relationship between asthma and gastroesophageal reflux. Med Hypotheses 2010;74:1075-80.
39. Ford PA, Barnes PJ, Usmani OS. Chronic cough and Holmes-Adie syndrome. Lancet 2007;369:342.
40. Brown CA, Mehler PS. Medical complications of self-induced vomiting. Eat Disord 2013;21:287-94.
41. Hershcovici T, Mashimo H, Fass R. The lower esophageal sphincter. J Neurogastroenterol Motil 2011;23:819-30.
42. Sloan S, Kahrilas PJ. Impairment of esophageal emptying with hiatal hernia. Gastroenterology 1991;100:596-605.
43. Pandolfino JE, Zhang QG, Ghosh SK, Han A, Boniquit C, Kahrilas PJ. Transient lower esophageal sphincter relaxations and reflux: mechanistic analysis using concurrent fluoroscopy and high-resolution manometry. Gastroenterology 2006;131:1725-33.
44. El-Serag H. Role of obesity in GORD-related disorders. Gut 2008;57:281-4.

Received for publication: 7 January 2022. Accepted for publication: 23 May 2022.

Licensee PAGEPress, Italy
Multidisciplinary Respiratory Medicine 2022; 17:832
doi:10.4081/mrm.2022.832