The Journal of Rheumatology 2020;xxxxx
doi:10.3899/jrheum.190313
First Release September 1 2020

The Journal of Rheumatology

Spectrum and Prognosis of Antineutrophil Cytoplasmic Antibody–associated Vasculitis-related Bronchiectasis: Data from 61 Patients

Raphael Lhote[1], Marie Chilles[2], Matthieu Groh[3], Xavier Puéchal[4], Philippe Guilpain[5], Félix Ackermann[3], Zahir Amoura[6], Isabella Annesi-Maesano[7], Thomas Barba[8], Emilie Catherinot[9], Fleur Cohen-Aubart[6], Pascal Cohen[4], Vincent Cottin[8], Louis-Jean Couderc[9], Hubert De Boysson[10], Xavier Delbrel[11], Stéphane Dominique[12], Pierre Duhaut[13], Olivier Fain[14], Eric Hachulla[15], Mohamed Hamidou[16], Jean-Emmanuel Kahn[3], Christophe Legendre[17], Alain Le Quellec[5], François Lhote[18], François Lifermann[19], Alexis Mathian[6], Antoine Néel[16], Hilario Nunes[20], Jean-François Subra[21], Benjamin Terrier[4], Luc Mouthon[4], Elisabeth Diot[22], Loïc Guillevin[4], Pierre-Yves Brillet[23], and Colas Tcherakian[9], for the French Vasculitis Study Group (FVSG) and the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERM"O"P)

ABSTRACT. ***Objective.*** To report on a large series of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and bronchiectasis, with a specific focus on the timeline of occurrence of both features.

Methods. Retrospective nationwide multicenter study of patients diagnosed with both AAV and bronchiectasis.

Results. Sixty-one patients were included, among whom 27 (44.25%) had microscopic polyangiitis (MPA), 27 (44.25%) had granulomatosis with polyangiitis (GPA), and 7 (11.5%) had eosinophilic GPA. Thirty-nine (64%) had myeloperoxidase (MPO)-ANCA and 13 (21%) had proteinase 3–ANCA. The diagnosis of bronchiectasis either preceded (n = 25; median time between both diagnoses: 16 yrs, IQR 4–54 yrs), was concomitant to (n = 12), or followed (n = 24; median time between both diagnoses: 1, IQR 0–6 yrs) that of AAV. Patients in whom bronchiectasis precedes the onset of AAV (B-AAV group) have more frequent mononeuritis multiplex, MPA, MPO-ANCA, and a 5-fold increase of death. The occurrence of an AAV relapse tended to be protective against bronchiectasis worsening (HR 0.6, 95% CI 0.4–0.99, $P = 0.049$), while a diagnosis of bronchiectasis before AAV (HR 5.8, 95% CI 1.2–28.7, $P = 0.03$) or MPA (HR 18.1, 95% CI 2.2–146.3, $P = 0.01$) were associated with shorter survival during AAV follow-up.

Conclusion. The association of bronchiectasis with AAV is likely not accidental and is mostly associated with MPO-ANCA. Patients in whom bronchiectasis precedes the onset of AAV tend to have distinct clinical and biological features and could carry a worse prognosis.

Key Indexing Terms: age, antineutrophil cytoplasmic antibody-associated vasculitis, bronchiectasis, immunosuppressive agents

[1]R. Lhote, MD, Department of Pulmonology, Hôpital Foch, Suresnes, Faculté des Sciences de la Vie, Simone Veil, Université de Versailles, UPRES EA 220, and Sorbonne Université, University of Pierre and Marie Curie (UPMC), Pierre Louis Institute of Epidemiology and Public Health (IPLESP UMRS 1136), Epidemiology of Allergic and Respiratory Diseases Department (EPAR), Saint-Antoine Medical School, Paris; [2]M. Chilles, MD, Department of Internal Medicine, Orléans, and Department of Internal Medicine, CHU, Tours; [3]M. Groh, MD, F. Ackermann, MD, J.E. Kahn, MD, PhD, Department of Internal Medicine, CEREO (National Referral Center for Hypereosinophilic Syndromes), Hôpital Foch, Suresnes; [4]X. Puéchal, MD, PhD, P. Cohen, MD, B. Terrier, MD, PhD, L. Mouthon, MD, PhD, L. Guillevin, MD, Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP-HP, Université Paris Descartes, Paris; [5]Philippe Guilpain, MD, PhD, A. Le Quellec, MD, PhD, Department of Internal Medicine, Saint Eloi Hospital, Montpellier; [6]Z. Amoura, MD, MSc, F. Cohen-Aubart, MD, PhD, A. Mathian, MD, PhD, Sorbonne Université, INSERM UMRS 1135, Department of Internal Medicine 2, Centre National de Référence Maladies Auto-Immunes et Systémiques Rares Lupus et Syndrome des Anticorps Antiphospholipides Centre de Référence des Histiocytoses, Institut E3M, AP-HP, Hôpital Pitié-Salpétrière, Paris; [7]I. Annesi-Maesano, MD, PhD, Sorbonne Université, UPMC, Pierre Louis Institute of Epidemiology and Public Health (IPLESP UMRS 1136), Epidemiology of Allergic and Respiratory Diseases Department (EPAR), Saint-Antoine Medical School, Paris; [8]T. Barba, MD, V. Cottin, MD, PhD, Department of Pulmonology , Louis Pradel Hospital, Lyon; [9]E. Catherinot, MD, PhD, L.J. Couderc, MD, C. Tcherakian, MD, PhD, 1Department of Pulmonology, Hôpital Foch, Suresnes, Faculté des Sciences de la Vie, Simone Veil, Université de Versailles, UPRES EA 220; [10]H. De Boysson, MD, Departments of Internal Medicine, University Hospital, Caen; [11]X. Delbrel, MD, Department of Internal Medicine, François Mitterand Hospital, Pau; [12] S. Dominique, MD, Department of Pulmonology Department, Charles Nicolle University Hospital, Rouen;

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of inflammatory diseases characterized by small- to medium-size vessel necrotizing vasculitis involving various organs and the presence of autoantibodies targeting neutrophil's cytoplasmic proteolytic enzymes[1].

AAV-associated lung involvement encompasses a wide spectrum of manifestations including pulmonary hemorrhage, pulmonary nodules in granulomatosis with polyangiitis (GPA), and eosinophilic-related bronchial hyperresponsiveness in eosinophilic GPA (EGPA)[2]. Several case series reported the association of interstitial lung disease (ILD; mostly usual interstitial pneumonia) and AAV, occurring predominantly in patients with anti-myeloperoxydase (MPO) autoantibodies[3,4,5]. Likewise, the association of bronchiectasis and AAV has also been reported in case reports and small case series[6,7,8,9,10], and it has been shown that patients with bronchiectasis are at increased risk of GPA onset[11,12,13].

We previously reported the case of a patient with lung-limited microscopic polyangiitis (MPA) in whom bronchiectasis (1) positively correlated with both ANCA titers and AAV activity, and (2) dramatically improved with immunosuppressive therapy[10]. This case suggested that bronchiectasis might be another specific feature of AAV. Moreover, by analogy with rheumatoid arthritis (RA)-associated bronchiectasis (where early-onset bronchiectasis carries a worse prognosis), the timeline of occurrence between both conditions might significantly affect disease prognosis[14,15].

The aim of our present study was to report on the clinical and radiological characteristics of a large series of patients with both AAV and bronchiectasis, with a specific focus on the time frame between both disease features.

MATERIALS AND METHODS

Patients. We conducted a retrospective study of adult (> 18 yrs) patients with AAV enrolled in the French Vasculitis Study Group (FVSG) registry prior to May 2015 who were diagnosed with bronchiectasis [according to a chest computed tomography (CT) scan, as defined by Barker, *et al*][16]. Specifically, the database was queried manually using the following keywords: "bronchiectasis," "bronchitis," "bronchial dilatation," and "bronchial wall thickening." Next, a nationwide retrospective survey was performed using complementary multidisciplinary networks (Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires, Société Nationale Française de Médecine Interne) to identify additional patients. All patients fulfilled either the 1990 American College of Rheumatology classification criteria[17,18] and/or the algorithm of the European Medicines Agency for AAV[19]. Patients were excluded from the study if they had fibrosis-related traction-bronchiectasis and/or secondary bronchiectasis due to other well-defined conditions (e.g., cystic fibrosis, alpha-1 antitrypsin deficiency)[16]. Patients previously reported in the study by Néel, *et al* were not included in the present work[9].

Our study complied with Good Clinical Practice guidelines and the Declaration of Helsinki. Owing to the retrospective design of this study, and in compliance with the French legislation in force at the time of the study (Loi Huriet-Sérusclat 88-1138, December 20, 1988, and its subsequent amendments), an observational study that does not change routine management of patients does not need to be declared or submitted for the review of a research ethics board.

Baseline measurements. All medical records were reviewed regarding demographic, clinical, biological, radiological, pulmonary function, and histological findings. Studied biological variables included proteinuria (> 0.4 g/24 h), hematuria (> 10 red blood cells per high-power field), serum creatinine level, C-reactive protein level, and the results of ANCA testing by immunofluorescence and/or ELISA at AAV diagnosis[20]. AAV disease activity was assessed at the time of AAV diagnosis using the Birmingham Vasculitis Activity Score (BVAS) version 3 (scores range from 0 to 63, with higher scores indicating more active disease)[21]. The modified BVAS was used for GPA[22], and AAV disease prognosis was assessed by the 1996 Five-Factor Score (FFS; with severe disease corresponding to a FFS ≥ 1: i.e., presence of cardiac, central nervous system or gastrointestinal involvement, peak creatinine level > 140 μmol/l, and/or proteinuria > 1 g/d)[23].

All diagnoses of bronchiectasis were reassessed by the investigators (RL, MC, and CT). Available chest CT scans were retrospectively reviewed by an expert thoracic radiologist (PYB) blinded to clinical and histopathological data. The severity of bronchiectasis was gauged using the FACED score [FEV1, age, chronic *Pseudomonas aeruginosa* colonization, extension, and dyspnea; a tool validated for patients with noncystic fibrosis bronchiectasis leading to 3 levels of severity: mild bronchiectasis (0–2 points), moderate bronchiectasis (3–4 points), or severe bronchiectasis (5–7 points)], and in all patients with available high-resolution CT scan, using the Bhalla scoring system[24,25]. Briefly, the Bhalla score (ranging from 0 to 25 points, the latter corresponding to the most severely involved patients) depicts various aspects of the pulmonary involvement (e.g., the maximum diameter of bronchiectasis, peribronchial thickening, and the presence of sacculation and/or abscesses). For patients with more than 1 available CT scan, Bhalla score was assessed yearly (or more in case of disease progression).

An obstructive ventilatory defect was defined by a forced expiratory volume in 1 s (FEV1)/ forced vital capacity ratio of < 70%, while a restrictive ventilatory defect was defined as a total lung capacity of 80% or less than the predicted value[26].

Long-term outcome measures. During follow-up, several long-term events were recorded: the evolution of bronchiectasis, respiratory function, the occurrence of chronic respiratory failure[26], severe lower respiratory tract infections, death, and AAV relapse. Specifically, bronchiectasis worsening and AAV relapse were defined, respectively, as (1) a decline of ≥ 1 point(s) of the Bhalla score; and (2) the reappearance or worsening of AAV features with BVAS > 0 and requiring treatment escalation[27].

Treatment procedures. Drugs used both to induce and maintain remission were recorded, as well as those used as antibiotic prophylaxis (i.e., cotrimoxazole and/or azithromycin).

[13]*P. Duhaut, MD, PhD, Department of Internal Medicine, University Hospital, Amiens;* [14]*Olivier Fain, MD, PhD, Department of Internal Medicine, Saint Antoine Hospital, Paris;* [15]*E. Hachulla, MD, PhD, Department of Internal Medicine, Centre de Reference des Maladies Auto-immunes Systémique Rares du Nord et du Nord-Ouest de France (CeRAINO), CHRU de Lille, Université de Lille, Lille;* [16]*M. Hamidou, MD, PhD, A. Néel, MD, PhD, Department of Internal Medicine, CHU, Nantes;* [17]*Christophe Legendre, MD, PhD, Department of Nephrology, Necker Enfants Malades Hospital, Paris;* [18]*F. Lhote, MD, Department of Internal Medicine, Delafontaine Hospital, Saint Denis;* [19]*F. Lifermann, MD, Department of Internal Medicine, Dax Hospital, Dax;* [20]*H. Nunes, MD, PhD, Department of Pulmonology, Avicenne Hospital, Bobigny;* [21]*J.F. Subra, MD, PhD, Department of Nephrology-Dialysis-Transplantation, Angers University Hospital, Angers;* [22]*E. Diot, MD, PhD, Department of Internal Medicine, CHU, Tours;* [23]*P.Y. Brillet, MD, PhD, Department of Radiology, Avicenne Hospital, Bobigny, France.*

R. Lhote and M. Chilles contributed equally to this work.

Address correspondence to Dr. C. Tcherakian, Service de Pneumologie, Hôpital Foch, 40 Rue Worth, 92150, Suresnes, France.
Email: colastcherakian@gmail.com.

Accepted for publication November 8, 2019.

Statistical analysis. Patient characteristics are reported as the number and percentage for categorical variables and as the median and IQR for continuous variables. Patient subsets were differentiated based on the type of AAV and on the first disease manifestation. Hence, patients in whom bronchiectasis preceded the diagnosis of AAV were classified as the "B-AAV" subgroup, while patients in whom bronchiectasis was diagnosed concomitantly or after the diagnosis of AAV were grouped into the "AAV-B" subgroup. For these subsets, quantitative variables were compared using the Wilcoxon-Mann-Whitney U test (or the Kruskal-Wallis test when > 2 independent groups), and categorical variables were compared using Fisher's exact test.

Pulmonary outcomes were assessed by comparing respiratory findings at diagnosis of bronchiectasis (whether it was assessed prior to or after that of AAV) and at last follow-up. Patient's survival after onset of AAV was analyzed using the Kaplan-Meier method and compared using log-rank tests. Results are presented as HR with 95% CI. The Cox proportional hazard model was used to estimate HR using variables with $P < 0.2$ in univariable analysis. P values < 0.05 were considered significant. All statistical analyses were conducted using R 3.3.3 for Windows (R Foundation for Statistical Computing).

RESULTS

Patient characteristics at diagnosis of AAV and treatments. Of the 2035 AAV patients included in the FVSG database in May 2015, 43 (2%) were reported to have bronchiectasis. Forty-six additional patients with both AAV and bronchiectasis were included from a national survey. After exclusion of 28 patients (ILD-related traction bronchiectasis: n = 2; insufficient data: n = 26), 61 patients (16 males, 45 females) from 19 centers were included in our present study. Their baseline characteristics are reported in both Table 1, and Supplementary Table 1 (available with the online version of this article).

Median age at AAV diagnosis was 64 (IQR 55–75) years. AAV consisted either of MPA (n = 27), GPA (n = 27), or EGPA (n = 7). Thirty-nine patients (64%) had anti–MPO-ANCA (including 2 patients with concomitant antibactericidal/permeability-increasing protein ANCA), and 13 patients (21%) had anti-proteinase 3-ANCA, while ANCA lacked specificity (n = 6) or were absent (n = 5) in the remaining cases (consisting of ANCA-negative EGPA patients with biopsy-proven and/or clinical surrogates of vasculitis)[25]. The diagnosis of bronchiectasis preceded that of AAV in 25 cases (41%), with the median time between both diagnoses 16 years (IQR 4–54). Both diagnoses were simultaneous in 12 cases (20%), while bronchiectasis occurred after the diagnosis of AAV in the last 24 remaining cases (39%; median time between both diagnoses: 1 yr, IQR 0–6). Patients belonging to the B-AAV subgroup had more frequent neurological involvement (64% vs 28%, $P = 0.01$), MPO-ANCA (80% vs 53%, $P = 0.03$), and a trend toward more frequent MPA (60% vs 33%, $P = 0.07$) than their counterparts from the AAV-B subgroup. At the diagnosis of AAV, the median BVAS was 13 (IQR 7–18) and the median FFS was 0 (0–1), without difference between patient subgroups.

Glucocorticoids were the cornerstone of therapy (n = 60, 98%), alone or associated with another immunosuppressive therapy (n = 53, 87%), consisting either of cyclophosphamide (CYC; n = 45, 74%), azathioprine (n = 32, 52%), mycophenolate mofetil (n = 12, 20%), rituximab (RTX; n = 15, 25%), or methotrexate (n = 14, 23%). Long-term antibiotics with cotrimoxazole (n = 33, 54%) and/or azithromycin (n = 12, 20%) were also frequently prescribed (Table 1).

Pulmonary characteristics at diagnosis of bronchiectasis. Table 2, and Supplementary Table 2 (available with the online version of this article) summarize patients' pulmonary characteristics at diagnosis of bronchiectasis. Respiratory symptoms were present in 45 cases (74%): cough (n = 32, 52%), dyspnea (n = 29, 48%), and hemoptysis (n = 16, 26%). Among the 61 patients, 8 had low-resolution chest CT scans that, although showing bronchiectasis, lacked sufficient resolution to accurately assess the Bhalla score. Among the 53 remaining patients, the median Bhalla score was 9 (IQR 6–12; Supplementary Table 3, available with the online version of this article). Bronchiectasis was usually widespread [affecting > 6/20 bronchopulmonary segments in 27 cases (51%)] and presented up to the fifth generation of bronchial division in 46 cases (87%). The dilatation of bronchi was usually moderate to severe [diameter of the lumen ≥ 3× of normal features in 30 (56.5%) cases], while peribronchial thickening tended to be mild to moderate [bronchi wall thickness being superior to twice the diameter of adjacent vessel in 44 cases (83%); Supplementary Figure 1, available with the online version of this article]. Besides bronchiectasis, other findings on the initial high-resolution chest CT scan included nodules (n = 19, 36%), nodule excavations (n = 2, 4%), ILD (n = 1, 2%; in a patient with focal bronchiectasis unrelated with ILD), and ground-glass opacities suggestive of alveolar hemorrhage (n = 1, 2%), without differences between patient subgroups.

Respiratory function tests were performed in 35 patients (57%) at the diagnosis of bronchiectasis. Twenty patients (57%) had airway obstruction [the latter being more frequent in EGPA (100%) than in MPA (35%) and GPA (5%); $P = 0.01$]. Five patients (14%) exhibited airway restriction (without differences between patient subgroups), while the latter tests were unremarkable in the remaining 10 patients.

Long-term outcomes. Table 3, and Supplementary Table 4 (available with the online version of this article) summarize patient outcomes. After a median AAV follow-up of 7 (4–13) years, the overall survival was 100% at 1 year, 97% at 5 years, and 89% at 10 years but tended to be worse in the B-AAV subgroup (overall survival at 10 yrs of 62% vs 93%, $P = 0.03$; Figure 1A). The leading causes of death consisted of pneumonia (n = 2, 22%), acute renal failure (n = 2), massive hemoptysis due to uncontrolled AAV (n = 1), myocardial infarction (n = 2, 22%), chronic respiratory failure due to bronchiectasis (n = 1, 11%), and sudden death of unknown origin (n = 2). Vasculitis relapses occurred in 26 patients (43%) and chronic respiratory failure in 1 case (2%), without differences between patient subgroups. In the B-AAV subgroup, there were no significant differences regarding patients' survival between those treated with RTX and/or CYC and those who received neither of these drugs (HR 0.14, 95% CI 0.01–1.7, $P = 0.1$; Figure 1B).

As for respiratory outcomes, 32 patients (52%) presented

Table 1. Patients' characteristics and treatment at diagnosis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) according to whether bronchiectasis occurred before AAV.

Characteristics	All, n = 61	B-AAV, n = 25	AAV-B, n = 36	*P*
Median age at AAV diagnosis, yrs, (IQR)	64 (55–75)	67 (56–75)	62 (51.25–73)	0.3
Sex (male), n (%)	16 (26)	6 (24)	10 (28)	0.8
Tobacco users, n (%)	19/56 (34)	9/56 (39)	10/56 (30)	0.6
Prior autoimmune disease	12 (20)	5 (20)	7 (19)	1
Median duration between the diagnoses of B and AAV, yrs (IQR)	–	16 (4–54)	–	
Median duration between the diagnoses of AAV and B, yrs (IQR)	–	–	1 (0–6)	
AAV subtype, n (%)				
GPA	27 (44.25)	9 (36)	18 (50)	0.4
MPA	27 (44.25)	15 (60)	12 (33)	0.07
EGPA	7 (11.5)	1 (4)	6 (17)	0.2
ANCA specificity, n (%)				
MPO	39 (64)	20 (80)	19 (53)	**0.03**
PR3	13 (21)	4 (16)	9 (25)	**0.03**
Other*	6 (10)	1 (8)	3 (8)	1
Negative	5 (8)	0 (0)	5 (14)	0.07
Symptoms, n (%)				
Respiratory	45 (74)	17 (68)	28 (78)	0.6
ENT	31 (51)	11 (44)	20 (56)	0.4
Neurologic	26 (43)	16 (64)	10 (28)	**0.01**
Mononeuritis multiplex	23 (38)	15 (60)	8 (22)	0.004
Renal	21 (34)	9 (36)	12 (33)	1
Proteinuria > 0.4 g/24 h	20 (33)	9 (36)	11 (31)	0.8
Creatinine > 140 μmol/l	11 (18)	5 (20)	6 (17)	0.7
Myocarditis	4 (6.5)	1 (4)	3 (8)	0.6
BVAS, median (IQR)	13 (7–18)	14 (10–21)	13 (7–18)	0.4
FFS 1996, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0.6
Treatments, n (%)				
Corticosteroids	60 (98)	25 (100)	35 (97)	1
Immunosuppressants during follow-up	53 (87)	21 (84)	32 (89)	0.7
Cyclophosphamide	45 (74)	17 (68)	28 (78)	0.6
Rituximab	15 (24.5)	3 (12)	12 (33)	0.3
Azithromycin	12 (20)	5 (20)	7 (19)	1

Values in bold face are statistically significant. * 2 patients had both anti-MPO and anti-BPI ANCA. B: bronchiectasis; AAV-B: bronchiectasis post vasculitis; B-AAV: bronchiectasis before vasculitis; BPI: bactericidal/permeability-increasing protein; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; FFS: Five-Factor Score; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3.

at least 1 pulmonary infection with a median rate of annual severe infection of 0.1 per year (IQR 0–0.4). *P. aeruginosa* colonization occurred in 18 cases (30%), and infection due to nontuberculous mycobacteria in 3 cases (5%). Of the 37 patients with more than 1 available CT scan, 6 B-AAV patients (17%) improved their Bhalla score while under immunosuppressants versus 5 (22%) AAV-B patients ($P = 0.3$); the median improvement being 1 (IQR 1–2) point. Among the 17 patients who exhibited pulmonary nodules and underwent follow-up chest CT, such nodules resolved (or significantly improved, with only mild sequelae) in 12 patients (71%). Follow-up evaluations of the respiratory function tests were available in 16 cases (26%), with a median FEV1 decrease of 4.5% (IQR -14 to 4.5) between the first and last follow-up visits. Although nonsignificant, the FEV1 tended to be lower [-10%, (IQR -18 to 2) vs 1% (IQR –6 to 5), $P = 0.2$] in the AAV-B subgroup.

Factors associated with the worsening of bronchiectasis. Factors associated with the worsening of bronchiectasis are reported in Table 4. Thirty-seven patients (61%) had more than 1 chest CT scan that could be further analyzed. Age at diagnosis of AAV and arthralgia were predictors of bronchiectasis worsening. Conversely, AAV relapse requiring treatment escalation tended to be protective (HR = 0.6, 95% CI 0.4–0.99, $P = 0.049$), with at the end of follow-up, a mean Bhalla score variation of 2.1 (SD ± 3) points in patients who underwent AAV relapse (vs +2.5, SD ± 3.7 points variance in nonrelapsing patients). Results persisted in multivariate analysis.

Factors associated with death. Factors associated with death are reported in Table 5. Those that were statistically significant

Table 2. Respiratory characteristics at diagnosis of bronchiectasis according to whether bronchiectasis occurred before AAV.

Characteristics	All, n = 61	B-AAV, n = 25	AAV-B, n = 36	*P*
Age at B diagnosis, yrs	59 (44–73)	44 (8–55)	66 (57.75–75.25)	< 0.001
Respiratory manifestations, n (%)	45 (74)	17 (68)	28 (78)	0.6
Dyspnea	29 (48)	10 (40)	19 (53)	0.4
Cough	32 (52)	12 (48)	20 (56)	0.9
Hemoptysis	16 (26)	6 (24)	10 (28)	0.8
FACED score (0–7), n = 32	2 (1–3.25)	2 (2–4)	2 (1–3)	0.2
Bhalla score* (0–25), n = 53	9 (6–12)	10 (8–12)	9 (6–12)	0.1
Other radiologic findings, n (%)				
Nodule	19 (36)	9 (39)	10 (33)	0.1
Nodule excavation	2 (4)	1 (4.5)	1 (3.5)	1
Intraalveolar hemorrhage	2 (4)	1 (4.5)	1 (3.5)	1
Interstitial lung disease	1 (2)	1 (4.5)	0 (0)	0.4
Respiratory function				
FEV1, ml, n = 34	1625 (1085–2060)	1500 (785–1965)	1750 (1177–2245)	0.3
FEV1%, n = 34	72 (59–88)	67 (43.5–83.5)	77 (66–89)	0.2
FEV1/FVC %, n = 40	69 (64–78.6)	68 (64.5–75)	68 (64.5–75)	0.8
TPC, ml, n = 31	5320 (4450–6470)	5270 (4850–6215)	5320 (4330–7000)	0.8
TPC%, n = 31	96.5 (90.25–106)	96.5 (90.25–108.5)	96.5 (90.75–101.5)	0.7

Values are median (IQR) unless otherwise specified. * Full details of the Bhalla score is reported in Supplementary Table 3 (available with the online version of this article). ANCA: antineutrophil cytoplasmic antibodies; AAV: ANCA-associated vasculitis; B: bronchiectasis; AAV-B: bronchiectasis post vasculitis; B-AAV: bronchiectasis before vasculitis; FACED: FEV1, age, chronic *Pseudomonas aeruginosa* colonization, extension, and dyspnea; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; TPC: total pulmonary capacity; %: percentage of predicted value.

included age at diagnosis of AAV (HR 1.2, 95% CI 1.1–1.3; $P = 0.003$), MPA (HR 18.1, 95% CI 2.2–146.3; $P = 0.01$) and belonging to the B-AAV subgroup (HR 5.8, 95% CI 1.2–28.7; $P = 0.03$), while ENT involvement was associated with lower mortality (HR 0.1, 95% CI 0.01–0.6; $P = 0.01$). Statistical significance disappeared in multivariate analysis but within the same trends as for HR (data not shown).

DISCUSSION

We report on patients with both AAV and bronchiectasis from a large nationwide multicenter series set up through complementary multidisciplinary networks. While bronchiectasis can both precede the onset of AAV or occur during vasculitis follow-up, each scenario seems to correlate with a specific patient phenotype: patients with bronchiectasis preceding AAV (B-AAV) tend to have more frequent neurological symptoms (especially mononeuritis multiplex), MPA, MPO-ANCA, and are at a 5-fold increased risk of death compared to patients with AAV preceding (AAV-B). Moreover, bronchiectasis can also be reported in a substantial proportion of ANCA (mainly MPO)-positive patients with initially no other systemic manifestation of vasculitis. This is an important finding, highlighting that ANCA serology should be part of the initial diagnostic investigation of newly diagnosed patients with bronchiectasis and that, in the context of ANCA-associated bronchiectasis, pulmonologists should look for nonrespiratory manifestations of AAV[28,29,30,31].

Various underlying pathophysiological processes might account for the highlighted differences in both disease presentation and ANCA subtypes. On the one hand, up to two-thirds of the patients developed bronchiectasis during the follow-up of AAV, often shortly after AAV diagnosis, suggesting an active immune-related process leading to the onset and worsening of bronchiectasis. Hence, in AAV-B patients, analogous to chronic graft-versus-host disease-related bronchiectasis[32], bronchiectasis seems to be a dynamic inflammatory process that can, at least partially, be reversed. Because neither cartilage nor small vessels are found in the wall of small bronchioles, the disease's pathophysiology is likely not related to genuine vasculitic manifestations. Yet, a plausible explanation could be the activation of neutrophils by ANCA in the lumen of bronchi, thus triggering bronchial inflammation[33]. On the other hand, in B-AAV patients, analogous to chronic *Staphylococcus aureus* nasal carriage in GPA, chronic bronchial suppuration might be a contributing factor to the development of autoimmunity and AAV onset. Strikingly, and in line with this hypothesis, Pearce, *et al* demonstrated in a case-control study involving 757 GPA patients and 7546 controls that GPA patients were 5 times more likely than controls to have a previous diagnosis of bronchiectasis (OR 5.1, 95% CI 2.7–9.4; $P < 0.0001$), even when patients were diagnosed with bronchiectasis more than 5 years before vasculitis onset[11]. Unfortunately, given the retrospective design of our present study, cytobacteriological examination of the sputum was not performed sequentially, and further longitudinal microbiological studies would be of paramount interest to better decipher the interplay between bacteriological findings and bronchiectasis onset and/or worsening.

The rates of bronchiectasis reported in patients with AAV are highly variable from one study to another. In our present study,

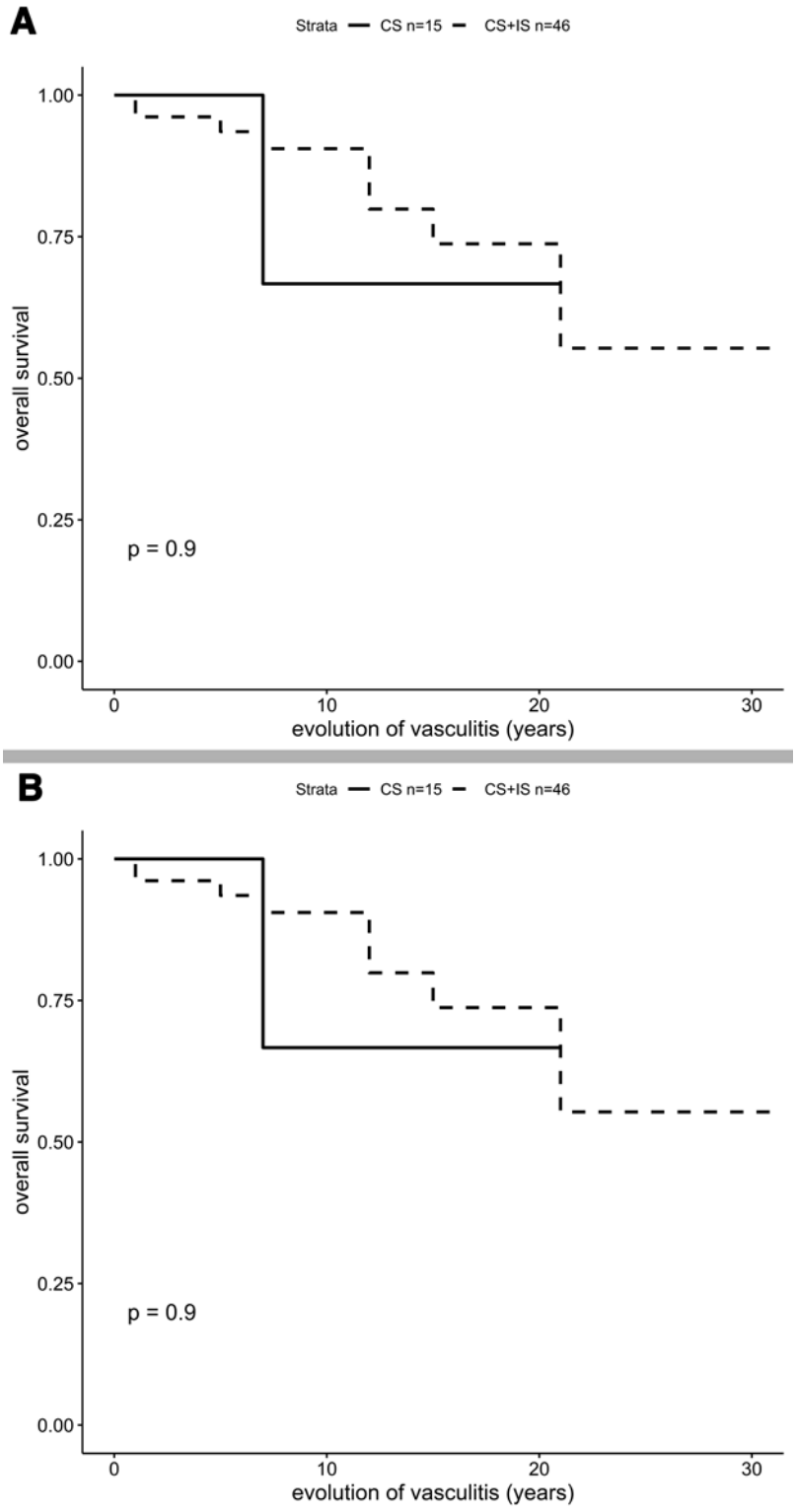

Figure 1. Kaplan-Meier survival curves of patients with AAV-associated bronchiectasis according to (A) the first disease manifestation: AAV ("AAV-B," thick line) or bronchiectasis ("B-AAV," dashed line); and (B) the treatment regimen during follow-up: glucocorticoids alone ("CS alone," thick line) or glucocorticoids in combination with cyclophosphamide and/or rituximab ("CS + CYC/RTX", dashed line). AAV: antineutrophil cytoplasmic antibody-associated vasculitis; B: bronchiectasis; CS: corticosteroids; CYC: cyclophosphamide; IS: immunosuppressive agent CYC and/or RTX; RTX: rituximab.

Table 3. Patients' long-term outcomes according to whether bronchiectasis occurred before AAV.

First Diagnosis	All, n = 61	B-AAV, n = 25	AAV-B, n = 36	*P*
AAV follow-up, yrs, median (IQR)	7 (4–13)	7 (4–12)	7 (3–14)	1
AAV relapse, n (%)	26 (43)	12 (48)	14 (39)	0.4
Median no. AAV relapses, (IQR)	0 (0–1)	0.5 (0–1)	0 (0–1)	0.5
Death, n (%)	9 (15)	7 (28)	2 (6)	**0.03**
Overall survival during AAV follow-up, %				**0.03**
5 yrs	97	96	97	–
10 yrs	89	62	93	–
Median absolute variation of Bhalla score, point (IQR), n = 37	1 (0–4)	2.5 (0.25–3)	1 (0–4.5)	0.7
Variation of Bhalla score, n (%), n = 37				0.3
Degradation	22 (59.5)	10 (71.5)	12 (52)	
Stability	9 (24.5)	3 (21.5)	6 (26)	
Improvement	6 (16)	1 (7)	5 (22)	
Median absolute variation of FEV1 (IQR), n = 16	–4.5 (–14, 4.5)	1 (–6, 5)	–10 (–18, 2)	0.2
Median annual infection rate (IQR)	0.2 (0–0.35)	0.1 (0–0.7)	0.2 (0–0.4)	0.5
P. aeruginosa colonization, n (%)	18 (29.5)	9 (33)	8 (29.5)	0.8

Values in bold face are statistically significant. ANCA: antineutrophil cytoplasmic antibodies; AAV: ANCA-associated vasculitis; B: bronchiectasis; AAV-B: bronchiectasis post vasculitis; B-AAV: bronchiectasis before vasculitis; FEV: forced expiratory volume in 1 s; *P. aeruginosa*: *Pseudomonas aeruginosa.*

a high-resolution CT scan was not mandatory at enrollment in the FVSG database, and it was not a queryable menu item — the most likely explanations for the low rate reported herein, which is likely to be considerably underestimated. Moreover, in another large series of patients with AAV, bronchiectasis was found in 21% of patients with AAV and considered severe in 2%[8]. More recently, in a monocentric retrospective study of French AAV patients with available chest CT scans (and that did not overlap with the present work), the prevalence of ANCA-associated bronchiectasis was reported as high as 38% (n = 22/58) of AAV patients, although the severity of bronchiectasis was not specified[9]. Further large-scale studies with systematic implementation of chest CT are warranted to better assess the epidemiology and true burden of AAV-associated bronchiectasis.

There are no guidelines available for the management of patients with both bronchiectasis and AAV. Interestingly, AAV relapse had a protective effect toward the deterioration of bronchiectasis, but treatment with either CYC or RTX was not associated with improved survival, and the same conclusions were drawn when specifically studying highest-risk patients (i.e., B-AAV subgroup). Hence, to date there is no rationale for AAV treatment escalation based only on the presence of bronchiectasis. Conversely, given the low annual infection rates (that tend to be the same as those of patients with AAV but without bronchiectasis) reported in both the present study and that of Néel, *et al*[9], the presence of bronchiectasis (even with bronchorrhea or mucoid impaction on chest CT) should not prevent the use of potent immunosuppressive drugs, when required. Yet, a study of 192 patients with AAV treated with RTX suggested that the presence of bronchiectasis was associated with a 6-fold increased risk of severe respiratory tract infections[34]. Moreover, life-threatening nontuberculous mycobacterial infections have also been reported in this setting[35]. Hence, we recommend that all patients receive influenza and pneumococcal vaccinations[36], ideally at a time when they are treated with neither CYC nor RTX, which reduce the vaccination's immunogenicity[37]. Because of their antimicrobial and antiinflammatory properties, both cotrimoxazole and azithromycin deserve to be investigated in this setting, particularly in patients with frequent acute exacerbations[30,38,39]. Last, although ciprofloxacin was used in combination with wide-spectrum beta-lactams in selected cases of patients with acute infection related to *P. aeruginosa*, fluoroquinolones were never prescribed in the long term, to prevent antimicrobial drug resistance.

We acknowledge some limitations of our study, such as its retrospective design, the small sample of patients, and the limited number of events, which did not enable multivariate analysis in some cases. Last, because both vasculitis and bronchial disease were diagnosed concomitantly in 12 AAV-B patients, we cannot rule out that some of the patients with concomitant diagnosis already had long-lasting mild bronchiectasis and thus were misclassified. Yet bronchiectasis is seldom asymptomatic, and the comparison of 3 subgroups (i.e., B-AAV vs AAV-B vs patients with concomitant diagnoses of both bronchiectasis and AAV) yielded the same results, with MPA, neurologic involvement, and MPO positivity being more frequent in the B-AAV subgroup (the latter patients also presenting higher mortality rates; data not shown). Moreover, such dichotomization tends to reflect daily practice, with bronchiectasis being diagnosed either by pulmonologists (prior to AAV onset), or by AAV-treating physicians during vasculitis follow-up, in patients previously free from respiratory symptoms. For the sake of completeness, crude

Table 4. Factors associated with bronchiectasis worsening.

Variables	Bronchiectasis Worsening, HR (95% CI)	*P*	Bronchiectasis Worsening, Adjusted HR* (95% CI)	*P*
Age at AAV diagnosis	1.046 (1.005–1.088)	0.03	1.06 (0.9–1.7)	0.10
Age at B diagnosis	1 (0.98–1.017)	0.7	–	
Sex (male)	1.5 (0.5–4.6)	0.5	–	
Tobacco use	1.6 (0.6–4.5)	0.3	–	
B-AAV	1.7 (0.7–3.9)	0.2	–	
AAV				
GPA	0.7 (0.3–1.7)	0.4	–	
MPA	1.3 (0.6–3.1)	0.5	–	
ANCA specificity				
MPO	2.5 (0.9–7.1)	0.08	0.12 (0.01–1.8)	0.10
PR3	0.8 (0.3–2.3)	0.6	–	
Symptoms and manifestation, n (%)				
Weight loss	1.3 (0.5–3)	0.6	–	
Arthralgia	2.8 (0.99–7.8)	0.052	44.6 (1.7–1199.2)	0.02
Respiratory	0.7 (0.3–1.7)	0.4	–	
ENT	0.6 (0.2–1.3)	0.2	–	
Neurologic	0.8 (0.3–1.8)	0.5	–	
Renal	0.5 (0.1–2.1)	0.3	–	
BVAS	1 (0.93–1.1)	0.9	–	
FFS 1996	0.8 (0.4–1.4)	0.4	–	
Baseline Bhalla score > 9	1.1 (0.4–2.9)	0.8	–	
Baseline FACED score > 4	3.4 (0.8–15)	0.1	0.02 (0.0003–1.4)	0.07
Radiologic findings				
Nodules	1.6 (0.7–3.7)	0.3		
Interstitial lung disease	7.3 (0.8–63.1)	0.1		
AAV relapse	0.6 (0.4–0.99)	0.049	0.01 (0.0002–0.5)	0.02
Annual infection rate	1.8 (0.7–4.4)	0.2	–	
P. aeruginosa colonization	0.7 (0.2–1.9)	0.5	–	
Use of azithromycin	0.8 (0.3–2.5)	0.7	–	
Use of cotrimoxazole	0.9 (0.3–2.2)	0.8	–	
Immunosuppressants	0.4 (0.1–1.4)	0.1	–	
Cyclophosphamide	0.6 (0.2–2.1)	0.4	–	
Rituximab	0.8 (0.3–2)	0.6	–	
Mycophenolate mofetil	1.3 (0.5–3.5)	0.7	–	
Azathioprine	1.2 (0.5–2.9)	0.6	–	

* Cox proportional hazard model adjusted using variables with $P < 0.2$ in univariable analysis. ANCA: antineutrophil cytoplasmic antibodies; AAV: ANCA-associated vasculitis; B: bronchiectasis; BVAS: Birmingham Vasculitis Activity Score; FACED: FEV1, age, chronic *P. aeruginosa* colonization, extension, and dyspnea; FFS: Five-Factor Score; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; *P. aeruginosa*: *Pseudomonas aeruginosa*.

data of patients according to both vasculitides' phenotypes and ANCA specificity are also presented in Supplementary Tables 1 and 2 (available with the online version of this article).

Our findings suggest that the association of bronchiectasis with ANCA and vasculitis may not be accidental, especially among patients with MPO-ANCA and/or MPA. Two clinical phenotypes seem to coexist, according to the timeline between both bronchiectasis and AAV diagnoses. Bronchiectasis is usually a mild disease, but patients in which bronchiectasis precedes the diagnosis of AAV tend to have a poorer prognosis. Last, ANCA serology should be part of the diagnostic investigation of patients with newly diagnosed bronchiectasis, and because systemic vasculitis is likely to occur even decades after the diagnosis of bronchial disease, pulmonologists should look for nonrespiratory (especially neurological) manifestations of AAV.

ACKNOWLEDGMENT

We thank the members of both the French Vasculitis Study Group and the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires for their help in data collection.

Table 5. Factors associated with death during patient follow-up.

Variables	HR* for Risk Factor of Death (95% CI)	*P*
Age at AAV diagnosis	1.2 (1.1–1.3)	0.003
Age at B diagnosis	0.99 (0.97–1.02)	0.6
Sex (male)	1.7 (0.4–7)	0.4
Tobacco use	1.4 (0.3–5.5)	0.7
AAV		
GPA	0.1 (0.01–0.7)	0.02
MPA	18.1 (2.2–146.3)	0.01
ANCA specificity		
MPO	3.6 (0.7–18.4)	0.1
PR3	0.5 (0.1–3.9)	0.5
B-AAV vs others	5.8 (1.2–28.7)	0.03
Symptoms and manifestations, n (%)		
Weight loss	1.2 (0.3–4.6)	0.8
Arthralgia	1.1 (0.3–4)	0.9
Respiratory	0.8 (0.2–3.3)	0.8
ENT	0.1 (0.01–0.6)	0.01
Neurologic	2.8 (0.6–13.7)	0.2
Renal	3.1 (0.7–13.2)	0.1
BVAS	1 (0.98–1.13)	0.7
FFS 1996	1.2 (0.5–2.8)	0.7
Baseline Bhalla score	1.1 (0.9–1.3)	0.5
Baseline FACED score > 4	1.8 (0.2–17)	0.6
Radiologic findings		
Nodules	1.3 (0.3–5.9)	0.7
Interstitial lung disease	0 (0–∞)	1
AAV relapse	0.5 (0.2–1.3)	0.2
Annual infection rate	1.7 (0.4–7)	0.5
P. aeruginosa colonization	1.4 (0.4–5.2)	0.6
Use of azithromycin	1.3 (0.3–6.5)	0.7
Use of cotrimoxazole	2 (0.5–8.5)	0.3
Immunosuppressants	0.9 (0.1–7.1)	0.9
Cyclophosphamide	0.6 (0.1–3)	0.5
Rituximab	0 (0–∞)	1
Mycophenolate mofetil	1.3 (0.3–6.3)	0.8
Azathioprine	2.18 (0.5–8.8)	0.3

AAV: antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; B: bronchiectasis; B-AAV: bronchiectasis before AAV; BVAS: Birmingham Vasculitis Activity Score; FACED : FEV1, age, chronic *P. aeruginosa* colonization, extension, and dyspnea; FEV1: forced expiratory volume in 1 s; FFS: Five-Factor Score; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; *P. aeruginosa*: *Pseudomonas aeruginosa*.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Kallenberg CG. Pathogenesis of ANCA-associated vasculitides. Ann Rheum Dis 2011;70:i59-63.
2. Brillet PY, Brauner M. [Pulmonary imaging in ANCA-associated vasculitides]. [Article in French] Presse Medicale 2007;36:907-12.
3. Hervier B, Pagnoux C, Agard C, Haroche J, Amoura Z, Guillevin L, et al. Pulmonary fibrosis associated with ANCA-positive vasculitides. Retrospective study of 12 cases and review of the literature. Ann Rheum Dis 2009;68:404-7.
4. Comarmond C, Crestani B, Tazi A, Hervier B, Adam-Marchand S, Nunes H, et al. Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a series of 49 patients and review of the literature. Medicine 2014;93:340-9.
5. Alba MA, Flores-Suárez LF, Henderson AG, Xiao H, Hu P, Nachman PH, et al. Interstitial lung disease in ANCA vasculitis. Autoimmun Rev 2017;16:722-9.
6. Kadowaki T, Yano S, Yamadori I, Araki K, Kimura M, Wakabayashi K, et al. A case of sinobronchial syndrome complicated with myeloperoxidase antineutrophil cytoplasmic antibody associated vasculitis: review of the literature. Intern Med 2012;51:763-7.
7. Koninck JC, Diot E, Hazouard E, Machet MC, Valentin JF, Lemarie E, et al. [Bronchectasia and microscopic polyangeitis]. [Article in French] Rev Pneumol Clin 2002;58:290-5.
8. Mohammad AJ, Mortensen KH, Babar J, Smith R, Jones RB, Nakagomi D, et al. Pulmonary involvement in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: the influence of ANCA subtype. J Rheumatol 2017;44:1458-67.
9. Néel A, Espitia-Thibault A, Arrigoni PP, Volteau C, Rimbert M, Masseau A, et al. Bronchiectasis is highly prevalent in anti-MPO ANCA-associated vasculitis and is associated with a distinct disease presentation. Semin Arthritis Rheum 2018;48:70-6.
10. Lhote R, Theodore C, Issoufaly T, Francois D, Kahn JE, Guillevin L, et al. Successful treatment of antineutrophil cytoplasmic antibody-associated bronchiectasis with immunosuppressive therapy. Eur Respir J 2015;46:554-7.
11. Pearce FA, Lanyon PC, Watts RA, Grainge MJ, Abhishek A, Hubbard RB. Novel insights into the aetiology of granulomatosis with polyangiitis-a case-control study using the Clinical Practice Research Datalink. Rheumatology 2018;57:1002-10.
12. Lachenal F, Nkana K, Nove-Josserand R, Fabien N, Durieu I. Prevalence and clinical significance of auto-antibodies in adults with cystic fibrosis. Eur Respir J 2009;34:1079-85.
13. Carlsson M, Eriksson L, Pressler T, Kornfält R, Mared L, Meyer P, et al. Autoantibody response to BPI predict disease severity and outcome in cystic fibrosis. J Cyst Fibros 2007;6:228-33.
14. Wada Y, Kuroda T, Murasawa A, Nakano M, Narita I. Anti-neutrophil cytoplasmic autoantibodies against bactericidal/permeability-increasing protein in patients with rheumatoid arthritis and their correlation with bronchial involvement. Mod Rheumatol 2010;20:252-6.
15. Puéchal X, Génin E, Bienvenu T, Le Jeunne C, Dusser DJ. Poor survival in rheumatoid arthritis associated with bronchiectasis: a family-based cohort study. PLoS One 2014;9:e110066.
16. Barker AF. Bronchiectasis. N Engl J Med 2002;346:1383-93.
17. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.
18. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
19. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007;66:222-7.
20. Bossuyt X, Cohen Tervaert JW, Arimura Y, Blockmans D, Flores-Suárez LF, Guillevin L, et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol

2017;13:683-92.
21. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87:671-8.
22. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum 2001;44:912-20.
23. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine 1996;75:17-28.
24. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, Giron RM, Maiz Carro L, de la Rosa Carrillo D, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. Eur Respir J 2014;43:1357-67.
25. Bhalla M, Turcios N, Aponte V, Jenkins M, Leitman BS, McCauley DI, et al. Cystic fibrosis: scoring system with thin-section CT. Radiology 1991;179:783-8.
26. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. Eur Respir J 2017;49:1700214.
27. Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2007;66:605-17.
28. Cottin V, Bel E, Bottero P, Dalhoff K, Humbert M, Lazor R, et al. Revisiting the systemic vasculitis in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Autoimmun Rev 2017;16:1-9.
29. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Non-CF Bronchiectasis Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010;65:577.
30. Araújo D, Shteinberg M, Aliberti S, Goeminne PC, Hill AT, Fardon T, et al. Standardised classification of the aetiology of bronchiectasis using an objective algorithm. Eur Respir J 2017;50:1701289.
31. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J 2017;50:1700629.
32. Loiseau C, Lemonnier F, Randrianarivelo O, Itzykson R, Nguyen S, Hélène Becquemin M, et al. Home spirometry in bronchiolitis obliterans post allogeneic haematopoietic cell transplant. Eur Respir J 2018;52:1702328.
33. Cobanoğlu N, Ozcelik U, Cetin I, Yalçin E, Doğru D, Kiper N, et al. Anti-neutrophil cytoplasmic antibodies (ANCA) in serum and bronchoalveolar lavage fluids of cystic fibrosis patients and patients with idiopathic bronchiectasis. Turk J Pediatr 2010;52:343-7.
34. Kronbichler A, Kerschbaum J, Gopaluni S, Tieu J, Alberici F, Jones RB, et al. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2018;77:1440-7.
35. Barba T, Khouatra C, Traclet JJ, Cordier JF, Cottin V. Diffuse bronchiectasis and airflow obstruction in granulomatosis with polyangiitis. Sarcoidosis Vasc Diffuse Lung Dis 2018;35:81-4.
36. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-18.
37. Groh M, Puéchal X, Terrier B, Le Jeunne C, Batteux F, Launay O. Failure of pneumococcal immunization during remission induction treatment of ANCA-associated vasculitis: The Pneumovas Pilot 1 study. Joint Bone Spine 2017;84:643-4.
38. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. Eur Respir J 2013;42:239-51.
39. Chalmers JD, Polverino E; European Respiratory Society Bronchiectasis Guidelines Task Force. Macrolides, mucoactive drugs and adherence for the management of bronchiectasis. Eur Respir J 2018;51:1702033.