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A qualitative synthesis of gastro-oesophageal reflux in bronchiectasis: Current understanding and future risk

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Abstract (200 words):

Gastro-oesophageal reflux disease (GORD) is a common comorbidity in bronchiectasis, and is often associated with poorer outcomes. The cause and effect relationship between GORD and bronchiectasis has not yet been fully elucidated and a greater understanding of the pathophysiology of the interaction and potential therapies is required. This review explores the underlying pathophysiology of GORD, its clinical presentation, risk factors, commonly applied diagnostic tools, and a detailed synthesis of original articles evaluating the prevalence of GORD, its influence on disease severity and current management strategies within the context of bronchiectasis. The prevalence of GORD in bronchiectasis ranges from 26%-75%. Patients with co-existing bronchiectasis and GORD were found to have an increased mortality and increased bronchiectasis severity, manifest by increased symptoms, exacerbations, hospitalisations, radiological extent and chronic infection, with reduced pulmonary function and quality of life. The pathogenic role of *Helicobacter pylori* infection in bronchiectasis, perhaps via aspiration of gastric contents, also warrants further investigation. Our index of suspicion for GORD should remain high across the spectrum of disease severity in bronchiectasis. Identifying GORD in bronchiectasis patients may have important therapeutic and prognostic implications, although clinical trial evidence that treatment targeted at GORD can improve outcomes in bronchiectasis is currently lacking.

Introduction:

Bronchiectasis is an umbrella term for patients with a chronic inflammatory lung disease characterised radiologically, by the permanent dilation of bronchi, and clinically, by persistent cough, sputum production, and recurrent respiratory tract infections.(1) Data across multiple healthcare systems suggest that the prevalence of bronchiectasis is increasing.(2-4) The common pathophysiological pathway of bronchiectasis consists of Cole's "vicious cycle" hypothesis of infection, inflammation and airway structural changes.(5) The interesting feature is that the initial herald event may be a once-off phenomenon such as aspiration, an inhaled foreign body or pneumonia, but once initiated, the vicious cycle is often self-perpetuating. The clinical profile of bronchiectasis is frequently punctuated by acute exacerbations, which are associated with accelerated lung function decline and deterioration in quality of life (QoL).(6) Bronchiectasis patients are also frequently afflicted by comorbidities, often associated with severe disease and poor clinical outcomes, many of which confer an independent risk of death and might be missed unless specifically searched for.(7)

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.(8) It is a common upper gastrointestinal condition, affecting 9-27% of Europeans, and may be associated with either oesophageal or extra-oesophageal syndromes.(8, 9) Reflux may be acidic, weakly acidic or non-acidic (alkaline), and may be liquid, gaseous or mixed.(10) The main factors that determine the significance of GORD include the frequency, duration and extent of episodes as well as the volume, composition and destination of the refluxed contents.

As both bronchiectasis and GORD are highly prevalent conditions, the possibility of an interaction has long been recognised. GORD has been attributed as an aetiological factor in several aetiological studies of bronchiectasis but is more commonly perceived as a comorbidity that may exacerbate the underlying lung disease. Given the potential for bronchiectasis and GORD to aggravate each other in a bi-directional manner, it is important to better understand the relationship and possible consequences of the two conditions co-existing. This area has generated significant interest despite the relative paucity of good-outcome data because the potential landscape for the treatment of GORD, both medically and surgically, is significant. This review explores the underlying pathophysiology of GORD, its clinical presentation, risk factors, commonly applied diagnostic tools, and a detailed synthesis of original articles evaluating the prevalence of GORD, its influence on disease severity and current management strategies within the context of bronchiectasis.

Pathophysiology of GORD

Gastro-oesophageal reflux (GOR) is a normal physiological occurrence. In health, reflux is prevented through the combined action of the components of the anti-reflux barrier: the lower oesophageal sphincter (LOS), the crural diaphragm and the anatomical flap valve.(11) GORD usually occurs in the event of failure of one or more of the anatomical or physiological protective mechanisms of the anti-reflux barrier, such that the aggressive forces (injurious properties of gastric acid, bile, pepsin and duodenal contents) outweigh the defensive forces (anti-reflux barrier and oesophageal clearance), leading to histological damage in the oesophagus and extra-oesophageal organs, including the exposed respiratory epithelium.(12, 13) GORD typically occurs during periods of gastro-oesophageal junction incompetence that may be functional (due to an increased number of transient LOS relaxations or the presence of a hiatal hernia) or mechanical (due to reduced LOS tone, oesophageal body dysfunction, delayed proximal gastric emptying, or increased intragastric pressure); with age, gender, smoking, obesity, spicy foods, alcohol consumption, positional and physiological changes in respiratory mechanics and medications all potential contributing factors.(11, 12, 14) It is also important to consider that GORD may result from progressive incompetence of the anti-reflux barrier due to the failure of multiple anti-reflux mechanisms rather than one single process, with the

frequency and duration of reflux events increasing progressively with each protective mechanism that becomes compromised.

Clinical presentation

GORD may manifest as typical reflux symptoms such as heartburn, acid regurgitation, chest pain, epigastric pain or sleep disturbances.(8, 11, 15) These clinical features together with oesophageal complications, including reflux oesophagitis, Barrett's oesophagus, and adenocarcinoma, are collectively referred to as oesophageal syndromes.(8) Symptoms such as a hoarse voice, chronic cough or wheeze that may lead to laryngitis or respiratory complications are classed as extra-oesophageal syndromes. The prevalence of extra-oesophageal reflux is difficult to determine; extra-oesophageal symptoms can occur concurrently with typical GORD symptoms or in isolation.(15) It is estimated that approximately one third of patients with GORD have concurrent extra-oesophageal symptoms; however, establishing that an individual patient's extra-oesophageal symptoms are caused by reflux is extremely difficult.(9) An outline of oesophageal and extra-oesophageal clinical presentations of GORD is presented in Figure 1. Either may be present in patients with bronchiectasis.

Diagnostic assessment of GORD

The most common approach to the diagnosis of GORD is through an accurate medical history, enquiring about typical symptoms and their relationship to food, posture, and stress.(15) However, some of the extra-oesophageal symptoms of GORD may be similar to those of bronchiectasis. Therefore, it is necessary to enquire as to the timing of GORD symptoms and their association with awakening from sleep, or the presence of respiratory symptoms or coughing after meals.(16) Symptom evaluation alone may be insufficient for a diagnosis of GORD due to limited sensitivity and specificity.(17) Symptom assessment through validated questionnaires, which ideally incorporate both oesophageal and extra-oesophageal symptoms so as not to limit their applicability in the setting of silent reflux, may be needed.(18) In the presence of typical reflux symptoms, an empirical trial of acid suppression therapy is often undertaken, with resolution of symptoms considered clinically indicative of GORD.(15) In those with persisting symptoms despite therapy, objective tools such as an oesophago-gastro-duodenoscopy may be used to identify secondary complications of mucosal injury and oesophagitis.(19)

In patients without typical symptoms or where asymptomatic reflux is suspected, alternative options for diagnosing GORD include ambulatory 24-hour oesophageal pH monitoring, with or without multichannel intraluminal impedance testing – the current "gold standard" for diagnosing GORD.(10, 15, 20-23) pH-monitoring is generally performed after cessation of acid suppression drugs for a minimum period of five days to allow tracking of overall oesophageal acid exposure and investigate whether or not a temporal relationship is present between symptoms and reflux events.(11) Oesophageal manometry testing is generally performed prior to insertion of the pH-impedance probe to ensure correct positioning for electrode placement and to rule out severe oesophageal motility disorders.(24) Dual-channel pH monitoring measures proximal and distal oesophageal pH, providing data on the frequency and duration of reflux episodes and the proximal spread of the refluxed material over a complete circadian cycle.(21, 22). A variation on this is telemetry capsule pH monitoring, which offers increased patient tolerability and the option to extend the monitoring period to 48 or 96 hours, but which does not allow for a combined impedance assessment.(25) Combining pH monitoring with multichannel intraluminal impedance allows the additional identification of acid versus weakly acid or non-acid reflux, and measurement of gaseous versus liquid or mixed reflux, recording GORD at all pH levels and enabling confirmation in patients whose diagnoses may have been missed using pH-testing alone.(10) This technique quantifies the type, number, composition, duration and extent of each reflux episode, giving an exact assessment of the proximal extent of refluxed material and a detailed characterisation of each reflux episode.(10, 26, 27)

Diagnosis of pulmonary microaspiration

Pulmonary micro-aspiration of duodeno-gastric contents into the lungs, hypothesised to drive the progression of an exaggerated bronchial inflammatory response, can be detected through various methods.(28, 29) This hypothesis is very difficult to test, due to both the difficulties in assessing the presence of reflux clinically and diagnostically, and the potential confounding effects of anti-inflammatory and prokinetic therapies used in the treatment of bronchiectasis.(29) Although dual chamber pH and impedance monitoring both detect proximal reflux, the extent of reflux within the hypopharynx and airway is not measured. The detection of pepsin and bile salts, as markers of gastric and duodenal reflux, respectively, in saliva, sputum, tracheal aspirates or bronchoalveolar lavage (BAL) fluid have been proposed as surrogate markers of reflux aspiration.(17, 18) Pepsin has been detected in lung transplant recipients with GORD confirmed on oesophageal pH monitoring or impedance monitoring, and more recently in sputum and exhaled breath condensate (EBC) in individuals with bronchiectasis, suggesting that these biological markers are reliable in assessing the effect of pulmonary micro-aspiration in lung disease severity.(30, 31)

Treatment of GORD

Current therapy for GORD focuses on modifying risk factors, inhibiting the production of gastric acid and enhancing oesophageal and gastric motility.(15) Lifestyle modifications to minimise GORD include weight loss, avoidance of late-night meals, avoidance of food and drink that might relax the LOS, stress reduction and altered posture, including adapting a semi-recumbent posture when sleeping.(15, 32) Medical approaches include the use of antacids, histamine antagonists and proton pump inhibitor (PPI) therapy, as determined by the severity of GORD.(11, 15, 33, 34) The beneficial effect of antacids, with or without alginic acid, is related to the neutralisation of acid, which provides temporary symptomatic relief. PPIs and histamine antagonists inhibit gastric acid secretion. PPIs are thought to be more effective and promote faster healing than histamine antagonists. However, recent population-based studies have suggested that long-term PPI use may be associated with a variety of adverse events including osteoporosis-related hip and spine fractures, community-acquired and nosocomial pneumonia, vitamin B12 deficiency, various enteric and non-enteric infections, and many others.(35) Studies involving oesophageal multichannel intraluminal impedance have revealed a potential role of weakly acidic or non-acid reflux in patients with persistent symptoms despite treatment with a PPI.(36) PPI therapy may result in a paradoxical increase in the number and frequency of weakly acid and non-acid reflux events rather than eradicating the problem, and therefore do not provide a long-term solution for GORD.(36) The mechanism by which weakly acidic reflux causes GORD-related symptoms remains poorly understood but could be related to one or both of oesophageal distension by increased reflux volume or oesophageal hypersensitivity to weakly acidic reflux.(36)

In cases of oesophageal dysmotility, prokinetic therapy can be trialled to speed up gastric emptying by increasing peristaltic muscle contractions of the lower oesophagus and strengthening the LOS, limiting exposure of acid to the oesophagus. More commonly used drugs are domperidone and metoclopramide, but the prokinetic effects of erythromycin and azithromycin should not be ignored. Macrolides work by increasing gastric emptying, increasing proximal stomach tone and lowering LOS pressure via a cholinergic pathway mediated by motilin receptors.(37) Given their success in the treatment of bronchiectasis exacerbations, further work into the effect of GORD and bronchiectasis exacerbations is needed.

There is currently a growing interest in non-PPI-related therapeutic strategies for GORD with a resurgence in endoscopic treatment and anti-reflux surgeries, which at present are reserved for patients with persistence of the underlying mechanism causing GORD.(38) A Nissen's fundoplication is the most commonly performed surgical procedure for GORD, consisting of a complete 360° wrap to create an antireflux valve at the fundus of the stomach that inhibits the regurgitation of gastric

contents into the oesophagus. 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 patients seeking relief from lifelong dependence on pharmacological therapy, its cost, associated side effects, and long-term adverse outcomes.(15)

Methodology

Literature search: We searched electronic databases including Pubmed, Medline (Ovid), EMBASE, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) for all reports published from inception until May 2017 using the following search string: reflux[majr] OR gastro-oesophageal reflux[Majr] OR GORD[tiab] OR gastroesophageal reflux[majr] OR GERD[tiab] OR duodenogastric reflux[Majr] OR laryngopharyngeal reflux[Majr] AND bronchiectasis[majr] OR NCFB[tiab] OR NCFBr[tiab]. To ensure a complete review of available studies, manual review of conference proceedings and review of references from selected papers was also performed.

Study selection: Limits were not applied to the search strategy to enable a comprehensive search to be performed. However, the following article types were excluded from our qualitative synthesis: reviews, editorials, case reports, case series and non-English publications. Full-text articles were independently reviewed by two investigators with disagreements regarding eligibility resolved by consensus. Data on study type and design, population characteristics, diagnosis of GORD (method of assessment and result) and outcome variables were extracted. A positive association was defined as worsening of any bronchiectasis outcome associated with the presence of GORD. As bronchiectasis outcomes differed between studies (e.g. reduced pulmonary function, increased radiological severity, etc), we report bronchiectasis outcomes as defined in the study manuscripts. Due to known heterogeneity in the methods of GORD detection and the number of different bronchiectasis outcomes, a decision was made *a priori* not to perform a meta-analysis or generate quantitative summary estimates. Instead a qualitative summary in tabular format was planned, with studies divided into those assessing the prevalence of GORD in bronchiectasis, the role of *Helicobacter pylori (H.pylori)* in bronchiectasis, and treatment options for GORD in bronchiectasis.

Results

Study selection: Of 961 citations, 24 studies (n=4,605) fulfilled the eligibility criteria (Figure 1), including 7 prospective case control studies (n=662), 13 prospective cohort studies (n=3,375) and 4 retrospective cohort studies (n=568). No randomised controlled trials have been performed to date. 15 studies assessed the prevalence of GORD in bronchiectasis (n=3,679) with 2 of these incorporating the prevalence of pulmonary micro-aspiration in bronchiectasis (n=57); 7 assessed the role of *H. pylori* (n=662), and 2 assessed treatment options for GORD in bronchiectasis (n=264). Effects of GORD on markers of bronchiectasis disease severity were noted in 12 studies (n=3,876). 2 studies focussed on the effects of chest physiotherapy on GORD in bronchiectasis (n=62). 4 studies were paediatric-based (n=330); the remaining 20 (n=4, 275) were adult-based.

Studies on the prevalence of GORD in bronchiectasis

The prevalence of GORD in individuals with bronchiectasis has been explored in a number of studies to date.(7, 30, 31, 39-50) A range of diagnostic tools have been used, including symptom assessment, questionnaires and objective measurements, outlined in Table 1. Based on self-reported symptoms and questionnaires, the prevalence of GORD ranges from 34% to 74%.(7, 30, 47-50) Although a detailed clinical history of symptom presentation is recommended, this method of diagnosis is reliant

upon the provocation of symptoms by reflux events, which in the event of asymptomatic or clinically silent reflux is not a reliable indicator. By comparison, according to oesophageal pH monitoring, prevalence ranges from 11% to 75% were noted.(30, 31, 39-42, 44-46) Such a wide spread may be related to several factors, such as selective investigation which may miss patients with silent reflux, the application of different GORD criteria, and whether tests were undertaken on or off anti-reflux medication. Mixed patterns of reflux are evident, with distal reflux only, proximal reflux only, and a mix of both demonstrated. In those with bronchiectasis, a prevalence greater than that seen in COPD and more than twice that of healthy controls has been reported for proximal and distal reflux.(30) GORD can affect patients with mild, moderate and severe bronchiectasis and appears to be particularly prevalent among bronchiectasis patients with co-existing NTM disease.(42, 50) The confirmed presence of asymptomatic reflux in 42% to 73% of bronchiectasis patients emphasises the importance of objective confirmation of GORD in certain individuals.(30, 42)

Studies on the presence of pulmonary micro-aspiration in GORD

Surrogate indicators of pulmonary micro-aspiration of gastric contents have also been examined n bronchiectasis. Pepsin in sputum samples has been detected in 26% to 70% of individuals with mild to moderate bronchiectasis.(30, 31) Although no significant association between oesophageal pH monitoring indices or lung disease severity and pepsin concentrations in sputum has been demonstrated to date, this has been previously observed in individuals with other types of lung disease.(51-53) This may be explained by isolated reflux events that could be aspirated being insufficiently frequent to contribute to the criteria defining GORD. A pilot study of exhaled breath condensate (EBC) in ten individuals with bronchiectasis found pepsin in 60%, irrespective of a diagnosis of GORD on oesophageal pH monitoring.(31) The EBC pH was significantly lower in bronchiectasis patients compared to controls and was strongly correlated with higher concentrations of EBC pepsin.(31) Low EBC pH may be related to several factors including airway inflammation, oxidative stress, bacterial colonisation or severe GORD in bronchiectasis. Low EBC pH has been related to severe GORD symptoms in COPD, suggesting that EBC pH may reflect acid reflux rather than tracheobronchial inflammation.(16)

Studies on the influence of GORD on bronchiectasis severity

The relationship between the severity of bronchiectasis and GORD remains somewhat controversial. Although some studies performed to date have observed significant relationships between GORD and markers of bronchiectasis disease severity, the majority of these have been based on a subjective evaluation of GORD determined by symptom evaluation, questionnaires and medication review. Three large prospective observational cohort studies suggest that GORD (particularly in the presence of a hiatal hernia) is associated with increased symptoms, increased exacerbations and hospitalisations, increased radiological severity, increased colonisation rates, reduced lung function and reduced HrQoL in bronchiectasis patients.(47-49) An increase in mortality has been described in two studies, a single centre study of 212 patients and a multicentre study of 986 patients.(7, 48) Koh *et al* were the first and only group using 24h oesophageal pH monitoring to report an association with increased radiological disease extent in their cohort of bronchiectasis patients with co-existing NTM.(42) The increased prevalence of GORD in bronchiectasis and NTM has also been observed among patients in the US bronchiectasis registry.(50) Ahmed *et al* described a correlation between symptoms of nocturnal reflux and distal reflux on pH-monitoring, which suggests that GORD may influence nocturnal respiratory status in some patients. Two case-control studies of GORD in bronchiectasis failed to observe any association with reduced lung function or other markers of disease severity. However, due to the difficulties in recruiting, these studies were significantly underpowered to detect such effects, and a single dimension of time may be insufficient to accurately reflect the relationship between GORD and bronchiectasis.(30, 31)

Studies on the role of *Helicobacter pylori* in bronchiectasis

H. pylori is a pathogenic organism linked with a number of gastric (gastritis, peptic ulcer, gastric, colorectal and pancreatic malignancy) and non-gastric (ischaemic heart disease, cerebrovascular disease, diabetes mellitus, vitamin B12 deficiency, and idiopathic thrombocytopoenic purpura) disorders.(54) Interestingly, a potential role has also been described for lung diseases including bronchiectasis (table 2), COPD and lung cancer.(55-63) Different mechanisms of action have been proposed, ranging from the induction of a low grade inflammatory state to the occurrence of molecular mimicry mechanisms.(54, 64) There are no known common factors implicated in the susceptibility to both bronchiectasis and *H. pylori* infection, but it has been hypothesised that aspiration or inhalation of *H. pylori* or its endotoxins into the respiratory tract from upper respiratory territories or the gastric reservoir, particularly in bronchiectasis patients with symptomatic GORD, could be an underlying mechanism of the pathogenic role of *H. pylori* in bronchiectasis.(56) Given the lack of bronchial findings in the majority of studies, it is unlikely that *H. pylori* plays a direct role in the pathogenesis of bronchiectasis; however, we cannot exclude an indirect role of the products of *H. pylori* in the pathogenesis of bronchiectasis. Further work is also needed to corroborate previous findings that suggest *H. pylori* may be responsible for increased disease severity, manifest by reduced lung function and increased radiological severity.(56, 61)

Studies on the treatment of GORD in bronchiectasis

Two retrospective studies assessing potential treatment strategies for GORD have been performed in the bronchiectasis population (table 3). In a recent study of 257 bronchiectasis patients with GORD, a comparison of 27 patients treated with long-term PPIs compared to 230 without PPI treatment, was performed. No significant differences were observed between groups in terms of lung function 6 months after PPI therapy. However, there was a significant improvement in lung function in patients with high BMI in the PPI treatment group, thought to result from obesity causing increased oesophageal acid exposure time compared to the non-obese population.(65) However, there have been no randomised controlled trials of anti-reflux therapy in this patient population, and the effects of pharmacological management on other markers of disease severity, the co-occurrence of respiratory and GORD symptoms, and the use of respiratory medications remain to be clarified.

A retrospective review of the clinical outcomes of seven patients with GORD-related deteriorated bronchiectasis showed that active anti-reflux treatment with Stretta radiofrequency (SRF) and/or laparoscopic fundoplication was beneficial to patient symptoms and outcome.(66) Patients were followed up for a period of one to five years. Typical GORD symptoms, respiratory symptoms, medication consumption and general health status were assessed during follow-up. GORD symptoms disappeared in five people and were significantly improved in the remaining two.(66) Complete remission of both respiratory symptoms and bronchiectasis exacerbations was reported in two patients. Four had significantly improved respiratory symptoms to mild or moderate degrees as well as reduced or zero bronchiectasis exacerbations, enabling them to resume normal physical and social functions.(66) Surgical management, with a Nissen Fundoplication, has been successfully applied to bronchiectasis patients awaiting transplantation, with reductions in symptoms of GORD as well as of lung disease.(67, 68) Antireflux surgery is not widely used in bronchiectasis but should be considered when medical management fails, especially when GORD remains severe in individuals with bronchiectasis at risk of respiratory deterioration.

Discussion

GORD is a common comorbidity in bronchiectasis with a prevalence ranging from 26%-75%. Associations between the presence of GORD and increased bronchiectasis severity were observed in a number of large prospective cohort studies manifest by increased symptoms, exacerbations, hospitalisations, radiological extent, chronic infection, and mortality, with reduced pulmonary function and quality of life. However, this effect was not replicated in several case control studies,

most likely due to the small sample sizes and reduced power to detect such effects. All the above clinical studies of GORD in bronchiectasis are somewhat limited in that they lack a comprehensive multimodal assessment of GORD that can ascertain the mechanism of disease in this patient population which may increase the vulnerability to GORD in patients with bronchiectasis.

Two of the possible mechanisms by which GORD may impact on the severity of bronchiectasis are vagally mediated reflex bronchoconstriction and pulmonary microaspiration. Vagally mediated reflex bronchoconstriction originates from the shared autonomic innervation between the tracheobronchial tree and the oesophagus. The presence of oesophageal acid in the distal oesophagus activates a GORD-induced vagal reflex arc which stimulates airway irritation, and triggers the release of potent mediators associated with coughing and bronchoconstriction.(69) During microaspiration, refluxed gastric material extends proximally to the oesophagus and then enters the hypopharynx, directly triggering a laryngeal or tracheal response, which may manifest as coughing, wheezing, or a sensation of dyspnoea, and with the potential to enter the lungs and trigger a direct intra-pulmonary inflammatory response.(29) This process of inflammation involves a complex cascade of cellular, molecular and systemic events aimed at benefitting the clearance of noxious agents from the mucosal surface. In most pathophysiological cases, the inflammatory response appears to be in excess of the normal state, and is believed to play a role in disease progression.(29) This mechanism has been extensively studied in CF patients, whereby higher documented levels of BAL pepsin and bile acids were found compared with healthy controls, confirming active reflux and micro-aspiration, not suppressed by PPI therapy.(52, 70) Challenge of primary bronchial epithelial cells 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.(71) These findings suggest that duodeno-gastro-oesophageal reflux and subsequent micro-aspiration may contribute to the neutrophilic inflammation that is a hallmark of suppurative lung diseases.(72)

Other possible explanations for pulmonary aspiration secondary to GORD may be related to swallowing dysfunction in bronchiectasis. Precise coordination between swallowing and respiration is necessary, with the swallowing reflex an important defence against airway infection and aspiration.(16) Compared to healthy controls, the swallowing reflex may be impaired in patients with bronchiectasis, with a lack of coordination of the pharyngeal musculature and disruption of the breathing–swallowing coordination which, if altered, may increase the risk of aspiration in patients with bronchiectasis and contribute to exacerbations. Swallowing dysfunction may result from a range of pathologies, including neurological impairment, vocal cord injury, surgery, and radiation and is often overlooked as an aetiological cause of bronchiectasis.

It has long been postulated that the development of an abdomino-thoracic pressure gradient in patients with chronic respiratory disease may drive reflux and gastric aspiration.(29) Pulmonary hyperinflation contributes to flattening of the hemi-diaphragms and diaphragmatic dysfunction, which not only reduces the diaphragmatic crural support augmenting lower oesophageal pressures, but also changes the angle of the oesophagus, making it easier for reflux to occur. In primary lung disease, the intra-thoracic pressure is negative in relation to the abdominal cavity and varies during the respiratory cycle. As such, pre-existing LOS incompetence may be worsened by factors producing an increased trans-diaphragmatic pressure gradient, e.g. increased negative intra-thoracic pressure during inspiration and bouts of coughing, or with progressive bronchoconstriction of the airways.(49) Heightened anxiety is also known to aggravate GORD symptoms by increasing acid production.(73) As increased anxiety is common in bronchiectasis, this may be an additional contributory factor to GORD.(7, 74) Respiratory medications, including beta agonists, anticholinergics and corticosteroids, may alter oesophageal function by reducing LOS pressure or oesophageal motility.(18, 75) However, this association could also be a reflection of the severity of lung disease rather than the specific physiological effects of these medications on oesophageal function, therefore further exploration of

the cause and effect relationship between respiratory medications and GORD in bronchiectasis is needed.

Although oesophageal motility studies have not yet been extensively applied in bronchiectasis, one study using conventional manometry showed abnormal results in 71% of bronchiectasis patients, manifest by LOS hypotonia in 57% of patients and upper oesophageal sphincter hypotonia in 14%.(44) This would be expected to be relatively low in a healthy patient population. An increased prevalence of hiatal hernias has also been reported in patients with bronchiectasis.(49) A hiatal hernia occurs when part of the stomach protrudes into the thoracic cavity through the oesophageal hiatus of the diaphragm due to disruption of the anti-reflux barrier. If the anatomical flap valve disrupts, the LOS moves above the crural diaphragm, causing it to lose its synergistic configuration, hence both the LOS and diaphragm sphincters become appreciably weaker, compromising oesophageal acid clearance and facilitating the development of reflux.(11, 76) Pandolfino *et al* clearly demonstrated that a hiatal hernia was associated with an increased distensibility of the gastro-oesophageal junction, increasing the risk of liquid reflux and contributing to the increased acid exposure observed in patients with hiatal hernias.(77) The presence of a post-prandial acid pocket, a layer of unbuffered acidic gastric juice that sits on top of a meal, may be located more proximally or above the crural diaphragm in the presence of a large hiatal hernia, resulting in an increased number of acid reflux episodes during transient LOS relaxations.(78) Treatment with alginate-antacids and azithromycin have been shown to abolish or reduce the pocket, reducing acid oesophageal acid exposure. Azithromycin has been shown to reduce exacerbations in bronchiectasis and it is therefore tempting to speculate that perhaps some of its therapeutic benefit may relate to its ability to treat reflux.(79, 80)

A deficient mucus barrier function may play a role in facilitating lung injury associated with gastric aspiration.(29) Mucus hypersecretion is a common endpoint in many respiratory diseases, often arising as a result of increased release of mucin granules by epithelial goblet cells or IL-8 driven increased gland-based secretion.(29) In patients with impaired mucociliary clearance, the underlying tissues may become more susceptible to damage with an accumulation of pathogenic microbial organisms from elsewhere in the respiratory or gastro-intestinal tracts. Inflammatory responses may also be driven in part by the presence of specific receptors within the epithelium. Preliminary data suggests that some receptors may be triggered by the presence of gastric juice, pepsin and bile by receptor-mediated endocytosis.(81, 82) Uptake of pepsin in non-acid reflux was shown to cause mitochondrial damage by becoming reactivated inside the cell, changing the expression of several genes implicated in stress and toxicity. Irreversible inhibitors of peptic activity hold promise as a new therapy for reflux.(81)

The potential for horizontal transmission of microorganisms between the gut-lung axis may indicate that the upper gastrointestinal tract could act as a potential reservoir of microorganisms.(83) Chronic colonisation with *Pseudomonas aeruginosa (P. aeruginosa)* has been shown in several studies to be an independent predictor of mortality and lung function decline in bronchiectasis.(84-86) Horizontal transmission may be suggested by the demonstrated association between reflux and *P. aeruginosa* positivity in CF.(87, 88) After adjusting for age and FEV1, total reflux burden was found to be associated with *P. aeruginosa* positivity, suggesting that an increased reflux burden may predispose patients to *P. aeruginosa* infection and worse lung function.(87) More recently, similar bacterial profiles of CF sputum and gastric juice samples were demonstrated, which were distinct from non-CF gastric juice, perhaps providing novel evidence of an aerodigestive microbiome in CF.(88) However, it is difficult to establish whether cross-infection relates to swallowing of sputum leading to seeding of the gastrointestinal microbiome or if reflux and aspiration into the lungs may be causative. The microbiome in bronchiectasis is frequently dominated by enteric Gram-negative organisms suggesting that the lower airway is constantly being “replenished” by the upper airway, giving plausibility to there being a link in health and disease between the gut, the upper airway and the lung.(89)

Recent research investigating the impact of bile on the behaviour of *P. aeruginosa* and other CF-associated respiratory pathogens showed that bile increases biofilm formation and quorum sensing in *P. aeruginosa*, driving the switch from acute to persistent infection.(90) Bile also modulates biofilm formation in a range of other CF-associated respiratory pathogens, including *Burkholderia cepacia* and *Staphylococcus aureus*, suggesting, perhaps, that GORD-derived bile could be a host determinant contributing to chronic respiratory infection in chronic suppurative lung diseases.(90)

A mix of demographic factors may also increase the risk of GORD in bronchiectasis. Older age and female sex are well-described risk factors for GORD, and given the median age and female predominance of bronchiectasis patients, an increased co-existence of the two is perhaps not surprising.(7) A larger body mass index is also a risk for GORD, increasing as BMI increases.(91) A greater BMI has been demonstrated in bronchiectasis patients with GORD, and may impact on the contour of the diaphragm, increasing the elastic work of breathing.(49) When combined with respiratory-related risk factors, this may increase the contribution of a higher BMI to GORD in bronchiectasis. Comorbidities, such as ischaemic heart disease, have also been associated with a heightened risk of GORD and have been shown to occur frequently and contribute to mortality in patients with bronchiectasis.(7) Whether these are independent variables, common consequences of age, diet and obesity, or part of an integrated pathway of systemic inflammation, remains to be established.

Conclusion

In conclusion, GORD is a common comorbidity in patients with bronchiectasis and has a variety of clinical presentations. The index of clinical suspicion should remain high across the spectrum of disease severity in bronchiectasis, and objective measures should be used for diagnostic confirmation where possible due to high detection rates of asymptomatic or clinically silent reflux. The presence of GORD is associated with increased disease severity and mortality in patients with bronchiectasis. Identifying GORD in bronchiectasis patients may have important therapeutic and prognostic implications, although clinical trial evidence that treatment targeted at GORD can improve outcomes in bronchiectasis is currently lacking.

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Disclosure

The authors report no disclosures or conflicts of interest in this work.

Figures and tables:

Figure 1:

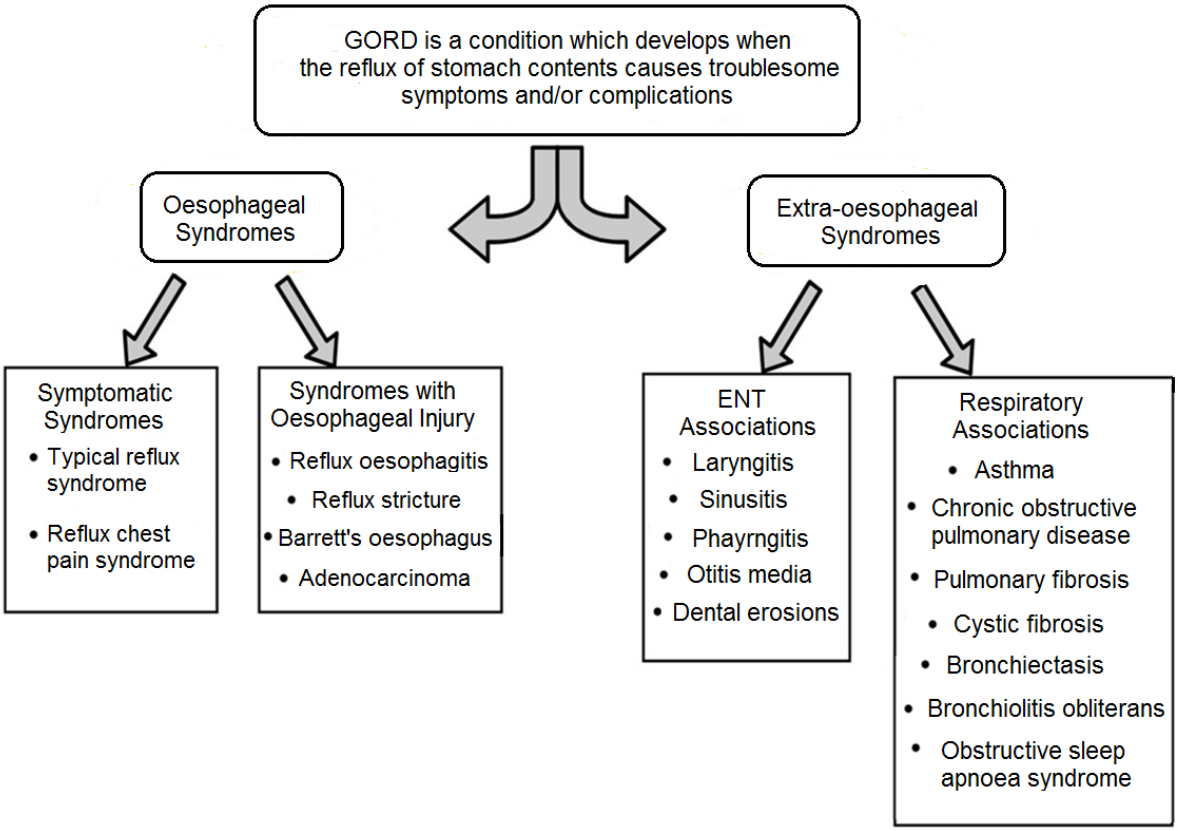

Figure 1 legend: Representation of the working definition of gastro-oesophageal reflux disease (GORD) encompassing oesophageal and extra-oesophageal end-organ effects and complications. Adapted from Vakil *et al. Am J Gastro* 2006; 101: 1900-1920.

Figure 2:

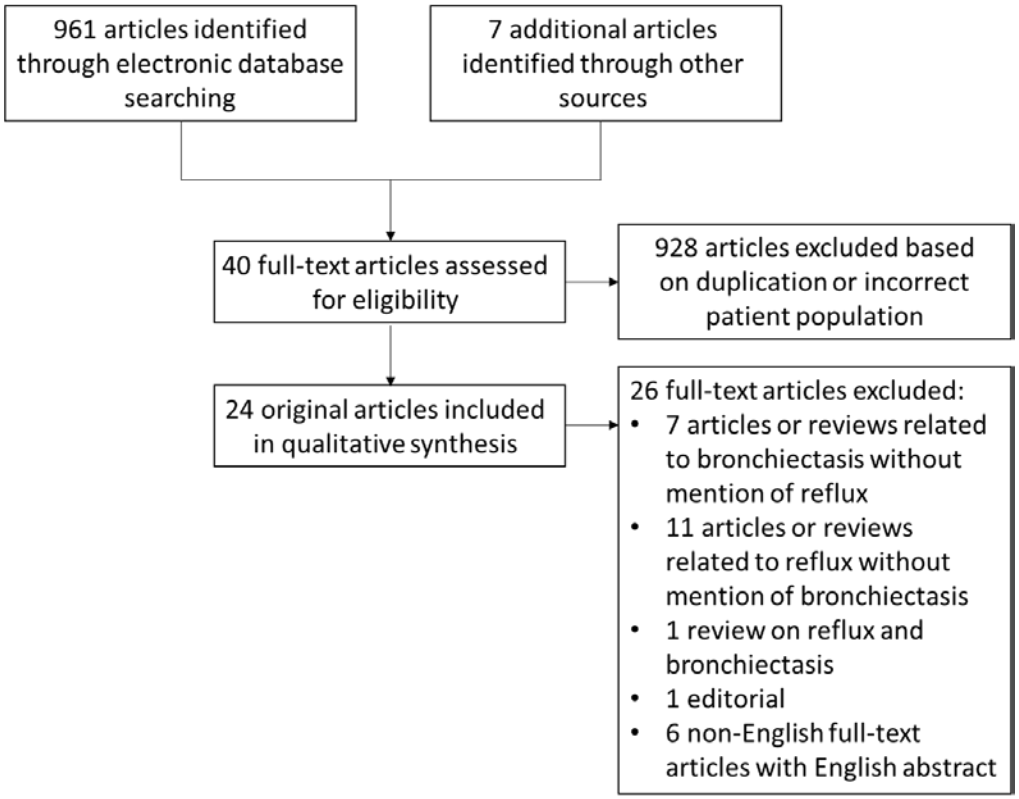

Figure 2 legend: Synthesis of literature search

Table 1: Summary of clinical studies of prevalence of gastro-oesophageal reflux disease and associations with disease severity in bronchiectasis

Original paper	Patient group	Investigations	Population and design	Outcome
Ahmed 1995(39)	Stable bronchiectasis	Single probe 24-hour oesophageal pH monitoring Tracheal monitoring	19 Adults Cohort Prospective	Prevalence of reflux = 42% using DeMeester score on pH monitoring Positive correlation with symptoms of nocturnal reflux and distal reflux on pH-monitoring No micro-aspiration of tracheal contents demonstrated on tracheal monitoring
Chen 1998(40)	Stable bronchiectasis during physiotherapy	Single probe 24-hour oesophageal pH-monitoring	32 Adults (bronchiectasis n=23, chronic bronchitis, n=9) Cohort Prospective	Prevalence of reflux = 41% using DeMeester score on pH monitoring Chest physiotherapy including postural drainage, percussion and forced expiration techniques in different positions did not induce or increase the incidence of reflux events in bronchiectasis or chronic bronchitis patients with or without confirmed GORD.
Sweet 2006(41)	End-stage bronchiectasis	Symptomatic evaluation (non-validated standard questionnaire) Manometry Dual-probe 24-hour oesophageal pH monitoring	4 Adults Cohort Prospective	Prevalence of distal reflux = 75% using DeMeester score on pH monitoring Prevalence of proximal reflux = 50% on pH monitoring Poor concordance noted between symptoms and pH diagnosis of GORD Increased oesophageal length noted in bronchiectasis patients
Koh 2007(42)	Non-tuberculous mycobacteria (NTM) bronchiectasis	Symptomatic evaluation (no questionnaire) Single probe 24-hour oesophageal pH monitoring	56 Adults Cohort Prospective	Prevalence of reflux = 26% using DeMeester score on pH monitoring Prevalence of clinically silent reflux = 73% (no reflux on symptom assessment in 27%) Presence of GORD associated with: • Increased positivity for AFB on sputum smear • Increased radiological lobar extent of bronchiectasis and bronchiolitis
Banjar 2007(43)	Stable bronchiectasis	Barium swallow, milk scan or combination of both where clinically indicated	151 Children Cohort Prospective	Prevalence of GORD = 32% using: • Barium swallow alone 67% • Milk scan alone 21% • Combination of both radiological procedures 12% 45% of those diagnosed with GORD required Nissen fundoplication
Fortunato 2008(44)	End-stage bronchiectasis	Dual probe 24-hour oesophageal pH-monitoring preceded by conventional oesophageal manometry	7 Adults Cohort Prospective	Prevalence of reflux = 50% using DeMeester score on pH monitoring Bronchiectasis patients had highest prevalence of GORD and highest mean DeMeester scores compared to all other lung diseases Abnormal manometry noted in 71% with LOS hypotonia in 57% and UOS hypotonia in 14%
Zaid 2010(45)	Stable bronchiectasis	Barium swallow and/or single probe 24-hour oesophageal pH monitoring	92 Children Cohort Retrospective	Prevalence of GORD = 11%

		where clinically indicated		
Lee 2012(46)	Stable bronchiectasis during physiotherapy	Dual-probe 24-hour oesophageal pH-monitoring	30 Adults Cohort Prospective	Prevalence of reflux = 40% using DeMeester score on pH monitoring 57% of all bronchiectasis patients experienced GORD during at least one physiotherapy task but irrespective of GORD diagnosis, there were fewer distal reflux episodes compared to background reflux time during all physiotherapy interventions of PEP, 6MWT and upper limb movements. No significant difference in reflux with any form of physiotherapy.
Mandal 2013(47)	Stable bronchiectasis	Hull Airway Reflux Questionnaire (HARQ)	163 Adults Cohort Prospective	Prevalence of reflux = 74% Presence of GORD associated with: • Increased cough severity contributing to reduced HrQoL • Increased sputum inflammatory markers • Reduced FEV1% predicted • Increased radiological severity • Increased chronic colonisation and polymicrobial culture growth • Increased exacerbations
Lee 2014(30)	Mild (n=15) and moderate (n=12) Bronchiectasis	Carlsson-Dent reflux symptom questionnaire Dual probe 24-hour oesophageal pH monitoring	27 Adults Cohort Prospective	Prevalence of reflux = 40% using questionnaires Of those, clinically silent reflux = 42% using dual-probe pH monitoring No association with sputum pepsin or disease severity markers
McDonnell 2015(49)	Stable bronchiectasis	Evaluation on high resolution computed tomography (HRCT) by independent expert radiologist	81 Adults Cohort Prospective	Prevalence of symptomatic reflux on PPI = 41% Prevalence of confirmed hiatal hernia = 36% Presence of a hiatal hernia associated with: • Increased prevalence of GORD • Increased no. of lobes affected • Cystic bronchiectasis • Decreased parenchymal attenuation • Reduced FEV1% • Increased disease severity (BSI and FACED)
McDonnell 2015(48)	Stable bronchiectasis	Symptomatic evaluation and medication review	212 Adults Cohort Retrospective	Prevalence of reflux = 34% Presence of GORD associated with: • Increased symptoms (cough, sputum production and wheeze) • Increased exacerbations and hospitalisations • Increased lobar extent and cystic bronchiectasis • Reduced FEV1% • Increased P. aeruginosa colonisation and polymicrobial culture growth

				• Increased disease severity (BSI) OR 2.2 (95% CI 1.1-6.7) • Increased mortality OR 2.5 (95% CI 1.1-7.8)
Lee 2015(31)	Stable bronchiectasis (n=10), COPD (n=10), healthy controls (n=10)	Dual probe 24-hour oesophageal pH-monitoring Exhaled breath condensate pepsin	30 Adults Case control Prospective	Prevalence of reflux = 40% using definition of positive distal AND proximal reflux on oesophageal pH monitoring Prevalence of reflux = 70% using sputum pepsin and 60% using exhaled breath condensate (EBC) pepsin Presence of EBC pepsin associated with: • Moderate correlation of sputum pepsin and EBC pepsin • No correlation of EBC pepsin with total DeMeester score, distal reflux index or proximal reflux index on oesophageal pH monitoring • No association with lung function
McDonnell 2016(7)	Stable bronchiectasis	Symptomatic evaluation and medication review	986 Adults Cohort Prospective	Prevalence of reflux = 34% Presence of GORD associated with: • Increased mortality (GORD non-survivors 48%, GORD survivors 32%; p=0.001)
Aksamit 2017(50)	Stable bronchiectasis (US registry data)	Symptomatic evaluation	1789 Adults Cohort Prospective	Prevalence of reflux = 47% Presence of GORD associated with: • NTM disease in bronchiectasis (GORD NTM 51%, GORD non-NTM 40%; p<0.01)

Table 2: Summary of clinical studies assessing the role of *Helicobacter pylori* in bronchiectasis

Original paper	Patient group	Investigations	No. of patients	Outcome
Tsang 1998(55)	Stable bronchiectasis (n=100), healthy controls (n=94)	*H. pylori* serology	194 Adults Case control Prospective	High seroprevalence of *H. pylori* among bronchiectasis patients vs. controls = 76% vs. 54%; p=0.001 Positive correlation with increased sputum volume and age No association with lung function or causes of bronchiectasis
Tsang, 1999(56)	Stable bronchiectasis (n=100), healthy controls (n=94)	Symptomatic evaluation (A patient questionnaire to identify bowel disease) Anti- *H. Pylori* Cag A serology	194 Adults Case control Prospective	Symptomatic prevalence of reflux = 32% Positive anti- *H. Pylori* Cag A serology in of bronchiectasis patients vs. controls = 24% vs. 12%; p=0.03 No association with anti- *H. Pylori* Cag A and lung function, sputum volume, respiratory symptoms or upper gastrointestinal symptoms Positive correlation of patients reporting acid reflux or upper abdominal distension with reduced FEV1% and FVC%
Yalcin 2002(57)	Idiopathic bronchiectasis	Bronchoalveolar lavage (BAL) fluid PCR	30 Children Cohort Prospective	PCR for *H. Pylori* negative in all BAL samples
Ilvan 2004(58)	Male patients with bronchiectasis (n=31), healthy male controls (n=56)	*H. pylori* serology Bronchial brush and biopsy for urease activity, culture and histopathological examination	87 Adults Case control Prospective	Seroprevalence of *H. pylori* noted in 58% bronchiectasis patients vs. 68% healthy controls. *H. pylori* was not isolated from protected brush or mucosal biopsy samples in any patient and urease test was negative in all patients. No associations were observed between *H. pylori* seropositivity and sputum volume, lung function or radiological extent.
Angrill 2006(59)	Stable bronchiectasis (n=46), controls undergoing bronchoscopic exploration in search of a primary malignancy (n=8)	*H. pylori* serology Immunostaining of bronchial biopsy for anti- *H. pylori* antibody	54 Adults Case control Prospective	Seroprevalence of *H. pylori* among bronchiectasis patients = 46% No evidence of *H. pylori* was obtained in the bronchial samples of bronchiectasis patients or controls.
Gulhan 2007(60)	Stable bronchiectasis (n=26), controls without pulmonary disease, (n=20)	*H. pylori* serology Bronchoalveolar lavage (BAL) fluid PCR and ELISA PCR in surgically removed tissues	46 Adults Case control Prospective	Seroprevalence of *H. pylori* noted in 92% bronchiectasis patients vs. 80% controls. PCR for *H. pylori* negative in all BAL samples from patients and controls and in surgically resected tissue in bronchiectasis patients
Aydin Teke 2016(61)	Stable bronchiectasis (n=41), healthy controls (n=16)	Bronchoalveolar lavage (BAL) fluid PCR and culture Gastric juice PCR and culture Urea breath test	57 Children Case control Prospective	PCR for *H. pylori* in BAL positive in 22% bronchiectasis patients vs. 19% controls (p>0.05) PCR for *H. pylori* in gastric juice positive in 39% bronchiectasis patients vs. 44% controls (p>0.05) Urea breath test positive in 27% bronchiectasis patients vs. 19% controls (p>0.05)

				No associations was observed between BAL *H. pylori* positivity and lung function. Positive association between BAL *H. pylori* positivity and increased CT score was observed ($p<0.05$)

Table 3: Summary of clinical studies assessing treatment options for GORD in patients with bronchiectasis

Original paper	**Patient group**	**Treatment intervention**	**No. of patients**	**Outcome**
Hu 2014(66)	Deteriorating bronchiectasis in presence of GORD	Stretta radiofrequency (SRF) and/or laparoscopic fundoplication	7 Adults Cohort Retrospective	Laparoscopic fundoplication (n=2) Laparoscopic fundoplication with repair of hiatal hernia (n=2) Stretta radiofrequency (n=2) Combined laparoscopic fundoplication and Stretta radiofrequency (n=1) Significant reduction in reflux and respiratory symptoms and exacerbations/hospitalisations noted on follow-up with negation of therapy for GORD in n=4 patients.
Ahn 2016(65)	Bronchiectasis and GORD with (n=27) or without (n=250) long-term PPI therapy	PPI therapy	257 Adults Cohort Retrospective	No significant differences were observed between groups in terms of lung function 6 months after PPI therapy. A significant improvement in lung function was noted in patients with high BMI in the PPI treatment group that was significantly related to the severity of obesity.

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