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Review article

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

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ABSTRACT

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% to 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.

1. 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.

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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.

1.1. 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.

1.2. 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 Fig. 1. Either may be present in patients with bronchiectasis.

1.3. 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-gastroduodenoscopy 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-h 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 h, 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].

1.4. 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].