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Asthma, bronchiectasis, and chronic obstructive pulmonary disease: the Bermuda Triangle of the airways

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Also known as the Devil's Triangle or Hurricane Alley, the Bermuda Triangle is an area of the Atlantic Ocean with vertices in Miami, San Juan de Puerto Rico, and Bermuda, which has been credited for causing mass disappearances and a number of wrecks over the years. While people love to throw around conspiracy theories about each of these Bermuda Triangle stories, there may be perfectly logical explanations for all of them.[1] A resemblance of the Bermuda Triangle to airway diseases can be made. Asthma, bronchiectasis, and chronic obstructive pulmonary disease (COPD) are the three most prevalent chronic inflammatory airway diseases.[2] It is estimated that 5%–10% of the general all-ages population suffers from asthma,[3] and 8%–10% of adults suffer from COPD.[4,5] The prevalence of bronchiectasis is largely unknown, but it is estimated that it can affect 350 to 500 individuals per 100,000 inhabitants, especially in the elderly.[6,7] It is widely recognized that these three diseases are greatly underdiagnosed.[8]

Although asthma and COPD are well-known diseases for most physicians, bronchiectasis is less known. Bronchiectasis is characterized by the bronchial lumen dilatation due to the progressive destruction of the bronchial wall because of a vicious circle of airway inflammation and chronic infection. Both inflammation (usually neutrophilic) and infection (usually of bacterial origin) cause an excess production of proteolytic molecules, which cause this irreversible destruction of the bronchial wall and systemic inflammation.[9] Bronchiectasis is clinically characterized by the presence of usual expectoration, sometimes with a mucopurulent component, isolation of pathogenic microorganisms (PM) in respiratory samples (*Pseudomonas aeruginosa* being the most associated with greater severity and worse prognosis), and multiple exacerbations of an infectious origin.[10,11] Bronchiectasis can be caused by dozens of pulmonary and extrapulmonary diseases, although its cause is unknown in 30%–50% of cases (idiopathic bronchiectasis).[7]

Therefore, bronchial inflammation is a pathophysiological necessary phenomenon of all three diseases. Importantly, their inflammatory characteristics vary widely, from a more frequently eosinophilic profile in asthma to predominantly neutrophilic in COPD and bronchiectasis. However, on the one hand there is evidence suggesting the existence of multiple combinations such as neutrophilic asthma,[12] eosinophilic bronchiectasis[13,14] and COPD with eosinophilia,[15-18] which also have a significant therapeutic impact. On the other hand, bacterial bronchial infection (often chronic) is a frequent (but not necessary) finding in COPD and bronchiectasis.[19-21]

One of the most striking findings about these three diseases is that, despite having in most cases a different origin, they overlap with a frequency that goes beyond the mere crossing of probabilities due to their high individual prevalence in the general population. Although there is no study that clearly demonstrates a causal relationship that explains these two-by-two relationships, several authors insist that this combined-disorders exist, generating three groups of "overlap" patients. With all likelihood, such overlapping patients require a different therapeutic approach, since some of the treatments usually used in each of these diseases are not recommended in others (some are even contraindicated). Therefore, early recognition of such patients with bronchiectasis-COPD overlap syndrome (BCOS), bronchiectasis-asthma overlap syn-

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drome (BAOS) and asthma-COPD overlap (ACO) is essential[22-24] [Supplementary Figure 1, http://links.lww.com/CM9/B110].

BCOS: Between 30% and 50% of patients with severe COPD present with bronchiectasis not attributable to any other etiology.[25] A recent study suggests that these bronchiectasis are part of the natural history of COPD in advanced stages, especially in those individuals with multiple exacerbations, higher bronchial inflammation (usually manifested by an increase in the quantity or purulence of sputum), and/or the isolation of PM in respiratory samples (usually sputum).[26] Among the hypotheses that attempt to explain a possible causal relationship between COPD and bronchiectasis is that of "*fall and rise*". Possibly in patients with advanced COPD in which there is a greater number of exacerbations, some PMs continue to infect the airways of some predisposed individuals after a period of exacerbation despite antibiotic treatment or the immune defense mechanisms. Both the persistence of these PM (chronic bronchial infection) and the inflammation generated by them produce an excess of proteolytic substances that is not compensated by local anti-inflammatory mechanisms. In these circumstances, the well-known "*Cole's vicious circle*" of bronchiectasis generation can be activated, whereby the proteolytic products generated both by the inflammation (fundamentally neutrophilic elastases) and by the bacteria themselves could destroy the bronchial wall to the point of dilating the bronchial lumen and, as a consequence generating bronchiectasis.[24] Several studies show that the presence of bronchiectasis in these patients with COPD is related to a worse prognosis.[27] For this reason, experts insist on the need to perform a computed tomography (diagnostic test of choice for bronchiectasis) in these more severe COPD patients.[28-31]

From a therapeutic perspective, international guidelines for both COPD and bronchiectasis highlight some key points: (1) Both diseases must be treated independently, following their individual guidelines; (2) inhaled corticosteroids (ICS), while indicated in some patients with COPD, should be avoided as much as possible in the presence of bronchiectasis, especially if there is chronic bronchial infection. The use of macrolides at immunomodulatory doses may be a valid anti-inflammatory alternative in these patients.[31-33] The role of eosinophilia as a marker of ICS response or side effects in patients with BCOS remains unclear.

BAOS: The prevalence of bronchiectasis in patients with asthma is lower than in severe COPD, but it is estimated in 20% of severe asthma.[34] It is still unknown how eosinophilic inflammation can generate bronchiectasis, although eosinophils also have antibacterial and pro-inflammatory proteolytic capacity with the secretion of some metalloproteases,[1,2,9] eosinophil cationic protein, and some elastases and collagenases.[35] Although the existing evidence is less than in the case of BCOS, some authors agree that the presence of bronchiectasis induces lack of control of asthma and a greater number of exacerbations.[35] A characteristic asthma clinical phenotype could be observed: severe long-lasting asthma, sometimes neutrophilic (non-atopic), smoker, with worse pulmonary function and greater requirement for bronchodilator and steroid treatment. Particularly prevalent in these patients is neutrophilic asthma (bronchial inflammation with a predominance of neutrophils), which tends to behave more aggressively clinically. It requires a higher dose of ICS or systemic steroids, and therefore presents a probability of more frequent infectious pulmonary complications, including the formation of bronchiectasis. Thus, Simpson *et al*[36] observed that the inflammatory pattern observed in neutrophilic asthma is similar to an increase in toll-like receptor (TLR) 2, TLR4 and CD14 receptors as well as the pro-inflammatory cytokines IL-8, IL1β and endotoxin. Finally, subjects with neutrophilic asthma had a greater prevalence of airway bacterial colonization (43% with a positive bacteria culture, similar to those with bronchiectasis) than those with other asthma subtypes (8% in eosinophilic asthma).

It seems that the prevalence of PM isolation in the sputum of these patients is lower than in BCOS, which indicates that it is perhaps more the inflammation than the infection itself that could be involved in the genesis of bronchiectasis.[29] Anyway, as it occurs with COPD, in any given patient with poorly controlled asthma or the isolation of PM in the sputum, especially when it is purulent, a CT scan should be obtained to rule out the presence of bronchiectasis.[37,38]

As in BCOS, existing guidelines recommend treating both diseases separately, although, unlike BCOS, treatment with ICS should not be discontinued, and it seems advisable to periodically reassess patients with the lowest ICS dose.[37,38] It is not known how effective new biological anti-asthma treatments in patients with BAOS are,[39] although preliminary results indicate that the presence of bronchiectasis does not negatively affect the positive effect of these therapies in patients with severe asthma.[40]

ACO: Recent research on this type of overlap patients has been abundant. The most accepted ACO definition would be that of a patient over 40 years of age with non-reversible airflow obstruction, who smoked or was exposed to biomass, and was diagnosed with asthma before the age of 40.[22] Until recently it was considered a specific endotype (own pathophysiological characteristics).[41] Other authors included the presence of a positive bronchodilator test or peripheral eosinophilia in the definition.[29,30] However, such descriptors of ACO have not been universally accepted, as both diseases can appear simultaneously given their high prevalence in the general population.[42] The irruption of peripheral eosinophilia as the marker of a good response to ICS in COPD is a consistent finding, more frequent in COPD with an eosinophilic component. It has been observed that ACO is associated with a greater severity of symptoms and worse quality of life than that of its two components separately, although it does not seem to induce a worse prognosis.[29] Regardless of the name adopted, and as with BCOS and BAOS, guidelines recommend the treatment of choice for both diseases with ICS and bronchodilators for most cases.[28,29,37,38]

As occurs with the Bermuda Triangle, there is confusion about the origin, diagnosis and consequences of the different airway overlap syndromes, although probably a general explanation could be made considering an unique airway disease with different endotypes leading to different clinical phenotypes included those less frequent such as neutrophilic asthma, eosinophilic bronchiectasis or COPD, each one with their own treatable traits. The identification of the pathophysiological mechanisms that precede the presence of different overlap syndromes is probably one of the most important future challenges: What is the mechanism by which some non-smokers with asthma present a predominance of neutrophils or the mechanism by which some non-asthmatic patients with bronchiectasis or COPD have a predominance of eosinophils? What are the mechanisms by which eosinophils are related to bronchiectasis? From a clinical point of view, it would be important to investigate the following questions: Is there a causal relationship between the different entities that make up the different overlap airway syndromes? Do patients with the different overlap syndromes require a specific treatment or do they have a specific prognosis? It is evident that future studies, especially therapeutic trials, should ensure that the investigated population is homogeneous (not including overlaps that may respond differently), or including only a certain type of overlap to increase knowledge about this particular group of patients.

It is important to establish the correct diagnosis of all different overlap airway syndromes, given that on many occasions they produce greater severity and require differentiated treatments. Out of the three diseases, bronchiectasis is probably the least known, and it is necessary to always bear in mind its possible presence in patients with COPD and asthma, especially in their most severe forms, in order to achieve optimal control of these airway overlap diseases in our patients. Just as in the Bermuda Triangle, overlaps in airways diseases can be further explained by more translational research.

Conflicts of interest

None.

References

1. Bermuda Triangle. Available from: https://www.britannica.com/place/Bermuda-Triangle. [Accessed on February 22, 2022].
2. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study. Lancet Respir Med 2020;8:585–596. doi: 10.1016/S2213-2600(20)30105-3.
3. Plaza V, Blanco M, García G, Korta J, Molina J, Quirce S. Highlights of the Spanish Asthma Guidelines (GEMA), Version 5.0. Arch Bronconeumol (Engl Ed) 2021;57:11–12. doi: 10.1016/j.arbres.2020.10.003.
4. Soriano JB, Alfageme I, Miravitlles M, de Lucas P, Soler-Cataluña JJ, García-Río F, *et al*. Prevalence and Determinants of COPD in Spain: EPISCAN II. Arch Bronconeumol (Engl Ed) 2021;57:61–69. doi: 10.1016/j.arbres.2020.07.024.
5. Zhang DD, Liu JN, Ye Q, Chen Z, Wu L, Peng XQ, *et al*. Association between socioeconomic status and chronic obstructive pulmonary disease in Jiangsu province, China: a population-based study. Chin Med J 2021;134:1552–1560. doi: 10.1097/CM9.0000000000001609.
6. Weycker D, Hansen GL, Seifer FD. Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013. Chron Respir Dis 2017;14:377–384. doi: 10.1177/1479972317709649.
7. 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 (Engl Ed) 2021;57:28–35. doi: 10.1016/j.arbres.2019.12.021.
8. Yorgancioglu A, Khaltaev N, Bousquet J, Varghese C. The global alliance against chronic respiratory diseases: journey so far and way ahead. Chin Med J 2020;133:1513–1515. doi: 10.1097/CM9.0000000000000851.
9. 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 (Engl Ed) 2021;57:21–27. doi: 10.1016/j.arbres.2019.12.017.
10. Aliberti S, Goeminne PC, O'Donnell AE, Aksamit TR, Al-Jahdali H, Barker AF, *et al*. Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. Lancet Respir Med 2022;10:298–306. doi: 10.1016/S2213-2600(21)00277-0.
11. Chen CL, Huang Y, Yuan JJ, Li HM, Han XR, Martinez-Garcia MA, *et al*. The roles of bacteria and viruses in bronchiectasis exacerbation: a prospective study. Arch Bronconeumol (Engl Ed) 2020;56:621–629. doi: 10.1016/j.arbr.2019.12.014.
12. Crisford H, Sapey E, Rogers GB, Taylor S, Nagakumar P, Lokwani R, *et al*. Neutrophils in asthma: the good, the bad and the bacteria. Thorax 2021;76:835–844. doi: 10.1136/thoraxjnl-2020-215986.
13. Martinez-Garcia MA, Posadas T, Sotgiu G, Blasi F, Saderi L, Aliberti S. Repeteability of circulating eosinophil measures and inhaled corticosteroids effect in bronchiectasis. A post hoc analysis of a randomized clinical trial. Arch Bronconeumol (Engl Ed) 2020;56:681–683. doi: 10.1016/j.arbres.2020.06.005.
14. Martinez-Garcia MA. Bronchiectasis and eosinophils. Arch Bronconeumol 2021;57:671–672. doi: 10.1016/j.arbr.2021.08.001.
15. Qi YJ, Sun XJ, Wang Z, Bin YF, Li YH, Zhong XN, *et al*. Richness of sputum microbiome in acute exacerbations of eosinophilic chronic obstructive pulmonary disease. Chin Med J 2020;133:542–551. doi: 10.1097/CM9.0000000000000677.
16. Asensio VJ, Tomás A, Iglesias A, de Llano LP, Del Pozo V, Cosío BG, *et al*. Eosinophilic COPD patients display a distinctive serum mirna profile from asthma and non-eosinophilic COPD. Arch Bronconeumol (Engl Ed) 2020;56:234–241. doi: 10.1016/j.arbres.2019.09.020.
17. Miravitlles M, Monteagudo M, Solntseva I, Alcázar B. Blood eosinophil counts and their variability and risk of exacerbations in COPD: a population-based study. Arch Bronconeumol (Engl Ed) 2021;57:13–20. doi: 10.1016/j.arbres.2019.12.015.
18. Golpe R, Dacal D, Sanjuán-López P, Martín-Robles I, Pérez-de-Llano LA. Plasma eosinophil count and patient-centered events in chronic obstructive pulmonary disease in real-life clinical practice. Arch Bronconeumol (Engl Ed) 2020;56:129–130. doi: 10.1016/j.arbres.2019.09.015.
19. Matkovic Z, Miravitlles M. Chronic bronchial infection in COPD. Is there an infective phenotype. Respir Med 2013;107:10–22. doi: 10.1016/j.rmed.2012.10.024.
20. de la Rosa Carrillo D, López-Campos JL, Alcázar Navarrete B, Calle Rubio M, Cantón Moreno R, García-Rivero JL, *et al*. Consensus document on the diagnosis and treatment of chronic bronchial infection in chronic obstructive pulmonary disease. Arch Bronconeumol (Engl Ed) 2020;56:651–664. doi: 10.1016/j.arbres.2020.04.023.
21. Monsó E. Look at the wood and not at the tree: The microbiome in chronic obstructive lung disease and cystic fibrosis. Arch Bronconeumol (Engl Ed) 2020;56:5–6. doi: 10.1016/j.arbres.2019.04.017.
22. Sin DD, Miravitlles M, Mannino DM, Soriano JB, Price D, Celli BR, *et al*. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. Eur Respir J 2016;48:664–673. doi: 10.1183/13993003.00436-2016.
23. Soriano JB, Serrano J. Bronchiectasthma and asthmectasis. Eur Respir J 2016;47:1597–1600. doi: 10.1183/13993003.00289-2016.

24. Martinez-Garcia MA, Miravitlles M. Bronchiectasis in COPD patients: more than a comorbidity. Int J Chron Obstruct Pulmon Dis 2017;12:1401–1411. doi: 10.2147/COPD.S132961.
25. Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2015;10:1465–1475. doi: 10.2147/COPD.S83910.
26. Martínez-García MÁ, de la Rosa-Carrillo D, Soler-Cataluña JJ, Catalan-Serra P, Ballester M, Roca Vanaclocha Y, *et al*. Bronchial infection and temporal evolution of bronchiectasis in patients with chronic obstructive pulmonary disease. Clin Infect Dis 2021;72:403–410. doi: 10.1093/cid/ciaa069.
27. Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a comorbidity of chronic obstructive pulmonary disease: a systematic review and meta-analysis. PLoS One 2016;11:e0150532. doi: 10.1371/journal.pone.0150532.
28. Global Initiative for Chronic Obstructive Lung Disease. GOLD Reports. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (2022 Report). Available from: https://goldcopd.org/2022-gold-reports-2/. [Accessed February 22, 2022].
29. Miravitlles M, Calle M, Molina J, Almagro P, Gómez JT, Trigueros JA, *et al*. Spanish COPD Guidelines (GesEPOC) 2021: Updated pharmacological treatment of stable COPD. Arch Bronconeumol 2022;58:69–81. doi: 10.1016/j.arbres.2021.03.005.
30. Miravitlles M, Calle M, Soler-Cataluña JJ. GesEPOC 2021: one more step towards personalized treatment of COPD. Arch Bronconeumol (Engl Ed) 2021;57:9–10. doi: 10.1016/j.arbres.2020.08.002.
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. doi: 10.1183/13993003.00629-2017.
32. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn SJ, Floto AR, *et al*. British thoracic society guideline for bronchiectasis in adults. Thorax 2019;74:1–69. doi: 10.1136/thoraxjnl-2018-212463.
33. Martínez-García MÁ, Máiz L, Olveira C, Girón RM, de la Rosa D, Blanco M, *et al*. Spanish Guidelines on treatment of bronchiectasis in adults. Arch Bronconeumol (Engl Ed) 2018;54:88–98. doi: 10.1016/j.arbres.2017.07.016.
34. Crimi C, Ferri S, Campisi R, Crimi N. The link between asthma and bronchiectasis: state of the art. Respiration 2020;99:463–476. doi: 10.1159/000507228.
35. Jackson DJ, Akuthota P, Roufosse F. Eosinophils and eosinophilic immune dysfunction in health and disease. Eur Respir Rev 2022;31:210150. doi: 10.1183/16000617.0150-2021.
36. Simpson JL, Grissell TV, Douwes J, Scott RJ, Boyle MJ, Gibson PG. Innate immune activation in neutrophilic asthma and bronchiectasis. Thorax 2007;62:211–218. doi: 10.1136/thx.2006.061358.
37. Padilla-Galo A, Olveira C, Fernández de Rota-Garcia L, Marco-Galve I, Plata AJ, Alvarez A, *et al*. Factors associated with bronchiectasis in patients with uncontrolled asthma; the NOPES score: a study in 398 patients. Respir Res 2018;19:43. doi: 10.1186/s12931-018-0746-7.
38. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, *et al*. Global Initiative for Asthma Strategy 2021. Executive summary and rationale for key changes. Arch Bronconeumol 2022;58:35–51. doi: 10.1016/j.arbres.2021.10.003.
39. Plaza V, Alobid I, Alvarez C, Blanco M, Ferreira J, García G, *et al*. Spanish asthma management guidelines (GEMA) v.5.1. Highlights and Controversies Arch Bronconeumol 2022;58:150–158. doi: 10.1016/j.arbres.2021.05.010.
40. Blanco-Aparicio M, Calvo-Alvarez U, González-Barcala FJ. Biologics in asthma: don't let the magic bullets sink the boat. Arch Bronconeumol (Engl Ed) 2021;57:383–384. doi:10.1016/j.arbres.2020.08.019.
41. Crimi C, Campisi R, Nolasco S, Cacopardo G, Intravaia R, Porto M, *et al*. Mepolizumab effectiveness in patients with severe eosinophilic asthma and co-presence of bronchiectasis: a real-world retrospective pilot study. Respir Med 2021;185:106491. doi: 10.1016/j.rmed.2021.106491.
42. Soler-Cataluña JJ, Novella L, Soler C, Nieto ML, Esteban V, Sánchez-Toril F, *et al*. Clinical characteristics and risk of exacerbations associated with different diagnostic criteria of asthma-COPD overlap. Arch Bronconeumol (Engl Ed) 2020;56:282–290. doi: 10.1016/j.arbres.2019.08.023.

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