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Original Article
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Respiratory Viruses in Acute Exacerbations of Bronchiectasis

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ABSTRACT

Background: Bacterial infections are well known factors underlying acute exacerbations in bronchiectasis. However, viral infections may also contribute to acute exacerbations. We aimed to assess the rate of viral detection in acute exacerbations of bronchiectasis, and the associated clinical factors.
Methods: Diagnostic tests for viral and bacterial etiologies were performed in 792 patients with bronchiectasis who visited the emergency room or the respiratory care inpatient unit in a tertiary referral center in South Korea. All patients were diagnosed with bronchiectasis by chest computerized tomography and were prescribed antibiotics for a minimum of 3 days.
Results: Viral pathogens were detected in 202 of the 792 enrolled patients (25.5%). The most common viral pathogen isolated was influenza A virus (24.8%), followed by rhinovirus (22.4%), influenza B virus (9.8%), respiratory syncytial virus B (8.9%), and human metapneumovirus (6.1%). In 145 patients, a viral, but not bacterial, pathogen was detected, whereas no pathogens were found in 443 patients with exacerbations. Multivariable analysis revealed that female sex and chronic heart disease as a comorbidity were positively associated with viral detection in acute exacerbations of patients with bronchiectasis, whereas the presence of radiographic infiltration was negatively associated.
Conclusion: Respiratory viruses were identified in approximately 25% of the acute exacerbations observed among patients with bronchiectasis. Of the viruses detected, influenza viruses and rhinovirus made up over 50%. More attention to viruses as possible causative pathogens for acute deteriorating symptoms in patients with bronchiectasis is warranted.

Keywords: Bronchiectasis; Acute Exacerbation; Respiratory Viruses

INTRODUCTION

Bronchiectasis is a chronic respiratory disease characterized by the permanent dilatation of bronchi and impairment of mucociliary clearance of bronchial secretions, which consequently lead to the clinical syndrome of cough, increased sputum production, and recurrent respiratory infection.[1] Approximately half of the patients with bronchiectasis experience exacerbations twice or more every year, which are characterized by the acute deterioration of respiratory and/or systemic symptoms that necessitate changes in treatment modalities and even lead to hospital admission.[2,3] Preventing the exacerbation is a key

target in the management of bronchiectasis because it is associated with increased airway inflammation, progressive lung damage, poor quality of life, and even mortality.[4,5]

Although the causes of bronchiectasis exacerbations are not known, bacterial infection is well known as one of the most important risk factors for frequent exacerbations and hospitalizations. However, there are still many patients who experience exacerbations without evidence of bacterial infection. Hence, recent studies have examined other etiologies for exacerbations, such as viruses and air pollution.[6-8] Gao et al.[8] first reported a higher prevalence of viral infections during exacerbations, as compared with during the steady state, in patients with bronchiectasis. Also, a recent pilot study investigating the incidence rate of respiratory viruses in patients with bronchiectasis revealed that only 28% of patients with exacerbations had viral polymerase chain reaction (PCR) performed on admission, with 39% (9/23) of those tests being positive for a respiratory virus, whereas a bacterial and fungal culture was performed in 88% of admissions, with 30% positive results.[7]

Due to the relatively low level of concern and awareness of viral etiologies in acute exacerbations of bronchiectasis, no studies have investigated the incidence rate and distribution of viral pathogens in a large number of patients. Therefore, we aimed to assess the rate of viral detection in acute exacerbations of bronchiectasis, and the clinical factors associated with viral detection.

METHODS

Study design and approval

We performed a retrospective, single-center study to assess viral infections in acute exacerbations of bronchiectasis.

Study subjects

The patients were diagnosed with bronchiectasis by chest computerized tomography, but did not have a past medical history of interstitial lung disease. In Asan Medical Center, which is a 2,700-bed referral hospital in Seoul, South Korea, we selected 2,867 medical visits that included records of antibiotic prescription for more than 3 days following admission to a respiratory care inpatient unit or emergency room between 2015 and 2019. After excluding cases: 1) that did not include diagnostic tests for bacterial and viral pathogens, 2) in which antibiotics were prescribed for reasons other than acute exacerbation of bronchiectasis, and 3) where admission was not during the first medical visit for deteriorating symptoms, 792 patients were included for analysis (**Fig. 1**).

Definition of exacerbation

In the present study, acute exacerbation of bronchiectasis was defined as deterioration of two or more of the following symptoms,[2] including at least one respiratory symptom, for at least 48 hours: 1) cough, 2) sputum volume and/or consistency, 3) sputum purulence, 4) breathlessness and/or exercise tolerance, 5) fatigue and/or malaise, 6) hemoptysis, and 7) fever, regardless of the presence of pneumonia.

Microbiological examination

A diagnostic test for viral identification, multiplex reverse-transcription PCR, was performed on all study subjects using a nasopharyngeal swab specimen or bronchoalveolar lavage

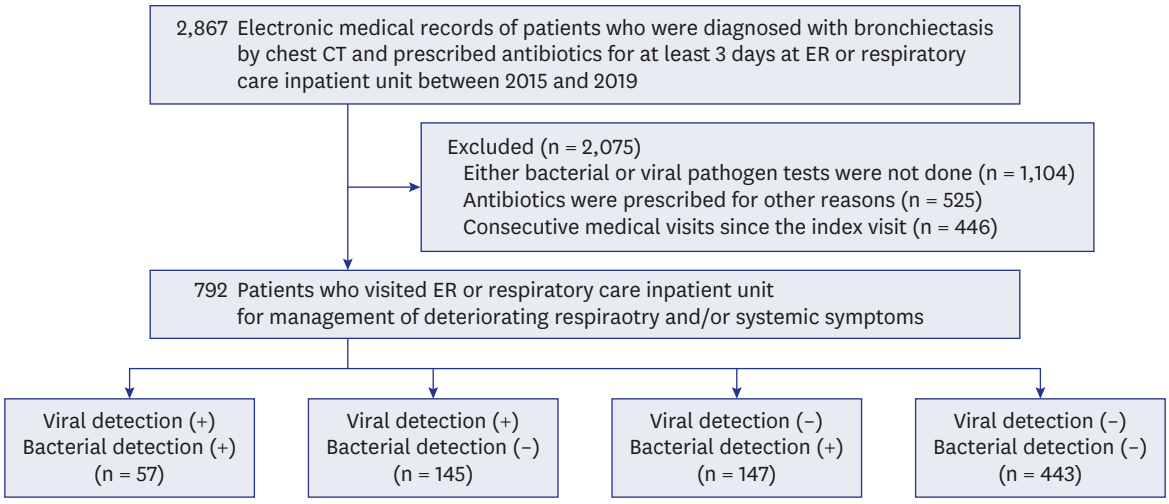

Fig. 1. Flow of patient selection. Index visit refers to the first medical visit for exacerbation during the study period.
CT = computerized tomography, ER = emergency room.

(BAL) fluid to detect influenza viruses, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, parainfluenza virus types 1 to 4, enterovirus, rhinovirus, human coronavirus OC43/HKU1, human coronavirus 229E, human coronavirus NL63, and bocavirus using Anyplex RV16 (Seegene Inc., Seoul, Korea) between January 2015 and November 2018 and Allplex RP (Seegene Inc.) between December 2018 and December 2019. In cases where BAL was conducted, we additionally included shell viral culture for influenza virus, parainfluenza virus, RSV, cytomegalovirus, and adenovirus (Diagnostic Hybrids, Inc., Athens, OH, USA).

Diagnostic tests for bacterial pathogens were performed by gram staining and culture of either expectorated sputum or lower respiratory tract specimens in all study subjects. In applicable cases, the results of diagnostic tests, including a Binax NOW™ urinary antigen test for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 (Binax Inc., Portland, ME, USA) and PCR for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae,* and *L. pneumophila* using Seeplex PneumoBacter assay (Seegene Inc.) between January 2015 and August 2015 and AmpliSens® for *M. pneumoniae, Chlamydophila pneumoniae,* and *L. pneumophila*-FRT (InterLabService Inc., Moscow, Russia) between September 2015 and December 2019, were also included in the analysis. In cases where BAL was conducted, gram staining and culture of BAL fluid were incorporated. Sputum adequacy was determined based on the Murray and Washington's grading system, and sputum specimens of grades 4 to 6 were considered acceptable in the present study.[9]

Laboratory and pulmonary function tests

Data on laboratory findings were collected and reviewed, including white blood cell count, eosinophil count and C-reactive protein, as well as pulmonary function tests, including forced expiratory volume in 1 second. These data were obtained when the patients were in a non- exacerbated state between 2 years and at least 1 week before the beginning of the exacerbation.

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Statistical analyses

All data are presented as means (± standard deviations) or medians (interquartile ranges) for continuous variables, and numbers (%) for categorical variables. Data were compared using Student *t*-tests or Mann-Whitney U tests for continuous variables, and χ^2 or Fisher's exact tests for categorical variables. All tests were two-sided, and *P* values less than 0.05 were considered statistically significant. Multivariate regression analyses were used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Variables employed in the multivariate regression analyses were selected on the basis of a statistical significance level of less than 0.1 in the univariate analysis, together with the treatment duration. All data were analyzed using SPSS software (version 24.0; SPSS, Chicago, IL, USA).

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2020-0397), which waived the requirement for informed consent because of the retrospective nature of the study.

RESULTS

Characteristics of subjects

Our eligibility screening identified 792 patients with bronchiectasis who visited the emergency room or a respiratory care inpatient unit due to deteriorating respiratory and/or systemic symptoms and were prescribed antibiotics during the 5-year study period (**Fig. 1**). The median age of the 792 patients was 70.0 years, and 40.3% were female. Of the eligible patients, 172 (21.7%) had chronic obstructive pulmonary disease (COPD) and 72 (9.1%) had asthma as comorbidities (**Table 1**).

Overall, a viral pathogen was identified in 202 (25.5%) patients and a bacterial pathogen was identified in 204 (25.8%) patients. Among these, 57 (7.2%) patients were infected with both viral and bacterial pathogens (**Table 1**).

Microbiological examination

PCR to detect respiratory viruses was performed with nasopharyngeal swab specimens in 788 patients (99.5%), whereas BAL fluid was used in 19 patients (2.3%). Both specimens were used in 15 patients (1.9%).

For gram staining and culture, expectorated sputum was submitted by 780 patients (98.5%), and 54.2% of the expectorated sputum specimens had acceptable sputum quality. However, lower respiratory tract specimens were obtained from 107 patients (13.5%), and 84.1% were of acceptable quality.

The urinary antigen tests for *S. pneumoniae* and *L. pneumophila* serogroup 1 were performed in 684 (86.4%) and 549 patients (69.3%), respectively. PCR for *M. pneumoniae* and *C. pneumoniae* was performed in 320 patients (40.4%), while PCR for *L. pneumophila* was performed in 306 patients (38.6%).

Viral pathogens and seasonality

Table 2 and **Fig. 2** show the proportions and seasonal distributions of the viral pathogens detected in patients whose exacerbations were due to viral infection. The most common viral

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Table 1. Characteristics of 792 patients with bronchiectasis exacerbation

Characteristics	Total (n = 792)	Viral detection (n = 202)	No viral detection (n = 590)	*P* value
Age	70.0 (62.0–76.0)	69.0 (63.0–77.0)	70.0 (61.0–76.0)	0.430
Female	319 (40.3)	94 (46.5)	225 (38.1)	0.036
BMI	21.2 (18.5–24.1)	21.2 (19.0–25.0)	21.3 (18.4–23.8)	0.061
Comorbidities				
DM	163 (20.6)	47 (23.3)	116 (19.7)	0.274
HTN	275 (34.7)	78 (38.6)	197 (33.4)	0.178
Previous TB history	299 (37.8)	72 (35.6)	227 (38.5)	0.474
Previous NTM history	125 (15.8)	24 (11.9)	101 (17.1)	0.078
Chronic liver disease	53 (6.7)	13 (6.4)	40 (6.8)	0.866
COPD	172 (21.7)	43 (21.3)	129 (21.9)	0.864
Asthma	72 (9.1)	19 (9.4)	53 (9.0)	0.857
Malignancy	236 (29.8)	62 (30.7)	174 (29.5)	0.747
Chronic heart disease	143 (18.1)	44 (21.8)	99 (16.8)	0.111
Chronic kidney disease	53 (6.7)	18 (8.9)	35 (5.9)	0.144
Transplantation	20 (2.5)	7 (3.5)	13 (2.2)	0.324
ER visit	700 (88.4)	181 (89.6)	519 (88.0)	0.531
Bacterial detection	204 (25.8)	57 (28.2)	147 (24.9)	0.354
Bronchoalveolar lavage	19 (2.4)	5 (2.5)	14 (2.4)	0.935
Baseline FEV1, %[a]	54.0 (37.0–75.0)	51.0 (36.3–71.0)	55.0 (38.0–77.0)	0.687
Baseline WBC, k[b]	7.0 (5.6–8.8)	6.9 (5.5–9.0)	7.0 (5.7–8.7)	0.641
Baseline eosinophil count[c]	132.3 (68.2–230.1)	121.8 (62.0–226.2)	138.6 (68.5–231.0)	0.398
Baseline CRP[d]	0.53 (0.17–1.67)	0.56 (0.21–1.68)	0.50 (0.15–1.66)	0.179
Radiographic infiltration	617 (78.0)	145 (71.8)	472 (80.1)	0.013
Consolidation	536 (67.8)	124 (61.4)	412 (69.9)	0.025
Ground glass opacity	289 (36.5)	69 (34.2)	220 (37.4)	0.416

Values are presented as median (interquartile range) or number (%).
Of the 792 patients, bacterial pathogens were found in 204 (25.8%) patients. Among the patients in whom bacterial pathogens were identified, both bacteria and viruses were detected in 57 (27.9%) patients.
BMI = body mass index, DM = diabetes mellitus, HTN = hypertension, TB = tuberculosis, NTM = nontuberculous mycobacterium, COPD = chronic obstructive pulmonary disease, ER = emergency room, FEV1 = forced expiratory volume in 1 second, WBC = white blood cell, CRP = C-reactive protein.
[a]Data on the baseline FEV1 were available for 363 patients; [b]Data on the baseline WBC count were available for 585 patients; [c]Data on the baseline eosinophil count were available for 583 patients; [d]Data on the baseline CRP were available for 442 patients.

Table 2. Viral pathogens detected in patients with acute exacerbation of bronchiectasis

Virus	Total (n = 214)
Influenza virus	74 (34.6)
Influenza A virus	53 (24.8)
Influenza B virus	21 (9.8)
Rhinovirus	48 (22.4)
Respiratory syncytial virus	28 (13.1)
Respiratory syncytial virus A	9 (4.2)
Respiratory syncytial virus B	19 (8.9)
Coronaviruses	22 (10.3)
Coronavirus OC43/HKU1	11 (5.1)
Coronavirus 229E	4 (1.9)
Coronavirus NL63	7 (3.3)
Parainfluenza virus	20 (9.3)
Parainfluenza virus 1	4 (1.9)
Parainfluenza virus 2	1 (0.5)
Parainfluenza virus 3	11 (5.1)
Parainfluenza virus 4	4 (1.9)
Metapneumovirus	13 (6.1)
Adenovirus	6 (2.8)
Bocavirus	2 (0.9)
Enterovirus	1 (0.5)
Total	214 (100.0)

Values are presented as number (%).
Two or more viral pathogens were detected in 12 patients.

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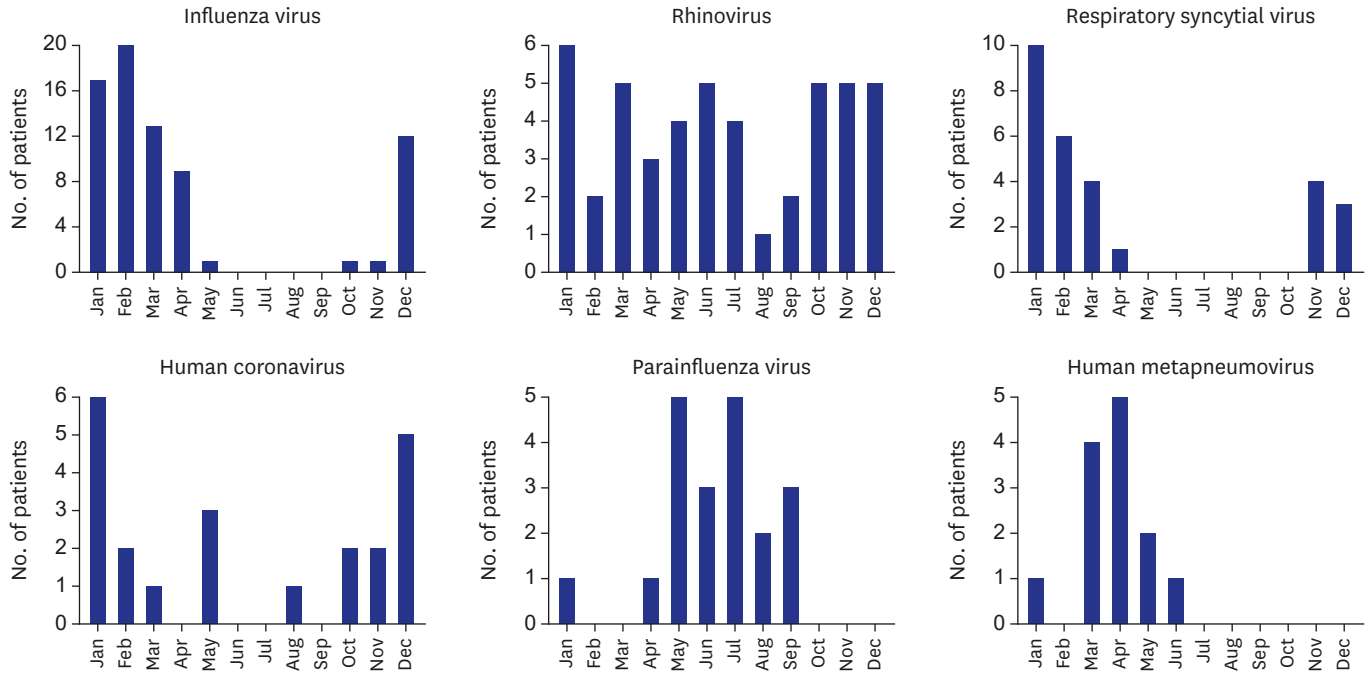

Fig. 2. Seasonal distribution of viral pathogens detected in patients with acute exacerbation of bronchiectasis. Adenovirus, bocavirus, and enterovirus were excluded because the number of cases detected was less than 10.

pathogen isolated was influenza A virus (24.8%), followed by rhinovirus (22.4%), influenza B virus (9.8%), RSV B (8.9%), and human metapneumovirus (6.1%).

Factors associated with viral infection in acute exacerbation of bronchiectasis

After excluding patients with evidence of bacterial detection to eliminate the effect of bacterial pathogens on exacerbation, we compared the characteristics of patients who experienced acute exacerbation with viral detection with those of patients who did not have any evidence of an infectious trigger (**Table 3**). In patients with acute exacerbation of bronchiectasis without bacterial detection, viral pathogens were detected in 148 patients, although no pathogens were found in 451 patients. These two groups were comparable except in the proportion of female patients (47.3% in the "viral detection only" group vs. 37.3% in the "no identified infectious cause" group; $P = 0.030$), proportions with a past medical history of chronic heart disease (25.7% vs. 17.1%, respectively; $P = 0.021$), and presence of radiographic infiltration at presentation (72.3% vs. 81.3%, respectively; $P = 0.019$).

A multivariable analysis revealed that female sex (adjusted OR, 1.608; 95% CI, 1.094–2.363; $P = 0.016$) and chronic heart disease as a comorbidity (adjusted OR, 1.723; 95% CI, 1.096–2.708; $P = 0.018$) were positively associated with viral detection in acute exacerbation in patients with bronchiectasis, whereas the presence of radiographic infiltration (adjusted OR, 0.612; 95% CI, 0.395–0.948; $P = 0.028$) was negatively associated (**Table 4**).

DISCUSSION

Acute exacerbation is a part of the natural course of bronchiectasis and, at the same time, is one of the most important prognostic factors of the disease.[4,5] Bacterial infection, especially

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Table 3. Characteristics of the 588 patients with bronchiectasis exacerbation after excluding patients with detected bacterial pathogens

Characteristics	Total (n = 588)	Viral detection only (n = 145)	No identified infectious cause (n = 443)	*P* value
Age	70.0 (61.0–76.0)	69.0 (62.0–77.0)	70.0 (61.0–76.0)	0.537
Female	233 (39.6)	68 (46.9)	165 (37.2)	0.039
BMI	21.3 (18.6–24.1)	21.1 (18.7–25.1)	21.3 (18.5–23.9)	0.319
Comorbidities				
DM	122 (20.7)	33 (22.8)	89 (20.1)	0.492
HTN	216 (36.7)	58 (40.0)	158 (35.7)	0.347
Previous TB history	209 (35.5)	46 (31.7)	163 (36.8)	0.268
Previous NTM history	96 (16.3)	17 (11.7)	79 (17.8)	0.084
Chronic liver disease	37 (6.3)	8 (5.5)	29 (6.5)	0.658
COPD	123 (20.9)	32 (22.1)	91 (20.5)	0.695
Asthma	43 (7.3)	9 (6.2)	34 (7.7)	0.556
Malignancy	174 (29.6)	44 (30.3)	130 (29.3)	0.819
Chronic heart disease	110 (18.7)	36 (24.8)	74 (16.7)	0.029
Chronic kidney disease	43 (7.3)	15 (10.3)	28 (6.3)	0.106
Transplantation	16 (2.7)	6 (4.1)	10 (2.3)	0.227
ER visit	526 (89.5)	131 (90.3)	395 (89.2)	0.688
Bronchoalveolar lavage	15 (2.6)	4 (2.8)	11 (2.5)	0.770
Baseline FEV1, %[a]	56.0 (38.0–74.8)	53.5 (40.3–76.0)	56.0 (38.0–74.8)	0.937
Baseline WBC, k[b]	6.9 (5.5–8.5)	6.9 (5.5–8.7)	6.9 (5.6–8.5)	0.692
Baseline eosinophil count[c]	136.8 (68.8–228.3)	117.0 (62.0–226.2)	140.6 (69.3–230.2)	0.281
Baseline CRP[d]	0.53 (0.15–1.67)	0.74 (0.21–1.68)	0.46 (0.14–1.66)	0.141
Radiographic infiltration	463 (78.9)	105 (72.4)	358 (81.0)	0.028
Consolidation	398 (67.8)	88 (60.7)	310 (70.1)	0.035
Ground glass opacity	225 (38.3)	49 (33.8)	176 (39.8)	0.195

Values are presented as median (interquartile range) or number (%).
BMI = body mass index, DM = diabetes mellitus, HTN = hypertension, TB = tuberculosis, NTM = nontuberculous mycobacterium, COPD = chronic obstructive pulmonary disease, ER = emergency room, FEV1 = forced expiratory volume in 1 second, WBC = white blood cell, CRP = C-reactive protein.
[a]Data on the baseline FEV1 were available for 264 patients; [b]Data on the baseline WBC count were available for 430 patients; [c]Data on the baseline eosinophil count were available for 429 patients; [d]Data on the baseline CRP were available for 315 patients.

Table 4. Analysis of factors related to viral detection in patients with acute exacerbation of bronchiectasis

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Female	1.488 (1.019–2.173)	0.040	1.580 (1.071–2.332)	0.021
Previous NTM history	0.612 (0.349–1.073)	0.086	0.594 (0.335–1.052)	0.074
Chronic heart disease	1.647 (1.048–2.588)	0.031	1.693 (1.068–2.684)	0.025
Radiographic infiltration	0.616 (0.399–0.951)	0.029	0.631 (0.406–0.981)	0.041

The analysis was conducted in 588 patients after excluding the patients with bacterial pathogens.
OR = odds ratio, CI = confidence interval, NTM = nontuberculous mycobacterium.

by *Pseudomonas aeruginosa*, is a well-established risk factor for developing exacerbations in patients with bronchiectasis; therefore, guidelines recommend using antibiotics during the exacerbation period if the patient is a known colonizer of the pathogen and even recommend long-term antibiotic therapy during stable periods if the patient experiences frequent (three or more) exacerbations each year.[1,10] However, it is apparent that not all exacerbations are solely attributable to bacterial infections.[6,7] In our real-world practice, we have come across numerous exacerbation cases in which we could not specify the causative bacterial pathogens despite repeated bacterial tests, including cultures and various antigen or antibody tests. Sometimes, viral pathogens are detected instead. Until recently, there has been low interest in viral roles in bronchiectasis exacerbations, because of which there are insufficient data to evaluate this. To the best of our knowledge, this is the first study to investigate the incidence rate and seasonal distribution of viral infection in a large number of patients who presented with exacerbation of bronchiectasis. The most important finding of the present study was that a viral pathogen was detected in approximately 25% of patients who were prescribed antibiotics for acute exacerbation of bronchiectasis with no evidence of bacterial infection.

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Of the viruses detected, influenza viruses were the most common (34.7%), followed by rhinovirus (22.7%), and RSVs (13.0%).

When analyzed according to a monthly timeline, influenza viruses, RSVs and coronaviruses were more common in winter, while parainfluenza viruses and human metapneumovirus were prevalent in the summer and spring seasons, respectively. Rhinoviruses were detected all year round. The seasonal distribution patterns of respiratory viruses shown in the present study mostly correspond with those of earlier studies, although a slight difference was found in the case of human metapneumovirus, which showed a winter preponderance in another study.[11-14] Various mechanisms underlying the seasonal variations of viral infections have been proposed in recent studies, including different meteorological factors, such as temperature and humidity, resulting from regional variations; differences in behavioral and environmental backgrounds; or the infectiveness of the virus itself.[15-18]

Exacerbations caused by respiratory viruses in patients with COPD and those with asthma are associated with more frequent and longer hospital stays, as well as a longer median symptom recovery time, when compared with nonviral exacerbations.[19-21] However, in bronchiectasis, the viral role in the severity of exacerbations remains unknown. One important prospective study that might give a hint to the viral role in bronchiectasis exacerbation was conducted by Gao et al.,[8] and it revealed that viruses were more frequently detected and that markers of systemic and airway inflammation, such as serum interleukin-6, tumor necrosis factor alpha, and sputum interleukin 1 beta, were higher during exacerbation than during the steady state. This may suggest a viral role in triggering bronchiectasis exacerbations; however, further investigations are needed to understand the mechanisms underlying this.

One notable finding in the present study is that the proportion of patients with preexisting cardiovascular diseases—including congestive heart failure, cardiomyopathies, valvular heart disease, and coronary artery diseases—was significantly higher in cases of virus-positive exacerbations than in those of exacerbations with no identified infectious cause. Although no study has investigated this phenomenon in patients with bronchiectasis, some studies have reported high rates of underlying cardiac disease in patients with symptomatic RSV, influenza, and human metapneumovirus infections.[22,23] In addition, Mehta et al.[24] reported in their post hoc analysis of patients with COPD that patients with preexisting congestive heart failure were significantly more likely to develop a symptomatic RSV infection than patients without congestive heart failure, which might suggest the possibility of an increased susceptibility to viral infections in patients with chronic heart disease.

However, we still could not specify the exact cause of exacerbation in a considerable number of patients (56.3%), which we labelled as having acute exacerbation with "no identified infectious cause." The possible explanations for the deteriorating conditions in this group of patients could be heterogeneous, including air pollution, bleeding, and combined cardiovascular decompensation. However, some patients in this group could have had mycobacterial or fungal infections, as we did not routinely screen sputum acid-fast bacilli and set up fungal cultures as part of our initial evaluation of bronchiectasis exacerbations.

The present study has some limitations. First and most significantly, the study was conducted at a single referral center, with a non-randomized, retrospective design. Larger, prospective studies will be needed to confirm the prevalence of viral infections in bronchiectasis exacerbations and their role in developing exacerbations. Second, because we included only

patients who were prescribed antibiotics and managed in the inpatient units and emergency room, a considerable number of patients with milder forms of acute exacerbations might have been excluded from this study, and this may have raised the severity level of the included patients. Third, due to the limitation of diagnostic tools, it is possible that the identified bacterial and viral pathogens are colonizers or contaminants rather than true pathogens. Additionally, the heterogeneous approach to microbiological examinations could have affected the viral and bacterial detection rates. Finally, in patients with underlying chronic heart disease, acute decompensated heart failure and pulmonary edema triggered by viral infection could have mimicked the respiratory symptoms and radiographic infiltration such as ground-glass opacity observed in the acute exacerbations of bronchiectasis. This might have affected the result of multivariable analysis in the present study.

In conclusion, we found that a viral pathogen was detected in approximately one-fourth of patients with acute exacerbation of bronchiectasis. Of the viruses detected, influenza viruses were the most common, followed by rhinovirus and RSVs. Larger, prospective studies to confirm this are needed, as well as more attention to viruses as causative pathogens for acute, deteriorating symptoms in patients with bronchiectasis.

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