



# Current therapies for gastro-oesophageal reflux in the setting of chronic lung disease: state of the art review

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**ABSTRACT** The inter-relationship between chronic respiratory disease and reflux disease in the airway reflux paradigm is extremely complex and remains poorly characterised. Reflux disease is reported to cause or contribute to the severity of a number of respiratory tract diseases including laryngeal disorders, sinusitis, chronic cough, asthma, COPD, idiopathic pulmonary fibrosis, cystic fibrosis, bronchiectasis and bronchiolitis obliterans post lung transplant. It is now appreciated that reflux disease is not simply caused by liquid acid reflux but rather by a variety of chemical refluxates originating from the stomach and duodenum due to a number of different mechanisms. Reflux disease can be challenging to diagnose, particularly proving its role in the causation of direct respiratory epithelial damage. Significant advances in oesophageal assessment and gastric biomarkers have emerged in recent years as our understanding increases. There are a number of treatments available for reflux disease, both medical and surgical, but there is a paucity of large randomised trials to evaluate their efficacy in the setting of chronic respiratory disease. Everyday clinical practice, however, informs us that treatment failure in reflux disease is common. This clinical review summarises associations between reflux disease in the setting of chronic respiratory diseases and examines available evidence regarding potential therapeutic strategies.



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**Gastro-oesophageal reflux disease is prevalent among patients with chronic respiratory disease. A number of medical and surgical treatment options are available for GORD. This review examines available evidence in the setting of chronic lung disease.** <https://bit.ly/34TcMJS>

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## Introduction

Gastro-oesophageal reflux (GOR) is a normal physiological event in healthy individuals, referring to the involuntary passage of gastric contents into the oesophagus [1, 2]. Gastro-oesophageal reflux disease (GORD) comprises symptoms or end-organ complications resulting from the reflux of gastric contents into the oesophagus, or beyond into the oral cavity, larynx or lung – a process termed extra-oesophageal reflux (EOR) [3]. The classical definition of GORD refers to liquid acid reflux defined by 24-h pH monitoring with most epidemiological studies of GORD referring to this phenomenon.

Typical GORD has been shown to affect up to a third of the normal population causing symptoms, mucosal damage and potentially malignant transformation of the epithelium in the oesophagus [4]. Oesophageal symptoms include epigastric pain, heartburn, odynophagia, gaseous reflux, acid and non-acid tasting reflux, dysphagia, epigastric pain and sleep disturbance [3, 5, 6]. Therefore, it is necessary to establish temporal relationships between GORD symptoms with food, posture and stress [7]. The prevalence of GORD could also be increasing due to the obesity epidemic, eating larger meals, greater ingestion of reflux-provoking food-stuffs (e.g. carbonated drinks, chocolate, caffeine, spiced foods and alcohol), an increase in the prevalence of hiatal hernias (HH) and an increasingly aged population [4]. Symptoms from EOR are frequently not inquired about by physicians or offered by patients and can include peri-prandial or persistent cough (laryngeal irritation), dysphonia, globus, laryngitis, sinusitis, metallic taste, dental caries and halitosis [8].

In recent years, however, the concept of airways reflux, which consists of neither acid nor liquid reflux but rather a gaseous mist containing mainly non-acid components, has become widely established, with 24-h pH-impedance studies now the gold standard investigation of choice for the same. pH impedance quantifies the type, number, phase, duration and proximal extent of each reflux episode [9–11]. Airways reflux may be entirely asymptomatic, and gaseous or mixed reflux may be as pathogenic to the oesophagus, oropharynx and upper and lower respiratory tract as liquid acid reflux [6, 9, 12–15]. It is also increasingly recognised that the refluxate may also be from the duodenum and contain bile acids, which again can be very pro-inflammatory and have been associated with changes in the gut microbiome [16].

The nomenclature remains confusing with GOR considered to be a normal physiological process and GORD a disease caused by pathological GOR. Does GOR refer only to the involuntary passage of liquid acid contents or does it encompass all potential gastric contents? Should airways reflux be considered under the same umbrella term of GORD if it contributes to a disease process comprising symptoms or end-organ complications? Airways reflux is more likely to contribute to extra-oesophageal reflux disease (EORD) caused by EOR, which can consist of liquid acid reflux (typical GORD) or gaseous non-acid reflux (airways reflux). In this review, therefore, reflux disease is the overarching term that refers to symptoms or end-organ complications resulting from the reflux of gastric contents into the oesophagus, or beyond, into the oral cavity, larynx or lung by any mechanism including typical GORD, airways reflux and micro-aspiration.

In the last decade there has been a huge interest in the role of reflux disease in the pathogenesis of a number of chronic airway and parenchymal lung diseases. Given the potential for reflux disease and chronic respiratory disease to act in a bidirectional manner with reflux disease driving respiratory disease and respiratory mechanics contributing to reflux disease, it is important to better understand the relationship and possible consequences of these conditions coexisting. The purpose of this review is to provide a summary of what is currently known about aerodigestive disease in terms of what causes reflux disease, individual respiratory diseases linked with reflux disease, and treatment of reflux disease with a proposed diagnostic and management approach. Very little of our current clinical practice in this area is evidence-based, and there is therefore inevitably a degree of informed speculation.

## What causes reflux disease?

In health, reflux is prevented through the combined action of the components of the anti-reflux barrier comprising the lower oesophageal sphincter (LOS), the crural diaphragm and the anatomical flap valve [5]. Initial research suggested that the most common cause of reflux was an excess of transient relaxations of the LOS, although it has since been demonstrated that patients with reflux disease are more likely to have acid reflux associated with these transient relaxations. Reflux disease is viewed as a multifactorial disorder with risk factors including genetic predisposition, lifestyle, body habitus, anatomical variation and presence of comorbid conditions and their treatment [1, 5, 17].

The strongest risk factor for reflux disease is the presence of a hiatal hernia where the integrity of the LOS is lost, and the acid pocket normally seen in the gastric fundus sits directly below the LOS [18]. A critical function of the LOS is to prevent reflux when recumbent. The presence of a hiatal hernia compromises

this essential function promoting GORD, EOR and potentially micro-aspiration. Recent data suggest that the presence and size of a hiatal hernia influence clinical presentation, oesophageal function, reflux profile and the degree of mucosal injury [18]. Hiatal hernias are more common with age, probably due to connective tissue change and, in particular, in centrally obese subjects due to raised gastric pressure. It is likely that the failure of multiple anatomical or physiological protective anti-reflux mechanisms, rather than one single process, results in progressive incompetence of the anti-reflux barrier, with compromise of each protective mechanism increasing the frequency and duration of reflux events, potentially leading to pathological damage to the oesophagus and extra-oesophageal organs [1, 19].

### Respiratory diseases linked with GORD

Most of the conditions linked with reflux disease are due to EOR where there is direct contact of the respiratory system with gastric refluxate, whether by typical liquid acid GORD, gaseous airways reflux or micro-aspiration of either. An increase in cough responsiveness observed on instilling hydrochloric acid into the distal oesophagus in seven patients with bronchial asthma suggesting a vagal reflex response [20]. Moreover, in patients with chronic cough and asthma with distal typical GORD on 24-h oesophageal pH monitoring, higher levels of tachykinin were seen in induced sputum in asthmatics compared with chronic cough controls without distal reflux suggesting neurogenic inflammation [21]. Postulated EOR-related diseases can be summarised and mapped from the larynx to the lung parenchyma (figure 1). Somewhat surprisingly, the proximal upper airway can also be affected potentially by gaseous reflux in the form of sinusitis.

A number of reflux disease-related conditions predominate in later life such as chronic cough, COPD, bronchiectasis and idiopathic pulmonary fibrosis (IPF). Why EOR can be both associated with airway disease and severe parenchymal lung disease remains unexplained. The magnitude of the reflux volume, its frequency and the constituents of the refluxate (pH, gastric or duodenal predominant, microbiology, food particles) may play a role along with genetic variation. What is inflammatory to one person's respiratory tract may not be to another individual. Evidence of this variation is demonstrated in daily clinical practice with, for instance, susceptibility of smokers to developing COPD or patients developing occupational asthma or post-viral cough syndrome.

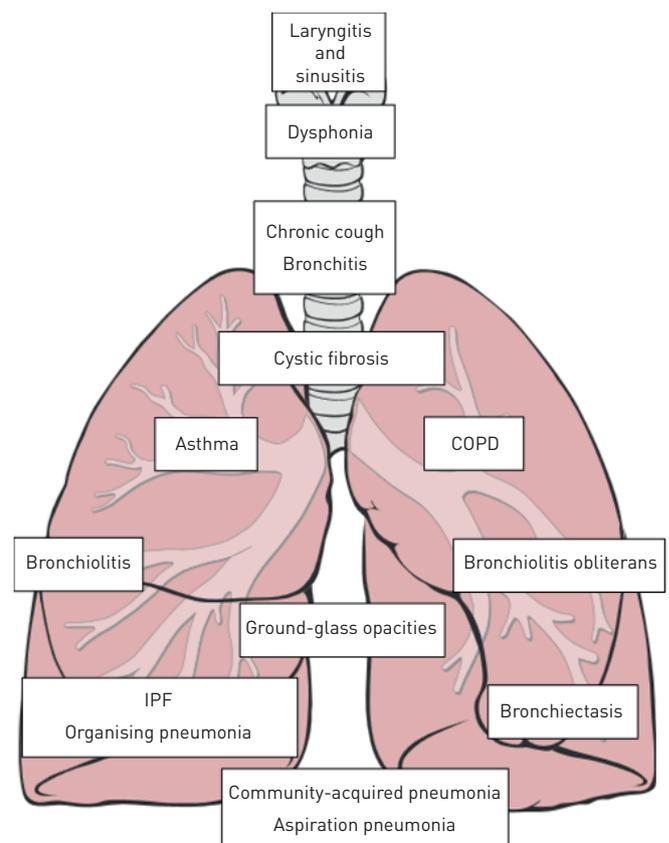


FIGURE 1 Diseases associated with gastro-oesophageal reflux disease.

### Reflux disease and chronic respiratory disease – is it a bidirectional process?

One tends to think of the respiratory tract as a passive recipient of noxious refluxate, but it is very likely that chronic respiratory diseases can worsen or precipitate reflux disease through a number of mechanisms setting up a potential vicious cycle of damage. Patients with obstructive lung disease such as symptomatic asthma, COPD, cystic fibrosis (CF) and bronchiectasis are hyperinflated with descent of the diaphragm, thus lowering the resting pressure of the LOS and predisposing to reflux. There may also be a greater pressure gradient across the LOS after eating if there is hyperinflation as seen by the early satiety of patients with severe COPD. With more severe airflow obstruction, a greater negative intra-thoracic pressure has to be created in order to inspire, and this may also have a siphoning effect of gastric contents into the oesophagus.

Coughing also involves sudden dynamic contracture of the abdominal muscles with an associated spike in intra-abdominal pressure which could provoke reflux. Inhaled anti-cholinergic agents may have a negative effect on oesophageal motility and gastric emptying. A lowering of the pressure of the LOS has also been demonstrated with salbutamol, theophylline and steroids. It is also interesting to speculate on the role played by the length of the oesophagus which, in hyperinflated patients, will be longer, and in patients with progressive restriction, such as IPF, will be shortened. A shorter oesophagus possibly has a lower resting pressure and more proximal reflux may occur in these patients.

It seems intuitive that patients with chronic cough are more likely to develop a hiatal hernia. Interestingly, an increased prevalence of hiatal hernia with worse disease outcomes has been demonstrated in IPF, bronchiectasis and, more recently, asthma patients [22–24]. These conditions have the most end-organ damage of the EOR-related diseases possibly due to greater refluxate associated with a hiatal hernia and, in all, cough is a very dominant symptom. Lengthening of the oesophagus in hyperinflation may also create a traction force on the stomach leading to a hiatal hernia. Patients with airways obstruction are also exposed to high-dose inhaled and oral corticosteroid which may contribute to tissue laxity and subsequent development of a hiatal hernia.

### Treatment of reflux disease

Proton pump inhibitors (PPIs) have been dramatically successful at ameliorating oesophageal and some extra-oesophageal symptoms of reflux disease and healing oesophageal mucosa. It is also now clear, however, that PPIs are not a panacea for reflux disease, and weakly acidic or non-acid reflux can continue or worsen without causing any local symptoms, and EOR-related respiratory tract damage *via* airways reflux can continue unabated [25]. PPIs are generally more effective and promote faster healing than H<sub>2</sub>-receptor antagonists, but long-term use may be associated with a variety of adverse events including osteoporosis and increased infections including community-acquired pneumonia [26]. However, whether or not this observed link is likely due to protopathic bias and confounding by indication remains a question of debate [27]. Prokinetic therapy with domperidone and metoclopramide are often trialled to speed up gastric emptying, limiting exposure of the oesophagus to acid. Prokinetic effects of macrolides have yet to be evaluated in this setting, although azithromycin has been shown to reduce hiatal hernia size and acid pocket position, thereby reducing acid reflux episodes [28]. Azithromycin is a panacea in numerous randomised controlled trials of a variety of airway diseases in successfully reducing exacerbation frequency and time to first exacerbation, and has been shown separately to act as agonists of the gut hormone motilin, so it is reasonable to hypothesise that some of the benefit of azithromycin may be related to its promotility effects [29]. Indeed, the success of azithromycin points to the importance of non-acid reflux as an important potential contributor of airways disease. Aside from lung transplant where patients taking azithromycin were found to have less objective GORD and bile acid aspiration thought to be due to enhanced oesophageal motility and accelerated gastric emptying, there is little direct evidence supporting the promotile effect of azithromycin as the potential mechanism of action in reducing exacerbations of chronic lung disease; therefore, further studies are greatly needed to confirm or refute these findings [30].

There is also increasing interest in endoscopic treatment and anti-reflux surgeries usually reserved for patients with persistent reflux disease [31]. A successful Nissen's fundoplication in select candidates with IPF and post transplant has been associated with improvements in symptoms, quality of life (QoL) and lung function decline attenuation [32–34]. Endoscopic treatments, such as the LINX or Stretta therapy, may not offer the same degree of relief provided by surgery, but might represent viable alternatives for non-surgical patients seeking relief from lifelong dependence on pharmacological therapy, its cost, associated side effects and long-term adverse outcomes [6].

A summary of the published literature on the relationship between reflux disease and chronic respiratory diseases is described below.

### **Reflux disease and chronic cough**

It is through the clinical observation of patients with chronic cough that the nature and associations of airway reflux as a causal mechanism of respiratory disease have been elucidated [35]. The prevalence of reflux, oesophageal dysmotility and aspiration in chronic cough has been estimated from 0 to almost 100% [36]. A low incidence, poor temporal relationship and poor response with PPIs *versus* placebo using acid reflux criteria alone has been found [37, 38]. The suggestion of non-acid reflux as a potential aetiological factor is difficult to confirm with existing technologies, and diagnosis relies primarily on the clinical history supported by validated questionnaires [36]. The picture is also complicated by the observation that there is a high prevalence of oesophageal dysmotility in patients with chronic cough and thus oesophago-larngo-pharyngeal reflux rather than GORD may be the problem [39]. Many of the signs and symptoms associated with chronic cough are explicable by reflux and aspiration and this is very important to consider in anyone presenting with these symptoms. Recent chronic cough guidelines have highlighted the different treatable traits in chronic cough with an emphasis on non-acid reflux being treated with promotility agents rather than anti-acid drugs [36].

### **Reflux disease and asthma**

Estimates of the prevalence of reflux disease among patients with asthma has varied from 25 to 80% [40]. A significant association between the presence of reflux disease and an increased frequency of exacerbations (OR 4.9 (95% CI 1.4–17.8)) and hospitalisations in asthmatic patients has been noted [41, 42]. Impedance studies in asthma have shown acid and non-acid reflux to occur with equal frequency [43]. Manometric studies have confirmed a lower LOS pressure in asthmatic patients compared to healthy controls that correlates with low forced expiratory volume in 1 s (FEV<sub>1</sub>) and may contribute to deterioration of spirometry in asthmatics [44].

There has been a paucity of research looking at the role of gastro-oesophageal biomarkers and associations with disease severity in asthma. A recent study of 78 patients with asthma of varying severity stratified according to Global INitiative for Asthma (GINA) guidelines showed detectable bronchoalveolar lavage (BAL) pepsin in 59% patients. However, no significant associations between pepsin level and disease severity, measures of asthma control, lung function, QoL or exacerbation frequency were noted, suggesting that the importance of aspiration on asthma outcomes may be overstated [45].

Numerous studies and randomised clinical trials (RCTs) examining the potential of PPIs to improve airways disease in asthma have demonstrated mixed findings (table 1) [16, 46–81]. A multicentre, double-blind RCT in adult patients with moderate-to-severe persistent asthma and symptoms of GORD showed that treatment with lansoprazole 30 mg twice daily for 24 weeks significantly reduced asthma exacerbations and improved QoL, particularly in the subset of patients on multiple medication types. However, treating GORD did not improve symptoms directly related to asthma, nor was there any effect on pulmonary function or reduction in rescue medication use [58]. In a larger RCT of 770 participants assigned to either esomeprazole 40 mg twice daily or placebo for 16 weeks, no overall significant improvement in morning peak expiratory flow rates (PEFR) over placebo was noted. Interestingly, an improvement in PEFR in asthmatic subjects with symptoms of GORD and nocturnal respiratory symptoms was observed [61].

A further study by the same group indicated that esomeprazole 40 mg once or twice daily in patients with moderate-to-severe asthma and GORD may improve pulmonary function and asthma-related QoL scores, but these improvements were minor and of limited clinical significance [67]. MASTRONARDE *et al.* [65] highlighted that while asymptomatic reflux amongst patients with poorly controlled asthma is highly prevalent, treatment with a PPI did not improve asthma control, perhaps suggesting that asymptomatic reflux is not a likely cause of poorly controlled asthma, or that PPIs simply do not prevent non-acidic reflux in this population. The benefit of PPI treatment has been questioned by many, with the most recent RCT for uncontrolled asthma and treatment with lansoprazole finding that the addition of lansoprazole, compared with placebo, improved neither symptoms nor lung function but was associated with increased respiratory infections [69].

Surgical targeting looking at the effect of laparoscopic Nissen's fundoplication in children with evidence of severe reflux disease and steroid-dependent asthma showed a 91% subjective improvement in symptoms, a reduction in both oral steroid and inhaler use and an increase in FEV<sub>1</sub> in the immediate post-operative period [82]. Similar results were observed in a smaller retrospective adult series [74]. Thus, although there is no clear evidence on the optimal management of GORD in asthma until further RCT results are available, the option of fundoplication may be considered in a carefully selected subpopulation of steroid-refractory asthma patients.

### **Reflux disease and COPD**

Reflux disease is a comorbidity in COPD with a reported prevalence of 17–54% using symptoms and questionnaires and 19–78% using oesophageal pH testing [7]. Numerous studies have reported associations

TABLE 1 Studies of gastro-oesophageal reflux treatment in asthma

First author [ref] Study type	n	Treatment	Asthma symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
<b>H2RAs</b>						
GOODALL [46] RCT crossover	18	Cimetidine 200 mg 5 times a day for 6 weeks	Improvement in nocturnal asthma symptom score	N/A	Unchanged	Improvement in evening PEFR
NAGEL [47] RCT crossover	14	Ranitidine 400 mg four times daily for 1 week	N/A	N/A	Unchanged	No change in use of asthma medications
EKSTROM [48] RCT crossover	48	Ranitidine 150 mg twice daily for 4 weeks	Improvement in nocturnal asthma symptom score	N/A	Unchanged	N/A
LARRAIN [49] RCT placebo or surgery parallel	27	Cimetidine 300 mg four times daily for 6 months	N/A	N/A	Minor improvement in FEV <sub>1</sub> after 6 months	N/A
<b>PPIs</b>						
MEIER [50] RCT crossover	15	Omeprazole 20 mg twice daily for 6 weeks	N/A	N/A	27% asthma patients with GORD had a ≥20% net improvement in FEV <sub>1</sub> after treatment	N/A
TEICHTAHL [51] RCT crossover	20	Omeprazole 40 mg once daily for 4 weeks <i>versus</i> placebo	Unchanged	N/A	N/A	Improvement in evening but not morning PEFR; improved reflux symptoms
HARDING [52] RCT crossover	30	Omeprazole 20–60 mg four times daily for 12 weeks	Improved	N/A	Improved FEV <sub>1</sub> and FVC	Improved PEFR; improved reflux symptoms
LEVIN [16] RCT crossover	9	Omeprazole 20 mg once daily for 8 weeks	Improved	N/A	Trend toward higher FEV <sub>1</sub> (mean difference 15.6%)	Improved Asthma Quality of Life Score (AQLS) including subdomains of activity limitation, symptoms and emotions
BOEREE [53] RCT crossover	36	Omeprazole 40 mg b for 12 weeks <i>versus</i> placebo	Unchanged	N/A	Unchanged	Improved reflux symptom scores and proportion of time with pH<4; no effect on peak flow or reversibility
KILJANDER [54, 55] RCT crossover	107	Omeprazole 40 mg once daily for 8 weeks <i>versus</i> placebo	Improved nocturnal asthma symptoms	N/A	Improved	No effect on peak flow; 18 (35%) patients had improved pulmonary symptom scores while receiving omeprazole
TSUGENO [56] Prospective observational		Rabeprazole 20 mg once daily for 8 weeks	Unchanged	N/A	N/A	Improved PEFR; improved reflux symptoms
JIANG [57] RCT	30	Omeprazole 20 mg once daily plus domperidone 10 mg three times daily for 6 weeks <i>versus</i> usual care	N/A	N/A	Improved	Improved PEFR and bronchial hyperresponsiveness

Continued

TABLE 1 Continued

First author [ref] Study type	n	Treatment	Asthma symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
LITNER [58] RCT	207	Lansoprazole 30 mg once daily for 24 weeks <i>versus</i> placebo	Unchanged	N/A	Unchanged	Improved AQLS emotional function; no change in PEFR or use of asthma rescue medications
STORDAL [59] RCT	38	Omeprazole 20 mg for 12 weeks <i>versus</i> placebo	Unchanged	N/A	Unchanged	Improved quality of life; improved reflux scores on pH; no change in asthma rescue medications
SHIMIZU [60] RCT	30	Lansoprazole 30 mg·day <sup>-1</sup> for 8 weeks <i>versus</i> roxatidine (H <sub>2</sub> RA), 150 mg·day <sup>-1</sup>	Improved	N/A	Unchanged	Improved peak flow and ACQ score
KILJANDER [61] RCT	770	Esomeprazole 40 mg twice daily <i>versus</i> placebo for 16 weeks	Unchanged	N/A	Unchanged	Improved PEFR in patients with GORD and nocturnal symptoms only; no safety concerns noted
WONG [62] Prospective observational	30	Lansoprazole 30 mg once daily	Improved	N/A	Unchanged	No effect on PEFR; improved pulmonary symptom scores
SHARMA [63] RCT		Omeprazole 20 mg twice daily plus domperidone 10 mg three times daily <i>versus</i> placebo for 16 weeks	Improved day and night-time symptom scores	N/A	Improved FEV <sub>1</sub> and FVC	Improved reflux symptom scores; improved PEFR; reduction in asthma rescue medications
KHORASANI [64] RCT Adolescents	36	Omeprazole 20 mg twice daily for 6 weeks <i>versus</i> placebo	N/A	N/A	Improved FEV <sub>1</sub> and FVC	Improved reflux symptoms
MASTRONARDE [65] RCT	412	Esomeprazole 40 mg twice daily for 24 weeks <i>versus</i> placebo	Unchanged	N/A	Unchanged	No effect on airway reactivity, asthma control, asthma symptom scores, nocturnal awakening or quality of life; no increase in adverse events compared to placebo
BUCKNALL [66] Prospective observational	51	Omeprazole up to 80 mg daily	N/A	N/A	N/A	Improved GORD symptoms and pH readings with increased therapy dose
KILJANDER [67] RCT	828	Esomeprazole 40 mg once/twice daily for 26 weeks	Unchanged	N/A	Improved FEV <sub>1</sub> in 40 mg TWICE DAILY group after 26 weeks compared to control	No effect on PEFR; improved AQLS score in both treatment groups compared to control
ADAMKO [68] Infants RCT	19	Combined omeprazole 10 mg once daily plus bethanacol <i>versus</i> either treatment alone <i>versus</i> placebo	Improved daytime coughing and respiratory symptom scores	N/A	N/A	Improved GORD symptoms and GORD measured by pH; no adverse events noted

Continued

TABLE 1 Continued

First author [ref] Study type	n	Treatment	Asthma symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
HOLBROOK [69] Children RCT	306	Lansoprazole 15 mg·day <sup>-1</sup> if <30 kg or 30 mg·day <sup>-1</sup> if ≥30 kg <i>versus</i> placebo	Improved	N/A	Unchanged	Improved ACQ score but no effect on asthma-related quality of life or rates of episodes of poor asthma control; in the subgroup with a positive pH study, no treatment effect was observed for any asthma outcome; increased respiratory infections noted in treatment group
SANDUR [70] Prospective observational	28	Omeprazole 40 mg once daily for 3 months; increased to 60 mg once daily at 2 months if pH study remained abnormal	Improved pulmonary symptom and night-time asthma symptom scores	N/A	Improved FEV <sub>1</sub>	Improved reflux symptom score and peak flow readings
YAMAJI [71] RCT	60	Omeprazole 10 mg once daily plus mosapride 5 mg three times daily <i>versus</i> omeprazole alone for 4 weeks	N/A	N/A	N/A	No additional amelioration of GORD symptoms when combined
<b>Surgery</b>						
PERRIN-FAYOLLE [73] Prospective observational	44	Nissen fundoplication	Improved	N/A	N/A	Pulmonary improvement classified as total cure 25%, marked improvement 16%, moderate improvement 25%, no improvement 34% 95% long-term improved reflux symptoms
LARRAIN [49] RCT	26	Nissen fundoplication	Improved	N/A	N/A	Clinical improvement and reduced use of asthma rescue medications
SPIVAK [74] Prospective observational	39	Nissen fundoplication (median follow-up 2.7 years)	Improved	N/A	N/A	Improved asthma scores; reduction in use of systemic steroids
EKSTROM [75] Prospective observational	13	Transabdominal/laparoscopic fundoplication	N/A	N/A	Unchanged	N/A
SONTAG [76] RCT	62	Antacids p.r.n. <i>versus</i> ranitidine 150 mg three times daily <i>versus</i> Nissen fundoplication for follow-up of 2 years	Surgery improves asthma symptoms	N/A	Unchanged	No effect of PEFr, rescue medications or survival
KHOSHOO [77] Children Prospective observational	18	Medical treatment (lifestyle changes, proton pump inhibitors and prokinetics) or surgical treatment	Improved	N/A	N/A	Reduction in need for rescue medications

Continued

TABLE 1 Continued

First author [ref] Study type	n	Treatment	Asthma symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
KHOSHOO [78] Children Prospective observational	44	(Nissen fundoplication) Esomeprazole plus metoclopramide 10 mg three times daily <i>versus</i> ranitidine <i>versus</i> Nissen fundoplication	N/A	Increased exacerbations in ranitidine group compared to other treatment groups	N/A	N/A
KILJANDER [79] Prospective observational	69	Esomeprazole 40 mg twice daily <i>versus</i> Nissen fundoplication after 3 months	Improved cough and dyspnoea with both treatment groups	N/A	Unchanged	Improved SGRQ quality of life after fundoplication
SILVA [80] Retrospective observational	30	Nissen fundoplication	Improved	N/A	N/A	Improvement in daily crises of asthma
HU [81] Prospective observational	137	Stretta radiofrequency (n=82) or laparoscopic Nissen fundoplication (n=55)	Improved	N/A	N/A	Improved reflux, respiratory and ENT symptoms in both groups, better in Nissen fundoplication group at both 1 and 5 years follow-up

Abbreviations: FEV<sub>1</sub>: forced expiratory volume in 1 s; H2RAs: histamine-2 receptor antagonists; PEF: peak expiratory flow rate; RCT: randomised controlled trial; GORD: gastro-oesophageal reflux; FVC: forced vital capacity; AQLS: Asthma Quality of Life Score; ACQ: Asthma Control Questionnaire; SGRQ: St. George's Respiratory Questionnaire; ENT: ears, nose and throat; N/A: not available.

with reflux disease and COPD severity, particularly in relation to increased exacerbations and hospitalisations and reduced QoL. Because lung function is not regained, exacerbations are pivotal events in COPD progression and other chronic lung diseases. In an influential study by HURST *et al.* [83], the frequency and associations of exacerbation in 2138 patients enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study were evaluated in a multivariate model. This included an exacerbation during the previous year (OR 5.72 (95% CI 4.47–7.31)), supporting the hypothesised “frequent exacerbator phenotype”. The second-best independent predictor in this model was typical GORD (OR 2.07 (95% CI 1.58–2.72)). A secondary analysis of the ECLIPSE cohort identified self-reported GORD in 26% patients: self-reported GORD and/or use of gastric suppression medication were associated with an increased risk of moderate-to-severe and hospitalised exacerbations [84].

Other studies have also consistently demonstrated this positive relationship, noting a higher rate of hospitalisation or emergency room visits among those with COPD and reflux disease [85–95]. One study with a 5-year follow-up found that those who experience both nocturnal and daytime symptoms experienced more exacerbations, with a higher risk in those who did not use regular acid inhibitory treatment (hazard ratio (HR) 2.7 (95% CI 1.3–5.4)) [94]. In a South Korean study, symptoms of laryngopharyngeal reflux (LPR) in patients with COPD were significant predictors for severe acute exacerbation of COPD, associated with diffuse oedema, erythema, and hyperaemia on laryngeal examination. The potential interest of this finding is that LPR symptoms are a potential precursor to aspiration [95]. A subsequent systematic review and meta-analyses clearly identified GORD as a risk factor for COPD exacerbations (RR 7.57 (95% CI 3.84–14.94)), with an increased mean number of exacerbations per year (mean difference: 0.79 (95% CI 0.22–1.36)). The prevalence of GORD was significantly higher in patients with COPD than in those without (RR 13.06 (95% CI 3.64–46.87);  $p < 0.001$ ) [96].

Although several small studies have reported minimal impact on disease-specific QoL among those with moderate-to-severe COPD, those with a greater sample size have reported a poorer QoL reflected in disease-specific and generic questionnaires as well as greater levels of anxiety and depression and a poorer perception of physical health [86, 88, 97, 98]. The effect of reflux disease on pulmonary function decline is

less clear. One study reported more frequent typical GORD symptoms in COPD patients with  $FEV_1 < 50\%$  compared to those with  $FEV_1 > 50\%$ , with another showing typical GORD symptoms to be associated with a reduced inspiratory capacity among patients with COPD [99, 100]. However, other studies have reported no correlation between reflux disease and lung function [101].

As impedance has yet to be performed in this patient population, the majority of these studies focus on “acid reflux” or typical GORD, which may underestimate overall reflux disease in COPD [102]. Non-acid components of reflux, such as pepsin and bile, are potentially aspirated, but are not necessarily denoted by symptoms associated with acid reflux [103]. Pepsin has been detected in sputum and exhaled breath condensate (EBC) in up to 60% of patients with COPD [101, 104]. A potential issue is that the reported association might overemphasise the role of anti-acid therapy, which may relieve symptoms associated with acid reflux but be less effective on overall reflux disease [105].

Unlike in asthma, there is a paucity of research into treatment options of reflux disease in the context of COPD (table 2) [33, 94, 106–112]. In a Japanese RCT, treatment with PPI in COPD patients without symptomatic typical GORD significantly lowered the number of exacerbations/year compared to the placebo group (OR 0.23 (95% CI 0.08–0.62)) [108]. However, these results may be related to a reduction in rhinovirus infections when taking lansoprazole through its effect on intercellular adhesion molecule (ICAM)-1, as opposed to its effect on GORD. A small observational study from Turkey showed improvement in COPD and LPR symptoms and LPR examination findings following 2 months of treatment with PPI symptomatic LPR-positive COPD patients [109]. Nissen fundoplication pre- and post-transplant COPD has showed significant improvements in  $FEV_1$  [33, 110]. Longitudinal observational studies assessing the effect of long-term anti-reflux treatment on COPD exacerbations and disease progression are conflicting [111, 112].

#### *Reflux disease and cystic fibrosis*

Reflux disease occurs frequently in children and adults with CF and estimates of prevalence range from 19 to 90%, depending on the modality used to define reflux disease [113]. Patients with CF are predisposed to reflux as a result of both primary and secondary mechanisms, particularly abnormal gastrointestinal motility manifesting as lower oesophageal pressures, delayed gastric emptying and an increased number of transient LOS relaxations [113–117]. Impedance studies in CF patients demonstrate increased numbers of total reflux episodes with a higher proportion of reflux episodes extending to the proximal oesophagus [115]. Several studies have suggested that patients with CF and reflux disease have more severe lung disease with lower pulmonary function and increased numbers of respiratory exacerbations [118–121].

The European Epidemiologic Registry of Cystic Fibrosis reported that patients with CF and GORD had a 5–10% lower  $FEV_1$  than those without GORD [122]. In a retrospective series of children with CF and evidence of both acid and non-acid reflux, a higher incidence of *Pseudomonas aeruginosa* in the lungs was noted compared to those who did not have reflux, and an inverse correlation between reflux burden and  $FEV_1$  as well as total number of reflux events and  $FEV_1$  was noted [118]. Similarly, VAN DER DOEF and colleagues [123] showed that GORD was associated with reduced pulmonary function and earlier acquisition of *P. aeruginosa* and *Staphylococcus aureus*, two major pathogens in CF lung disease. In their study, patients receiving treatment with gastric acid suppression had a significantly smaller yearly decline in maximal expiratory flow at 50% and maximal expiratory flow between 25 and 75% of forced vital capacity (FVC) compared with those not being treated with acid suppressors [123]. There are also suggestions in the literature that people with CF have an increased risk of Barrett’s oesophagus and gastrointestinal-related cancers, which become more marked following lung transplantation [124, 125]. While a direct causative effect of reflux disease in promoting worse lung and gastrointestinal health in the majority of these studies is not demonstrated, the results remain compelling.

Duodeno-gastro-oesophageal reflux and subsequent micro-aspiration of bile acids may be an under-recognised contributor to airway injury in CF lung disease. High levels of pepsin have been described in BAL samples from children with CF with corresponding high interleukin (IL)-8 levels, confirming active reflux and micro-aspiration, not suppressed by PPI therapy [126, 127]. Consistent with these observations, high concentrations of bile acids have been described in saliva, sputum and BAL of both adults and children with CF, although there is evidence to suggest that some assays used were not of sufficient sensitivity [114, 128–131]. Concentration of bile acids correlated with neutrophil elastase concentration in sputum, degree of lung function impairment and need for intravenous antibiotic treatment [130]. The markedly reduced biodiversity and increased colonisation by dominant proteobacterial CF-associated pathogens observed in the sputum of bile-aspirating patients suggest that bile may play a major role in disease progression in CF [132]. Although initial evidence suggested that bile acids were observed in patients with homozygous DF508 genotype, subsequent studies demonstrated similar bile acid concentrations in patients with a range of CF mutations [114, 130]. A recent study in patients with the

TABLE 2 Studies of gastro-oesophageal reflux treatment in COPD

First author [ref] Study type	n	Treatment	COPD symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
<b>MOKHLESI [106]</b> Prospective observational	100	Antacids (43%) PPI (28%) H2RA (6%) Treatment duration not specified	Resolution of chronic cough in 2% of patients	N/A	Unchanged	Resolution of GORD symptoms in 2% of patients
<b>HASANOGLU [107]</b> Prospective observational	30	Ranitidine 50 mg intravenous, 2-h measurement	N/A	N/A	Unchanged	N/A
<b>SASAKI [108]</b> RCT single-blind	100	Lansoprazole (15 mg·day <sup>-1</sup> ) versus usual care	N/A	Fewer exacerbations (0.34 versus 1.18, p=0.03); fewer patients experienced >1 exacerbation (24% versus 52%; p=0.004); PPI therapy independently reduced risk of exacerbation (OR 0.23, 95% CI 0.08–0.62)	N/A	Trend toward fewer common colds (1.22 versus 2.04) and less frequent common colds <3 per year) with PPI therapy compared to control
<b>ERYUKSEL [109]</b> Prospective observational	30	Anti-reflux therapy (2 months) PPI therapy	Reduced COPD symptoms (p<0.01)	N/A	N/A	Reduction in laryngopharyngeal reflux symptoms (p<0.01); improved laryngeal examinations (p<0.001)
<b>HARTWIG [33]</b> Prospective observational	20	Following bilateral lung transplantation, Nissen fundoplication (<365 days post-transplant) undertaken in selected patients	Unchanged	N/A	FEV <sub>1</sub> greater at 1 year with fundoplication compared to no fundoplication (8.8% difference)	N/A
<b>HOPPO [110]</b> Retrospective observational	11	Pre-transplant Nissen fundoplication	Unchanged	N/A	Improved FEV <sub>1</sub> and FVC % pred in overall group (separate outcomes for COPD not reported)	N/A
<b>LEE [111]</b> Prospective observational	17 498	Acid suppressive medication (PPI or H2RA)	N/A	N/A	N/A	Higher incidence rate ratio of pneumonia
<b>INGEBRIGTSEN [94]</b> Prospective observational	1259	Daily use of acid inhibitory therapy	N/A	Unchanged	N/A	N/A
<b>SU [112]</b> Prospective observational	17 423	Acid suppressive therapy (PPI or H2RA)	N/A	N/A	N/A	Lower risk of acute exacerbation (HR 0.31, 95% CI 0.20–0.50, p<0.0001) and mortality (HR 0.36, 95% CI 0.20–0.65, p=0.0007) with PPIs; no significant benefit observed for H2RAs

Abbreviations: FEV<sub>1</sub>: forced expiratory volume in 1 s; PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonist; GORD: gastro-oesophageal reflux; RCT: randomised controlled trial; FVC: forced vital capacity; HR: hazard ratio.

G551D mutation showed that treatment with ivacaftor was associated with a significant reduction of EOR symptoms denoted by the reflux symptom index and Hull airway reflux questionnaire [133].

Therapeutic targeting of reflux disease in CF patients is generally with high-dose PPIs and/or surgical intervention (table 3) [123, 133–139]. Use of PPIs in CF has increased consistently in recent years, initiated for a variety of reasons including improved efficacy of pancreatic enzymes in a higher pH environment, steatorrhoea, reflux symptoms, and treatment of cough or other respiratory or gastrointestinal complaints believed to be caused by GORD [140, 141]. A prospective RCT in adult patients with CF showed a trend towards shorter time to first exacerbation and increased number of exacerbations over a 6-month period in patients receiving esomeprazole compared with placebo, but the small sample size of this study precludes generalisability of the results [138]. Recent observational studies of PPIs in CF have shown an increased frequency of exacerbations and hospitalisations in patients with PPIs, but determining whether this increase is a genuine side effect of PPI treatment or a result of an increase in weakly acidic reflux events due to acid suppression remains to be determined [142, 143]. Challenge of primary bronchial epithelial cells (PBECs) cultured from CF lungs with physiologically achievable levels of primary and secondary bile acids led to increased release of the key pro-neutrophilic mediators IL-8 and IL-17 [129]. Stimulation of PBECs of one patient with CF and one healthy patient using gastric juice of 22 CF patients on and off PPIs showed higher pH and higher endotoxin levels in the gastric juice of CF patients treated with PPIs than those off treatment, resulting in a significantly enhanced inflammatory effect on CF PBECs in culture [144]. If chronic PPI treatment in CF results in a paradoxically increased inflammatory effect in the airways, alternative anti-reflux therapies need to be explored.

A recent limited literature has advocated fundoplication in CF. A retrospective study of the effect of Nissen fundoplication in patients with CF and GORD showed a significant decline in pulmonary exacerbation rate and improvement of FEV<sub>1</sub> and FVC during the 2 years after surgery compared with the 2 years preceding surgery [145]. In 48 patients with CF and evidence of uncontrolled reflux disease despite optimal medical management, fundoplication slowed decline in lung function and need for intravenous antibiotics for at least 1 year after surgery. Improvement in FEV<sub>1</sub> was lost by the end of the second year of follow-up in patients with an FEV<sub>1</sub> <60% at baseline. Therefore, patients with milder disease demonstrated the greatest benefit [146]. Fundoplication in children with CF has also been undertaken, but results have been varied [139].

Although some of these studies suggest that treatment of reflux disease might result in improved lung function or exacerbation rates, prospective studies have not been conducted in CF to determine whether reducing gastric pH or surgically reducing reflux has a beneficial effect on pulmonary exacerbations or other health-related outcomes.

### *Reflux disease and bronchiectasis*

The reported prevalence of reflux disease in bronchiectasis ranges from 34 to 74% using symptoms and questionnaires and from 11 to 75% using oesophageal pH monitoring [23, 101, 104, 147–158]. The confirmed presence of asymptomatic reflux in 42–73% of bronchiectasis patients emphasises the importance of objective confirmation of reflux disease in certain individuals [101, 150]. Three large prospective observational cohort studies suggest that typical GORD is associated with increased symptoms, increased exacerbations and hospitalisations, increased radiological severity, increased bacterial colonisation rates, reduced lung function and reduced QoL in bronchiectasis patients [23, 155, 156]. An increase in mortality has been described in two studies, a single centre study of 212 patients and a multicentre study of 986 patients [156, 157].

An increase in the prevalence of hiatal hernias has also been noted in bronchiectasis patients [23]. Increased radiological disease extent with typical GORD has been reported in bronchiectasis patients with coexisting non-tuberculous mycobacteria (NTM) [150]. The increased prevalence of typical GORD in bronchiectasis and NTM has also been observed among patients in the US bronchiectasis registry [158]. A correlation between symptoms of nocturnal reflux and distal reflux on pH monitoring has also been noted, which suggests that reflux disease may influence nocturnal respiratory status in some patients. Two case-control studies of reflux disease in bronchiectasis failed to observe any association with reduced lung function or other markers of disease severity. However, these studies were significantly underpowered to detect such effects, and a single dimension of time may be insufficient to accurately reflect the relationship between reflux disease and bronchiectasis [101, 104]. These studies also looked at pepsin as a marker of aspiration, detected in 26–70% of individuals with mild to moderate disease [101, 104].

Very few studies have assessed potential treatment strategies for reflux disease in bronchiectasis (table 3) [159, 160]. A retrospective comparison of 27 patients treated with long-term PPIs compared to 230

TABLE 3 Studies of gastro-oesophageal reflux treatment in cystic fibrosis and bronchiectasis

First author [ref] Study type	n	Treatment	CF symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
<b>Cystic fibrosis</b>						
MALFROOT [134] Prospective observational	16	Cisapride therapy	Improved weight gain and improved cough and wheeze	N/A	N/A	N/A
BRODZICKI [135] Prospective observational	19	Cisapride or cisapride with ranitidine for 3 months	N/A	N/A	N/A	Improved GORD outcomes on pH analysis: decrease in reflux index, longest episode duration and the no. of episodes >5 min; improvement of endoscopic picture post-treatment
VAN DER DOEF [123] Prospective observational	218	Gastric acid inhibition (proton pump inhibitors or histamine-2 receptor antagonists) for fat malabsorption or GORD	N/A	N/A	GORD was associated with significantly reduced FEV <sub>1</sub> and FVC Patients with gastric acid inhibition had a significantly smaller yearly decline of MEF <sub>50</sub> and MEF <sub>25-75%</sub>	GORD was associated with an earlier acquisition of <i>P. aeruginosa</i> and <i>S. aureus</i>
TRAN [136] Children Prospective observational	15	Lansoprazole 15 mg daily for 3 months	Improved faecal steatorrhea	N/A	N/A	Significant improvements in fat mass nutritional status and bone mineral content
HENDRIKS [137] Prospective observational	14	Lansoprazole 30 mg daily for 1 year	Improved faecal steatorrhea	N/A	Improved TLC, RV and inspiratory muscle capacity	Improved BMI, decreased fat losses and improved total body fat
DIMANGO [138] RCT	17	PPI (esomeprazole 40 mg BD) for 36 weeks	N/A	Trend to earlier exacerbation and more frequent exacerbations in esomeprazole group	FEV <sub>1</sub> unchanged	No change in Gastroesophageal Symptom Assessment Score or CF Quality of Life score between the two groups
ZEYBEL [133] Prospective observational	12	Ivacaftor (CF patients with G511D mutations)	N/A	N/A	Baseline FEV <sub>1</sub> lower in patients with extra-oesophageal reflux symptoms	Improved extra-oesophageal reflux symptoms using the Reflux Symptom Index and the Hull Airways Reflux Questionnaire
BOESCH [139] Children Prospective observational	25	Nissen fundoplication	N/A	N/A	No change in FEV <sub>1</sub> or body mass index after fundoplication; children who had an FEV <sub>1</sub> <60% predicted at time surgery had significantly improved FEV <sub>1</sub> compared to those with FEV <sub>1</sub> <60%	No mortality associated with fundoplication, but 12% had complications that required a subsequent surgical procedure

Continued

TABLE 3 Continued

First author [ref] Study type	n	Treatment	CF symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
FATHI [145] Prospective observational	6	Nissen fundoplication	N/A	50% reduction in exacerbations 2 years post-operatively	Small but significant improvement in FEV <sub>1</sub> and FVC 2 years post-operatively	Improved cough symptoms using the Leicester Cough Questionnaire
SHEIKH [146] Retrospective observational		Nissen fundoplication	Increased weight gain	Fewer pulmonary exacerbations	Slower decline in FEV <sub>1</sub> 2 years post-operatively	Better pulmonary and nutritional outcomes were noted among patients with milder lung disease compared to those with severe lung disease; no mortality associated with surgery
<b>Bronchiectasis</b> AHN [159] Prospective observational	257	PPI therapy (any type) for 6 months	N/A	N/A	Unchanged Subgroup analyses showed significant improvement in lung function in patients with high BMI related to the severity of obesity	N/A
Hu [160] Prospective observational	7	Stretta radiofrequency (SRF) n=2 Laparoscopic fundoplication with or without hiatal hernia repair n=4 Combined n=1	Improved	Improved exacerbations Improved hospitalisations	N/A	Improved GORD symptoms

Abbreviations: CF: cystic fibrosis; FEV<sub>1</sub>: forced expiratory volume in 1 s; GORD: gastro-oesophageal reflux; FVC: forced vital capacity; MEF<sub>50</sub>: maximal expiratory flow at 50 % of FVC; MEF<sub>25-75%</sub>: mean expiratory flow at 25–75% of FVC; TLC: total lung capacity; RV: residual volume; BMI: body mass index; RCT: randomised controlled trial; PPI: proton pump inhibitor.

without showed no significant differences in lung function after 6 months [159]. A review of the clinical outcomes of seven patients with GORD-related bronchiectasis showed that anti-reflux treatment with Stretta radiofrequency and/or laparoscopic fundoplication resulted in significant improvements in exacerbations, respiratory and typical GORD symptoms over a 1- to 5-year follow-up [160]. Routine interrogation for reflux disease and RCTs of anti-reflux therapy in this patient population are urgently needed.

#### Reflux disease and IPF

An association between IPF and reflux disease was demonstrated in an early study which noted an increased prevalence of hiatal hernias among IPF patients [161]. The limited available research has demonstrated, through pH monitoring, that reflux disease is significantly increased in patients with IPF as compared to normal subjects but may be clinically occult [162]. This has been confirmed by RAGHU *et al.* [163], demonstrating liquid acid GORD on 24-hour pH monitoring in 87% of their subjects. A recent systematic review, however, indicated that the prevalence of abnormal GORD in 23 studies ranged from 0 to 94% [164]. Patient selection, however, probably accounted for the results at the extremes.

Patients with IPF can experience acute exacerbations in their respiratory status leading to loss of lung function, morbidity and mortality. Occult aspiration of gastric contents has been proposed as a possible

mechanism. BAL pepsin levels have been shown to correlate with clinical features and disease course in IPF, but this was not an independent predictor of survival [165]. Combining reflux disease testing by pH-impedance and BAL markers of aspiration was evaluated in a study by SAVARINO *et al.* [166]. IPF patients were found to have higher levels of reflux disease in terms of proximal reflux events and BAL bile acids and pepsin than non-IPF patients and healthy volunteers.

Recently, lung disease severity in IPF has been found to be strongly associated with impedance measures of bolus reflux than pH parameters of acid reflux alone in a retrospective study of 45 patients undergoing assessment pre-transplant [167]. Some patients with IPF have marked asymmetry of their lung disease on high-resolution CT (HRCT), potentially suggestive of aspiration [168]. These patients showed an increased prevalence of acute exacerbations, with increased reflux symptoms.

Studies of anti-reflux treatment in IPF are lacking (table 4) [169–181]. An influential retrospective study of 204 patients showed that reflux disease therapy, consisting of PPIs and surgery, was associated with longer survival in IPF and a lower radiological fibrosis score, emphasising the need for further careful study [172]. Similar findings in an analysis of data from three RCTs have also been reported whereby, after adjustment for sex and baseline lung function, patients taking anti-acid treatment had a smaller decrease in FVC at 30 weeks compared to those not taking anti-acid treatment [172, 176, 177]. Recent meta-analyses of randomised trials and observational case-control studies of reflux disease in IPF suggest that pharmacological treatment of reflux disease may be associated with a reduction in IPF-related (adjusted HR 0.45 (0.24–0.84)) but not overall mortality and that the observed association with reflux disease may be confounded by smoking [177, 182, 183]. The most recently reported trials of PPIs and surgical fundoplication in IPF suggest non-significant reductions in FVC decline with both treatment entities, with a small increase in respiratory-related infections with twice-daily omeprazole use [34, 179].

Due to the older age and multimorbidity of IPF patients, lung and non-lung surgical procedures have a high degree of risk, indicating the need for very careful patient selection. The Newcastle group have pioneered the role of the aerodigestive multidisciplinary team and have shown that fundoplication is only suitable in a minority of IPF patients following an integrated approach due to the presence of oesophageal dysmotility and multiple comorbidities [184]. It is of potential concern that the current literature includes increasing numbers of statements supporting surgical treatment for IPF despite a lack of evidence from clinical trials [164]. Importantly, evidence-based guidelines for treatment of IPF approved conditional recommendation of PPIs for all patients with IPF regardless of their reflux disease status [185]. This could potentially limit the number of IPF patients enrollable in future treatment efficacy studies.

#### ***Reflux disease and lung transplant***

Reflux disease post lung transplantation is now identified as a major risk factor for the development of bronchiolitis obliterans syndrome (BOS), which is the commonest cause of late graft failure. Increased total proximal and distal reflux episodes on pre-transplant impedance and pH testing have also been associated with decreased time to early allograft injury after lung transplantation [186]. Damage to the vagal nerves is also common during the lengthy complex surgery. Calcineurin inhibitors to prevent rejection also significantly suppress oesophageal and gastric peristalsis. Up to 75% of post-transplant patients have demonstrable reflux disease with impedance or biomarker presence following lung transplantation [187–190]. Recent studies suggest that oesophageal dysmotility and impaired clearance of swallowed bolus or refluxed contents are also important risk factors in the development of lung allograft dysfunction [191]. A retrospective review of persistent PPI therapy in 188 patients post lung transplant demonstrated that PPIs are protective against rejection, independent of other clinical predictors including body mass index, suggesting that PPIs may have anti-reflux or anti-inflammatory effects in enhancing allograft protection [192]. Anti-reflux surgery has also been associated with an increased survival and improved lung function [33]. In particular, fundoplication within 3 months or, as has more recently been demonstrated, within 1 month of transplant may result in a significant reduction in the incidence of BOS [193]. Studies have also shown a potential therapeutic benefit of azithromycin post lung-transplant in improving FEV<sub>1</sub> in patients with BOS, but whether this is due to its immunomodulatory effect on small airways or prokinetic effect on the upper gut is unclear [194].

#### ***Diagnosis and treatment of reflux disease in chronic respiratory diseases***

Diagnosing GORD in respiratory patients can be very challenging, as there is a paucity of randomised trials to direct appropriate therapy. The authors recommend the following approach.

- 1) Very detailed history taking, nuanced also for the presence of EOR. Validated questionnaires for GORD and EOR could be very helpful. Reflux disease symptoms, however, may be entirely absent in some patients.

TABLE 4 Studies of gastro-oesophageal reflux treatment in interstitial pulmonary fibrosis

First author [ref] Study type	n	Treatment	IPF symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
<b>Medications</b>						
BRADFORD [169] Retrospective observational	262	Chronic anti-reflux medications (>6 months non-p.r.n. use of any antacid, sucralfate, H2RA or PPI) versus non-users (<6 months of use or none)	N/A	N/A	Unchanged	Increased risk of hospitalisation and respiratory hospitalisation in chronic anti-reflux medication users; no effect on mortality
GRIBBIN [170] Retrospective case-control	920	Anti-reflux medications (H2RA or PPI)	N/A	N/A	N/A	IPF diagnosis significantly associated with anti-reflux therapy (OR 2.20, 95% CI 1.88–2.58)
LEE [171] Retrospective observational	204	Anti-reflux medications (H2RA or PPI)	N/A	N/A	N/A	Anti-reflux medications were an independent predictor of longer survival time; anti-reflux medications were associated with a lower radiological fibrosis score
LEE [172] Retrospective observational	242	Anti-reflux medications (H2RA or PPI)	N/A	N/A	Unchanged	Patients taking anti-reflux medications at baseline had a smaller decrease in FVC at 30 weeks (–0.06 L, 95% CI –0.11 to –0.01) compared to those not taking anti-reflux medications (–0.12 L, 95% CI –0.17 to –0.08; difference 0.07 L, 95% CI 0–0.14; p=0.05). No change in all-cause mortality
KILDUFF [173] Prospective observational	18	Anti-reflux medications (H2RA or PPI) undergoing oesophageal pH-impedance	N/A	N/A	N/A	Significant decrease in the number of acid reflux events (p=0.02), but an increase in the number of non-acid reflux events (p=0.01); no change in cough frequency (p=0.70)
GHEBREMARIAM [174] Prospective observational	215	PPI therapy >12 months	N/A	N/A	N/A	Use of PPIs was associated with a significant reduction in the number of patients with lung transplantation or death (p=0.025) and a 1.4-year increase in longevity (median survival of 3.4 versus 2 years; p<0.001)
RAGHU [181] Prospective observational	406	Anti-reflux medications (H2RA or PPI) with and without nintedanib	N/A	N/A	N/A	Anti-reflux medication use at baseline did not influence the treatment effect of nintedanib on reducing decline in FVC in patients with IPF

Continued

TABLE 4 Continued

First author [ref] Study type	n	Treatment	IPF symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
LEE [176] Retrospective observational	786	PPI any type (mean follow-up 2.6 years)	N/A	N/A	N/A	Patients administered PPI >4 months had a lower IPF-related mortality rate than patients on PPI <4 months; younger age, higher initial FVC and longer duration of PPI use, but not a diagnosis of GORD, were significantly associated with lower IPF-related mortality
KREUTER [177] Pooled analysis	291	Anti-reflux medications (H2RA or PPI) For 52 weeks follow-up	N/A	Overall and pulmonary infections higher in patients with advanced IPF treated with anti-reflux medications compared to those not treated	Unchanged	No difference in overall or IPF-related mortality between groups; no difference in hospitalisations between groups
KREUTER [178] Post hoc RCT analysis	623	Anti-reflux medications (H2RA or PPI) with and without pirfenidone	N/A	Severe pulmonary infections higher in patients treated with anti-reflux medications compared to those not treated; no difference in all-cause hospitalisation rate	Unchanged	No significant differences in disease progression, all-cause mortality rate IPF-related mortality rate or mean change in percent FVC between groups; severe gastrointestinal adverse events were more frequent with anti-reflux medications
DUTTA [179] RCT	45	PPI (omeprazole)	N/A	Small excess of lower respiratory tract infection in omeprazole-treated group	Small reduction in FEV <sub>1</sub> in omeprazole-treated group	Non-significant reduction in geometric mean cough frequency at the end of treatment, adjusted for baseline in the omeprazole group compared with placebo; omeprazole was well tolerated and adverse event profiles were similar in both groups; non-significant reduction in FVC associated with omeprazole
<b>Surgery</b> LINDEN [180] Prospective observational	19	Nissen fundoplication (15-month follow-up)	N/A	N/A	Unchanged	Unchanged exercise capacity; stable oxygen requirements compared to IPF patients without fundoplication on transplant list

Continued

TABLE 4 Continued

First author [ref] Study type	n	Treatment	IPF symptoms	Exacerbations	FEV <sub>1</sub>	Other outcomes
RAGHU [181] Retrospective observational	27	Nissen fundoplication	N/A	N/A	Unchanged	Improvement in mean DeMeester scores from 42 to 4 (p<0.01); trend toward stabilisation in observed FVC
RAGHU (WRAP-IPF trial) [34] RCT	58	Nissen fundoplication	N/A	Non-significant reduction in exacerbations & respiratory hospitalisations in surgery-treated group	N/A	No 90-day deaths Non-significant reduction in rate of change of FVC (p=0.28) and mortality over 48 weeks

Abbreviations: IPF: interstitial pulmonary fibrosis; FEV<sub>1</sub>: forced expiratory volume in 1 s; H2RA: histamine-2 receptor antagonist; PPI: proton pump inhibitor; FVC: forced vital capacity; GORD: gastro-oesophageal reflux; RCT: randomised controlled trial.

- 2) If reflux disease is suspected, lifestyle modification, particularly weight loss if obese, avoidance of late-night meals or food triggers and elevating the head of the bed should be trialled.
- 3) In patients with reflux disease and/or suspected reflux disease-exacerbated lung disease, start treatment trial twice daily PPI for up to 8 weeks. If good response, continue PPI and reduce to the minimum beneficial dose. If poor response, check compliance (PPI should be taken 30–60 min pre-meal).
- 4) Response to treatment may be difficult to determine, but a reduction in exacerbation frequency of airway diseases, or clinical and radiological improvement in bronchiolitis and other infiltrative disorders would be encouraging and long-term PPI treatment advocated.
- 5) As yet, there is no evidence to support the addition of prokinetic drugs such as domperidone, metaclopramide or macrolides.
- 6) In non-responders with suspected reflux disease-exacerbated lung disease, again check compliance. If satisfactory, further investigation should be considered with oesophageal manometry to exclude achalasia or oesophageal spasm and determine presence and size of a hiatal hernia, and 24-h oesophageal pH and impedance monitoring to determine non-adequate suppression of acid, non-acid or gaseous reflux and its proximal extent.
- 7) In those with persistent oesophageal symptoms, particularly dysphagia, despite PPI, an oesophago-gastro-duodenoscopy (OGD) would be warranted to exclude persistent erosive disease, Barrett's oesophagus or malignancy, functional heartburn, oesophageal stricture or eosinophilic oesophagitis.
- 8) Detection of biomarkers such as pepsin and bile acids in BAL, EBC, induced sputum or saliva is not yet validated but may be promising as absolute proof of reflux disease.
- 9) In patients proven to be refluxing despite PPI with significant oesophageal and extra-oesophageal disease, anti-reflux surgery should be considered. Oesophageal physiology studies including dysmotility and pH-impedance studies should be performed to inform the risk:benefit ratio. All patients being considered for surgery should be discussed at an aerodigestive multidisciplinary team meeting with lung and gastroenterology representation. A Nissen's fundoplication is the most commonly performed surgical procedure, consisting of a complete 360° wrap to create an anti-reflux valve at the fundus of the stomach that inhibits the regurgitation of gastric contents into the oesophagus. Anecdotal successes abound, but there have been no randomised trials of its effect in reflux disease-related respiratory syndromes.
- 10) RCTs of anti-reflux medications and surgery are needed across the spectrum of chronic lung disease to determine effects of treatment and control for confounding and protopathic bias.

### Conclusion

Aerodigestive disease is a rapidly growing field within respiratory medicine with reflux disease suspected of having an adverse role in a number of chronic respiratory diseases, therefore our index of suspicion should

remain high. A vicious cycle of worsening reflux disease and lung disease may ensue. If the patient has typical GORD or suggestible EOR symptoms, an 8-week trial of PPIs is indicated followed by prokinetics after reviewing the potential benefits *versus* known risks. Lack of response warrants further investigation with oesophageal manometry, 24-h pH-impedance monitoring and an oesophageal mucosal inspection. If reflux disease is still suspected, anti-reflux surgery may be considered.

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