Editorial

What Have We Learned About Bronchiectasis From RIBRON (Spanish Bronchiectasis Registry)?

Bronchiectasis is one of the most common chronic inflammatory airway diseases.[1] It is characterized by a mixed (though predominantly neutrophilic) bronchial inflammatory pattern,[2–4] usual chronic bronchial infection by pathogenic microorganisms,[5,6] several exacerbations with an infectious profile[7] and great clinical heterogeneity, since bronchiectasis can have more than one hundred aetiologies, both pulmonary and extrapulmonary.[7] Up to less than two decades ago, there were no national or international management guidelines or registries for this disease anywhere in the world. Accordingly, the enormous lack of scientific evidence on its treatment led it to be considered an orphan disease. Even now, despite significant advances in our understanding of bronchiectasis and its therapy, and the publication of several specific guidelines and registries, some key aspects of the disease still remain unknown. In fact, many of the recommendations in the various guidelines continue to present evidence that does not go beyond an «expert consensus».[8–11]

The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) has been a pioneer in the study of this disease. In fact, the first bronchiectasis guidelines in the world were published by SEPAR, in 2008 (later reissued in 2018),[12] and these marked a significant advance in the management of the disease in Spain. Similarly, SEPAR also promoted the world's first national bronchiectasis registry, a historical registry that was launched in 2002 and closed in 2011, after collecting cross-sectional data from more than 2000 patients in 36 Spanish centres.[13] Thanks to this registry, we have been familiar with the peculiarities of bronchiectasis in our country for more than 20 years.

This was followed in 2015 by the ground-breaking creation of the Computerized Registry of Bronchiectasis (RIBRON), which is still active.[14] The great advantage of this registry is that, in addition to collecting cross-sectional data, a greater number of variables and longitudinal data were also collected prospectively (it currently includes patients with data covering more than eight years of follow-up). This has allowed us not only to analyse how the fundamental characteristics of bronchiectasis differed in comparison to those recorded by the historical registry but also to better understand its natural history. At present, RIBRON contains data from more than 2600 patients, so it can be considered one of the largest national registries in the world (the world's largest registry is the European EMBARC registry, with more than 17,000 patients, in which SEPAR has actively participated, mainly through patients also included in RIBRON).[15]

The scientific output of SEPAR's bronchiectasis registries has been of enormous importance, via the analysis and subsequent publication in international journals of features related to various dimensions of the disease, including comorbidities and aetiological, clinical–functional, pathophysiological, diagnostic, microbiological, nutritional, prognostic and therapeutic aspects.

For example, a preliminary analysis of 2047 patients with bronchiectasis from the historical record established that, in Spain, the mean age of patients with this disease was 64.9 years, with 54.9% of them being women, and that the most frequent aetiologies were post-infectious (30% of cases) and idiopathic (22.4%).[13] Moreover, it was observed that between 2002 and 2011 the diagnostic delay from the onset of symptoms was 12.2 years, this being more pronounced in women,[16] while in the period 2015–2022 the diagnostic delay decreased significantly to 6.2 years and idiopathic aetiology also decreased (to 18.9%). These decreases could possibly be explained by the implementation of the Spanish guidelines for the management of bronchiectasis, and the clear algorithm for carrying out an aetiological diagnosis recommended therein.[17] One crucial aetiological aspect was the finding that those patients with bronchiectasis who presented COPD as a comorbidity registered the highest mortality, despite not presenting a different microbiological profile.[18]

Another feature that has been studied extensively on the basis of data from RIBRON is peripheral biomarkers, both cellular and molecular. In the case of cellular biomarkers, various cluster studies have established that patients with neutrophilia[19] or a higher neutrophil/lymphocyte ratio[20] presented greater severity of bronchiectasis (according to the values of the validated multidimensional severity systems) and a greater number and severity of exacerbations. The role of the peripheral eosinophil count as a marker of severity and response to treatment has been closely examined. In this respect, a U-shaped relationship between the number of peripheral eosinophils and the severity of bronchiectasis was established for the first time in the literature in a large series of patients with bronchiectasis.[21] Thus, both the presence of peripheral eosinopenia (less than 50 eosinophils/μL)[22] and of eosinophilia (more than 300 eosinophils/μL)[21] were associated with greater disease severity and more frequent exacerbations. Furthermore, it was observed, for the first time, that treatment with inhaled corticosteroids was effective in reducing exacerbations in bronchiectasis only in those patients with peripheral eosinophilia, even after excluding patients with asthma and other eosinophilic diseases.[21] Meanwhile, the analysis of the role of peripheral eosinophils in

patients with bronchiectasis is still ongoing, based on data derived from the registry. When it comes to non-cellular biomarkers, the value of the peripheral C-reactive protein (CRP) concentration (especially with values higher than 4.2 mg/L) was associated with a greater risk of future exacerbations.[23] Moreover, Wang et al. observed, using a cluster analysis, that the cluster with the greatest severity of bronchiectasis, according to the multidimensional grade system, presented a higher degree of markers of systemic inflammation, such as leukocytes, platelets, CRP, erythrocyte sedimentation rate, fibrinogen and lower values of lymphocytes, albumin and total protein concentration.[24]

Finally, from a microbiological point of view, two studies based on the data provided by RIBRON have been especially important. On the one hand, the largest study to date on the impact of *Pseudomonas aeruginosa* (PA) infection on lung function decline was conducted in 849 patients with bronchiectasis and at least two spirometric studies, supported by a follow-up range of 1–4 years and the completion of more than 2200 tests. Patients with PA infection presented a greater decline in lung function than those without the isolation of this microorganism (-1.37% (52.1 mL) vs -0.37% (-24.6 mL); $p < 0.001$).[25] On the other hand, Garcia-Clemente et al. confirmed that PA is not the only microorganism that can cause an accelerated decline in lung function. Thus, chronic bronchial infection by *Staphylococcus aureus* could also be associated with spirometric impairment, as seen when such patients were compared with those in whom no pathogenic microorganism had ever been isolated -1.19% (CI: -2.09, -0.69; $p < 0.001$) vs -0.02% (CI: -0.07, -0.01; $p = 0.918$).[26]

In short, both the historical registry and, more particularly, the RIBRON registry of bronchiectasis have represented (and continue to represent) a very important advance in the understanding of this disease in our country. Longitudinal information continues to be collected, especially on important outcomes such as mortality and the effect of specific treatments,[27,28] as well as the impact on the lung microbiome,[29] enabling us to analyse more fully some of the many scientific unknowns that still surround bronchiectasis today.

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Conflict of interests

None of the authors declares any conflict of interest.

References

1. Chalmers JD, Chotirmall SH. Bronchiectasis: new therapies and new perspectives. Lancet Respir Med. 2018;6:715–26.
2. Martínez-García MÁ. Bronchiectasis and eosinophils. Arch Bronconeumol. 2021;57:671–2.
3. García-Río F, Alcázar-Navarrete B, Castillo-Villegas D, Cilloniz C, García-Ortega A, Leiro-Fernández V, et al. Biological biomarkers in respiratory diseases. Arch Bronconeumol. 2022;58:323–33.
4. Long MB, Chalmers JD. Treating neutrophilic inflammation in airways diseases. Arch Bronconeumol. 2022;58:463–5.
5. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of *Pseudomonas aeruginosa* colonization on prognosis in adult bronchiectasis. Ann Am Thorac Soc. 2015;12:1602–11.
6. Solarat B, Perea L, Faner R, de La Rosa D, Martínez-García MA, Sibila O. Pathophysiology of chronic bronchial infection in bronchiectasis. Arch Bronconeumol. 2023;59:101–8.
7. Scioscia G, Alcaraz-Serrano V, Méndez R, Gabarrús A, Fernández-Barat L, Menéndez R, et al. Factors associated with one-year mortality in hospitalised patients with exacerbated bronchiectasis. Arch Bronconeumol. 2022;58:773–5.
8. De la Rosa D, Prados C. Epidemiología y diversidad geográfica de las bronquiectasas. Open Respir Arch. 2020;2:102–12.
9. 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.
10. Martínez-García MA, Maiz L, Olveira C, Giron RM, de la Rosa D, Blanco M, et al. Spanish guidelines on the treatment of bronchiectasis in adults. Arch Bronconeumol. 2018;54:88–98.
11. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn S, Floto RA, et al. British thoracic society guidelines for bronchiectasis in adults. Thorax. 2019;74:1–69.
12. Vendrell M, de Gracia J, Olveira C, Martinez-Garcia MA, Giron R, Maiz L, et al. Diagnosis and treatment of bronchiectasis. Arch Bronconeumol. 2008;44:629–40.
13. Olveira C, Padilla A, Martinez-Garcia MA, de la Rosa D, Giron RM, Vendrell M, et al. Etiology of bronchiectasis in a cohort of 2047 patients. An analysis of the Spanish historical bronchiectasis registry. Arch Bronconeumol. 2017;53:366–74.
14. Martinez-García MA, Villa C, Dobarganes Y, Girón R, Maíz L, García-Clemente M, et al. RIBRON: the Spanish online bronchiectasis registry. Characterization of the first 1912 patients. Arch Bronconeumol. 2021;57:28–35.
15. Chalmers JD, Polverino E, Crichton ML, Ringhausen FC, De Soyza A, Vendrell M, et al. Bronchiectasis in Europe: data on disease characteristics from the European bronchiectasis registry (EMBARC). Lancet Respir Med. 2023, http://dx.doi.org/10.1016/S2213-2600(23)00093-0.
16. Giron RM, de Gracia J, Olveira C, Vendrell M, Martinez-Garcia MA, de la Rosa D, et al. Sex bias in diagnostic delay in bronchiectasis: an analysis of the Spanish historical registry of bronchiectasis. Chron Respir Dis. 2017;14:360–9.
17. Martínez-García MA, Maiz L, Olveira C, Giron RM, de la Rosa D, Blanco M, et al. Spanish guidelines on the evaluation and diagnosis of bronchiectasis in adults. Arch Bronconeumol. 2018;54:79–87.
18. De la Rosa D, Martinez-Garcia MA, Giron RM, Vendrell M, Olveira C, Borderias L, et al. Clinical impact of chronic obstructive pulmonary disease on non-cystic fibrosis bronchiectasis. A study on 1790 patients from the Spanish bronchiectasis historical registry. PLOS ONE. 2017;12, http://dx.doi.org/10.1371/journal.pone.0177931, e0177931.
19. Wang X, Olveira C, Giron R, Garcia-Clemente M, Maiz L, Sibila O, et al. Blood neutrophil counts define specific clusters of bronchiectasis patients: a hint to differential clinical phenotypes. Biomedicines. 2022;10:1044, http://dx.doi.org/10.3390/biomedicines10051044.
20. Martinez-Garcia MA, Olveira C, Giron R, Garcia-Clemente M, Maiz L, Sibila O, et al. Peripheral neutrophil-to-lymphocyte ratio in bronchiectasis: a marker of disease severity. Biomolecules. 2022;12:1399, http://dx.doi.org/10.3390/biom12101399.
21. Martinez-Garcia MA, Mendez R, Olveira C, Girón R, Garcia-Clemente M, Maiz L, et al. The U-shaped relationship between eosinophil count and bronchiectasis severity: the effect of inhaled corticosteroids. Chest. 2023, http://dx.doi.org/10.1016/j.chest.2023.04.029.
22. Wang X, Villa C, Dobarganes Y, Olveira C, Girón R, García-Clemente M, et al. Phenotypic clustering in non-cystic fibrosis bronchiectasis patients: the role of eosinophils in disease severity. Int J Environ Res Public Health. 2021;18:8431.
23. Posadas T, Oscullo G, Zaldivar E, Villa C, Dobarganes Y, Girón R, et al. C-reactive protein concentration in steady-state bronchiectasis: prognostic value of future severe exacerbations. Data from the Spanish registry of bronchiectasis (RIBRON). Arch Bronconeumol. 2021;57:21–7.
24. Wang X, Villa C, Dogarganes Y, Olveira C, Giron R, Garcia-Clemente M, et al. Differences in nutritional status and inflammatory biomarkers between female and male patients with bronchiectasis: a large-cohort study. Biomedicines. 2021;9:905, http://dx.doi.org/10.3390/biomedicines9080905.
25. Martinez-Garcia MA, Oscullo G, Posadas T, Zaldivar E, Villa C, Dobarganes Y, et al. *Pseudomonas aeruginosa* and lung function decline in patients with bronchiectasis. Clin Microbiol Infection. 2021;27:428–34.
26. Garcia Clemente M, Olveira C, Giron R, Maiz L, Sibila O, Golpe R, et al. Impact of chronic bronchial infection by *Staphylococcus aureus* on bronchiectasis. J Clin Med. 2022;11:3960, http://dx.doi.org/10.3390/jcm11143960.
27. De la Rosa Carrillo D, Martínez-García MÁ, Barreiro E, Tabernero Huguet E, Costa Sola R, García-Clemente MM, et al. Effectiveness and safety of inhaled antibiotics in patients with chronic obstructive pulmonary disease. A multicentre observational study. Arch Bronconeumol. 2022;58:11–21.
28. Alcaraz-Serrano V, Lee AL, Gimeno-Santos E. Respiratory physiotherapy and bronchiectasis. Arch Bronconeumol. 2022;58:377–8.
29. Aogáin MM, Jaggi TK, Chotirmall SH. The airway microbiome: present and future applications. Arch Bronconeumol. 2022;58:8–10.

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