CHEST

Original Research

RESPIRATORY INFECTIONS

Gastroesophageal Reflux Disease, Acid Suppression, and *Mycobacterium avium* Complex Pulmonary Disease*

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Background: **Weekly symptoms of gastroesophageal reflux disease (GERD) occur in 20% of the population, and GERD has been implicated in the pathophysiology of many respiratory diseases. Microaspiration of contaminated water is a potential portal of entry for *Mycobacterium avium* complex (MAC) organisms into the respiratory tract, and acid-suppression therapy may enhance the survival of mycobacteria in the stomach. This study aimed to assess the prevalence of GERD, swallowing disorders, reflux symptoms, and acid-suppression therapy in patients with MAC lung disease (MAC positive [MAC+]), and to compare these patients to control subjects without MAC lung disease (MAC negative [MAC−]).**

Methods: **Clinical information was collected on 58 MAC+ patients and 58 age- and sex-matched MAC− patients who were asked to complete a DeMeester questionnaire of reflux symptoms and to identify any acid-suppressive medication consumed.**

Results: **A clinical diagnosis of GERD was documented in 23 of 52 MAC+ patients (44.2%), compared to 16 MAC− patients (27.6%) [p = 0.019]. MAC+ patients consumed significantly more histamine type 2 receptor antagonists and prokinetic agents, and MAC− patients consumed more antacids. The mean DeMeester questionnaire score (± SD) for MAC+ patients was 1.39 ± 1.8, and for MAC− patients was 0.88 ± 1.4. (p = 0.098). Aspiration was suspected in nine MAC+ patients (15.5%), compared to three MAC− patients (5.2%) [p = 0.032]. There was no association between GERD and radiologic presentation of MAC disease. Consolidation and nodules > 5 mm were more common in those receiving acid suppression than those who were not.**

Conclusions: **GERD, acid suppression, and clinically suspected aspiration are more common in patients with MAC lung disease than in similar patients without MAC disease.**

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Key words: bronchiectasis; esophagus; gastroesophageal reflux; infection; mycobacterial

Abbreviations: GERD = gastroesophageal reflux disease; H2RA = histamine type 2 receptor antagonist; MAC = *Mycobacterium avium* complex; MAC+ = *Mycobacterium avium* complex positive; MAC− = *Mycobacterium avium* complex negative

In HIV-seronegative individuals, factors affecting susceptibility to infection with *Mycobacterium avium* and *Mycobacterium intracellulare* and progression to disease are poorly understood. Patients are typically either middle-aged men with underlying chronic lung disease such as COPD, who have upper-lobe cavity formation and nodules of various sizes, or elderly patients with nodules, bronchiolitis, and bronchiectasis involving the middle lobe and lingula. These latter patients are more commonly women, nonsmokers, with no preexistent lung disease.[1–5]

M avium complex (MAC) organisms are environmental, commonly found in natural waters, drinking water, and soils. They can be isolated from biofilms, aerosols, and dust.[6] The state of Queensland lies in northeast Australia. *M avium* is capable of growth between 10°C and 45°C, typical temperatures for this area. Not surprisingly, therefore, exposure to MAC organisms in Queensland is common, as shown by results of avian Mantoux testing in children.[7,8] The optimal pH for growth of most environmental mycobacteria is at acidic values, with little growth

occurring at values of pH > 7.5. The optimal growth pH for *M intracellulare* is between 5 and 6.5.[6]

Symptoms of gastroesophageal reflux disease (GERD) are reported to occur weekly in approximately 20% of the population.[9–11] Both acid reflux and nonacid reflux have been implicated in the pathophysiology of chronic cough, asthma, idiopathic pulmonary fibrosis, and laryngeal dysfunction.[12,13] Aspiration of upper respiratory tract bacteria into the lungs is thought to occur quite frequently (in approximately 50% of normal hosts during sleep)[14] and is generally of little consequence in the majority on individuals. Microaspiration of organisms probably occurs more frequently in the setting of altered sensorium, such as with alcohol or sedative drug use, and has been postulated as a cause of lower respiratory tract infections and chronic lung disease,[14,15] particularly if there is a large inoculum of bacteria, solid material, or acid. Deposition of relatively few mycobacteria can infect the host; estimates range from 2 to 3 bacteria, to as many as 50.[16] Esophageal disorders, particularly achalasia, have been described in association with pulmonary disease due to rapidly growing mycobacteria.[17–19] A similar association for slow-growing mycobacteria has not been established. We postulated that if acid-suppression therapy enhances the survival of mycobacterial organisms in the stomach, then aspiration of gastric/oropharyngeal contents may be a potential portal of entry of these organisms into the respiratory tract.

The aim of this study was to assess the prevalence of a medical diagnosis of GERD, reflux symptoms, and acid-suppression therapy in patients with MAC lung disease (MAC positive [MAC+]), and to compare these patients with control subjects without MAC lung disease (MAC negative [MAC−]). We also aimed to assess the prevalence of reported swallowing disorders in these patients, who were at risk of aspiration.

Materials and Methods

A prospective cohort of 58 patients (cases) with MAC lung disease was identified by laboratory notification of isolates of MAC in Queensland, Australia between January 1 and December 31, 1999. The protocol (138/98) was approved by the Princess Alexandra Hospital Research Ethics Committee in accordance with the Australian National Health and Medical Research Council guidelines. Consent to participate was sought, and clinical features of the disease (including risk factors, symptoms, radiology, and treatment prescribed) were then provided by the treating doctor. Each patient was asked to complete a DeMeester questionnaire of reflux symptoms (Fig 1). A maximum score of 3 points was assigned for each of heartburn, regurgitation, and dysphagia. Patients were also asked to identify from a comprehensive list any acid-suppressing medication they consumed regularly. A clinical diagnosis of GERD by the treating physician was recorded; when possible, supportive gastroscopy or pH probe findings were obtained.

Control patients (MAC−) were recruited from the Respiratory Outpatients Clinics. Each MAC+ case was matched to a MAC− control according to age (10-year groupings), gender, and smoking history (current smoker, ex-smoker, or nonsmoker). As other lung diseases can be associated with GERD, to minimize confounding, MAC− control subjects were matched according to the preexisting lung disease of the MAC+ cases (*eg*, COPD, preexisting bronchiectasis). If patients with mycobacterial disease had no preexistent lung disease, then they were matched with control subjects also without lung disease, or in some patients with mild COPD or asthma, but with similar respiratory symptoms such as chronic cough. When the underlying lung disease was COPD or bronchiectasis, the control subjects were required to have a minimum of three negative sputa for mycobacteria within the preceding 12 months and no history of mycobacterial disease. Each MAC− control subject was also asked to complete a DeMeester symptom questionnaire and to record any GERD medication consumed. Gastroscopy, pH probe, and radiographic contrast swallow findings were also recorded. Due to the difficulty in finding matched control subjects, they were not matched for factors such as steroid use, alcohol consumption, or diabetes; however, these were recorded and included in the statistical analysis. While obesity can be associated with an increased risk of GERD, the cases and controls were not matched according to body mass index. As most patients with MAC lung disease are thin, this would likely bias toward the null, rather than confound the findings.

MAC+ patients were classified as having cavitary disease (any cavities present, including those associated with bronchiectasis) or noncavitary disease (predominantly nodular bronchiectasis). The radiographic distribution of disease was divided into upper lobe, middle lobe (right middle lobe and lingula), and lower lobe according to the predominant diseased areas. Patients receiving medication for GERD were grouped into antacids, histamine type 2 receptor antagonists (H2RAs), proton-pump inhibitors, and prokinetic agents.

Data were analyzed using statistical software (SPSS v12.0 for Windows 2003; SPSS; Chicago, IL). Tests of association were performed using Fisher exact test for χ^2 two-by-two tables. DeMeester scores were compared using the Mann Whitney *U* test. DeMeester scores were also compared using a univariate analysis of variance that included both matched factors and

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