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The Role of Viral Infection in Pulmonary Exacerbations of Bronchiectasis in Adults

A Prospective Study

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BACKGROUND: Although viral infections are a major cause of exacerbations in patients with chronic airway diseases, their roles in triggering bronchiectasis exacerbations in adults remain unclear. Therefore, we prospectively investigated the incidence and clinical impacts of viral infection in adults with bronchiectasis exacerbations.

METHODS: The study cohort of 119 adults with bronchiectasis was followed up prospectively for 12 months. Nasopharyngeal swabs and sputum samples were assayed for 16 respiratory viruses, using polymerase chain reaction assays. Symptoms, spirometry, quality of life, bacterial cultures, and inflammatory markers were assessed during steady-state bronchiectasis and exacerbations.

RESULTS: A total of 100 exacerbations were captured from 58 patients during 1-year follow-up. Respiratory viruses were found more frequently in nasopharyngeal swabs and sputum during bronchiectasis exacerbations (49 of 100, 49.0%) than during steady state (11 of 58, 18.9%; $P < .001$). The most common viruses found in patients experiencing exacerbations were coronavirus (19 of 65, 39.2%), rhinovirus (16 of 65, 24.6%), and influenza A/B viruses (16 of 65, 24.6%). Virus-positive exacerbations were associated with a greater increase in markers of systemic and airway inflammation (serum IL-6 and tumor necrosis factor-α; sputum IL-1β and tumor necrosis factor-α) compared with virus-negative exacerbations, but the differences in spirometric indexes, quality of life, and bacterial density were unremarkable. In receiver operating characteristics analysis, serum interferon-γ-induced protein 10 yielded an area under curve of 0.67 (95% CI, 0.53-0.77; $P = .018$). Furthermore, a greater proportion of patients with virus-positive exacerbations received IV antibiotics.

CONCLUSIONS: Prevalence of viral infections, detected by polymerase chain reaction assay, is higher in cases of bronchiectasis exacerbations than in steady-state bronchiectasis, suggesting that respiratory viruses play crucial roles in triggering bronchiectasis exacerbations. The potential mechanisms of virus-induced bronchiectasis exacerbations merit further investigations.

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ABBREVIATIONS: BE = bronchiectasis exacerbation; BSI = Bronchiectasis Severity Index; CAT = COPD Assessment Test; CFU = colony-forming unit; CRP = C-reactive protein; HCoV = human coronavirus; HRCT = high-resolution CT; IP-10 = interferon-γ-induced protein 10; IQR = interquartile range; LCQ = Leicester Cough Questionnaire; NPS = nasopharyngeal swab; PCR = polymerase chain reaction; QoL = quality of life; SGRQ = St. George's Respiratory Questionnaire; TNF = tumor necrosis factor

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Patients with bronchiectasis frequently develop acute infective exacerbations characterized by increased cough frequency and sputum volume and purulence that readily lead to hospital admissions with high treatment costs.[1,2] More importantly, frequent exacerbations impose adverse effects on quality of life (QoL)[3] and might accelerate loss of lung function and increase mortality.[4,5] To date, however, triggers of bronchiectasis exacerbations (BEs) have been poorly elucidated. Because antibiotic treatment of BEs has been shown to mitigate clinical symptoms, restore lung function, and concurrently suppress systemic and airway inflammatory responses,[6,7] BEs have been postulated to result from airways bacterial infections of novel strains, increased bacterial density, or both.[8] However, Tunney et al[9] showed that total bacterial density and microbiota taxa, analyzed by culture and 16s ribosomal DNA pyrosequencing, did not change remarkably during antibiotic treatment of BEs, suggesting that changes in lung microbiota composition might not account significantly for BEs. This has led us to examine the roles of other potential pathogens, especially viruses, in adults with bronchiectasis.

It has been well established that respiratory viral infections are a major trigger of acute exacerbations of COPD,[10,11] asthma[12,13] and cystic fibrosis.[14,15] A recent study in children with bronchiectasis found that respiratory viruses were detected in 48% of 77 pediatric pulmonologist-defined BEs and were associated with worse clinical outcomes.[16] However, significance of viral infection in adults with BEs remains unknown. In addition, clinical characteristics and investigations regarding virus-associated BEs in adults are also lacking, and the interactions between respiratory viruses, bacteria, and host immune response, which might directly relate to pathogenesis of bronchiectasis, as shown in COPD,[17] deserve special attention from researchers and clinicians. Meanwhile, biomarkers such as serum interferon-γ-induced protein 10 (IP-10) have been proposed as surrogate markers for predicting virus-associated exacerbations of COPD,[18] but the utility in bronchiectasis has never been assessed. In this prospective study, we sought to (1) document the incidence of 16 common respiratory viruses in adults with bronchiectasis during steady-state bronchiectasis and BEs, (2) investigate the clinical differences between virus-positive and virus-negative BEs, and (3) assess the utility of serum IP-10 for predicting virus-related BEs.

Materials and Methods

Patients and Study Procedure

Patients with bronchiectasis, diagnosed by compatible history combined with bronchial dilatation on high-resolution CT (HRCT) scan, were recruited from outpatient clinics of The First Affiliated Hospital of Guangzhou Medical University and a previous cohort assessing the effects of anxiety and depression on BEs[19] between February and March 2013. Patients were aged ≥ 18 years and remained clinically stable, defined as no BEs or antibiotic treatment of respiratory infection within 4 weeks. The study was approved by Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (approval No. Medical Ethics 2012 [the 29th file]). Written informed consent was obtained from all participants.

Within the span of 12 months, patients were assessed at baseline, when clinically stable, and at BEs. During follow-up, patients were required to attend chest clinics routinely every 3 months. Between the neighboring scheduled visits, patients experiencing symptoms of exacerbations were requested to contact investigators immediately, with an additional visit being scheduled within 48 h. BEs were defined as persistent (> 24 h) deterioration in at least three respiratory symptoms, including cough, dyspnea, hemoptysis, increased sputum purulence or volume, chest pain, febrile, radiographic deterioration, systemic disturbances, or changes in chest auscultation.[20] Spontaneous or induced sputum was collected at each visit for bacterial culture, viral assays, and measurement of airway inflammation. Paired serum samples were collected for assessment of systemic inflammation. All parameters were measured when clinically stable and at times of BE.

Clinical Assessments

A comprehensive history including age, sex, BMI, influenza vaccination in the preceding year, the number of infective exacerbations and hospitalizations in the previous 24 months, and current treatment were recorded at baseline. Chest HRCT scan within 12 months was used for radiologic scoring based on the number of bronchiectatic lobes (with the lingula being scored as a separate lobe) and severity of bronchial dilatation (tubular: 1 point, varicose: 2 points, cystic: 3 points), with the maximal score of 18.[21] Etiology of bronchiectasis was determined after meticulous testing recommended by British Thoracic Society guidelines[2] and group discussion (Yong-hua Gao, W. G., and G. X.). Upper and lower airway symptoms were recorded when clinically stable and at BEs. Bronchiectasis severity at baseline was quantified according to Bronchiectasis Severity Index (BSI).[4] QoL was assessed using St. George's Respiratory Questionnaire (SGRQ), Leicester Cough Questionnaire (LCQ), and COPD Assessment Test (CAT)

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