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BRN Rev. 2022;8(1):58-69

BRN Reviews

REVIEW

Complexity and Heterogeneity in Bronchiectasis: Towards a Personalized Medicine

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ABSTRACT

Bronchiectasis is a complex and heterogeneous disease, defining complexity as to the non-linear relationship between the different characteristics that make up the disease, and heterogeneous in the sense that not all these variables appear in the same patient. As a consequence of the complexity and heterogeneity of bronchiectasis, different clinical phenotypes can be established (mainly chronic bronchial infection by *Pseudomonas aeruginosa*, the exacerbator patient, and the overlap with chronic obstructive pulmonary disease [COPD]), as well as endotypes (basically neutrophilic and eosinophilic). Beyond phenotypes and endotypes, some authors have recently developed some tools to capture the multidimensional nature of bronchiectasis such as the control panel and clinical fingerprint. These tools are based on the concepts of severity, activity and impact of the disease. Finally, the concept of treatable trait, initially described in COPD patients and defined as those characteristics of bronchiectasis that are treatable (or potentially treatable) is discussed.

Keywords: Chronic obstructive pulmonary disease. Endotypes. Exacerbation. Precision medicine. Phenotypes. Treatable trait.

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Received in original form: 01-11-2021
Accepted in final form: 26-11-2021
DOI: 10.23866/BRNRev:2021-0008
www.brnreviews.com

INTRODUCTION

The scientific evidence on bronchiectasis has grown considerably in the last two decades, although it still falls far behind that available for other airway diseases such as chronic obstructive pulmonary disease (COPD) and asthma. Nevertheless, progress has been made in many areas, partly due to the emergence of international guidelines, patient registers and research groups studying the disease. There is also greater consensus these days on the definition of bronchiectasis and related aspects such as exacerbations, the multidimensional measurement of severity, the impact of microbiology, the relationship with other diseases and the effects of different treatments. We are therefore ready (at least in theory) to go one step further and try to progress from a classical disease-based medicine to one centred on the patient – a scientific leap that is no simple matter. It has to be based on a fuller knowledge of bronchiectasis and our efforts to understand the complexity and heterogeneity associated with it. This investigation has given rise to concepts like clinical phenotypes, stratified medicine, bronchiectasic syndrome, endotypes and treatable traits, which serve to achieve homogeneity within heterogeneity, in order to personalize treatment more fully. This review analyzes the literature published to date on these new concepts in bronchiectasis and their possible application in clinical practice, and, in short, how a classical disease-based medicine has to advance towards a modern medicine based on patients and their characteristics.

COMPLEXITY IN BRONCHIECTASIS

In the context of bronchiectasis, complexity refers to the non-linear relationship between the different characteristics that make up the disease. This non-linear relationship means that knowledge of one particular variable or characteristic does not make it possible to calculate another, and so it is highly probable that each variable brings independent information (which may or may not be synergic) to the overall picture of the disease. Complexity can refer not only to clinical variables but also to diagnostic, pathophysiological, prognostic or therapeutic variables[1-4]. One illustration of this concept with respect to bronchiectasis was published over a decade ago in a study that found, through the application of factorial analysis, a negligible inter-relationship between dyspnoea, lung function and radiological images[5]. In other words, the presence or severity of one of these variables cannot predict the presence or severity of the others, and so, as they are all clinically relevant to bronchiectasis, they should be analyzed separately to obtain a more precise determination of the characteristics and severity of the disease. The various multidimensional scores of severity that subsequently emerged have effectively integrated these three variables, among others, each with a different relative weight with respect to the total value[6-8].

There are various ways to measure complexity. One of the strongest, in visual terms, is network analysis, which can be used to graphically represent a network of connections between different variables or important aspects of the disease[9]. This provides information about the inter-relationships between the variables (and their intensity) and even makes it possible to group together different variables with similar characteristics. An example of a network analysis applied to bronchiectasis can be seen in figure 1. This shows the

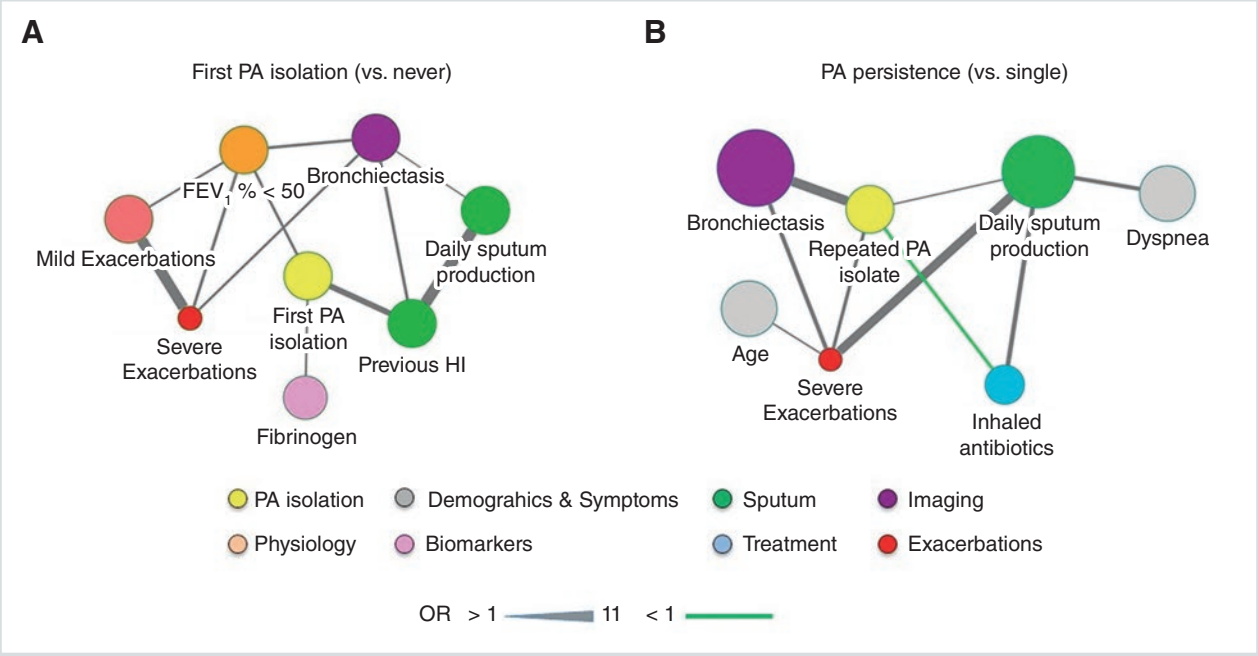

Figure 1. Example of a network applied to bronchiectasis.
FEV_1: forced expiratory volume in one second; HI: *Haemophilus influenza*; PA: *Pseudomonas aeruginosa*.

various inter-relationships found between different characteristics of COPD patients (including bronchiectasis) as risk factors for a first (or subsequent) isolation of *Pseudomonas aeruginosa* (PA)[10]. These risk factors include the presence of bronchiectasis. The intensity of the risk is depicted by the thickness of the connecting lines indicating the value of the odds ratio (OR), while the prevalence of each variable is proportional to the size of the circle.

HETEROGENEITY IN BRONCHIECTASIS

It is important not to confuse the term "complexity" with "heterogeneity", which indicates that not all the variables that make up a disease (in this case, bronchiectasis) appear in every patient, or do so with an equivalent degree of severity. Again, the term can be applied to clinical, diagnostic, prognostic, pathophysiological and therapeutic variables[11]. It is obvious, therefore, that bronchiectasis is an extremely heterogeneous disease, as more than 150 pulmonary or extrapulmonary diseases – each with its own characteristics – are capable of giving rise to bronchiectasis[12,13]. The concept of heterogeneity has propitiated, in its turn, the concepts of the clinical phenotype and the endotype, intended to find homogeneity within this heterogeneity by grouping together patients with similar characteristics so that they can be analyzed on a more individual level[14]. These concepts will be explored below in greater detail.

CURRENT DEFINITION OF BRONCHIECTASIS

Any discussion of complexity and heterogeneity in bronchiectasis must, however, be preceded by a general agreement within the scientific community of what we mean by "bronchiectasis".

In one very recent study, a group of experts of international standing participated in a hugely valuable exercise and came to an agreement about the definition of bronchiectasis. This highly significant achievement will enable both researchers and clinicians to speak in the same terms and overcome any possible individual discrepancies[15].

The definition of bronchiectasis reached by consensus was that of a chronic inflammatory lung disease that needs to satisfy both radiological criteria (mainly based on the broncho-arterial ratio) and clinical criteria (at least two of the following: chronic cough, chronic production of sputum or a history of exacerbations) for a diagnosis to be made. This combination is important, as it is well known that bronchial dilatations can appear without any accompanying clinical picture in elderly individuals[16].

THE BRONCHIECTASIC SYNDROME

One of the distinguishing aspects of bronchiectasis is its impact beyond the respiratory system, since it is capable of presenting systemic effects that also need to be treated for optimal control of the disease (see "Treatable traits" below). It is well known that, in some patients, bronchiectasis can cause systemic inflammation[17,18], malnutrition[19] and other consequences associated with greater severity of the disease. It may therefore be more exact, when we look for an overall definition of the disease, to refer to a *bronchiectasic syndrome* rather than bronchiectasis.

CLINICAL PHENOTYPES IN BRONCHIECTASIS

Once a definition of bronchiectasis has been established and the great heterogeneity associated with it has been accepted, the concept of a clinical phenotype can be applied to the disease – in other words, patients with similar characteristics (whether clinical, prognostic or related to the response to treatment) can be grouped together so that they can be offered differentiated treatment or care[14]. Large and complete databases on bronchiectasis patients can be used to obtain these groups with similar characteristics. Various statistical approaches can be used for this purpose but the most common one is cluster analysis. Once these groups (clusters) have been obtained, it is important to verify whether they have a solid clinical foundation. This approach does have some limitations, however: 1. It is very dependent on the initial variables used to obtain them. The inclusion or omission of an important variable can have a dramatic effect on the analysis. It is therefore very important to identify beforehand those clinically significant variables that are essential to the analysis. 2. This approach often fails to reflect reality as some patients can share different phenotypes, while others may not fit into any of the proposed categories[20]. 3. Finally, as clinical phenotypes are understood to be the expression of an inherent pathophysiological

mechanism or endotype (type of inflammation, type of infection, degree of obstruction, etc.), they should ideally remain stable over time, but this is often difficult to demonstrate[21].

This phenotypical approach is known as stratified medicine. It represents an intermediate step between the failure to distinguish one bronchiectasis patient from another (classical disease-based medicine) and a genuinely personalized or precision medicine (one disease, one patient, one specific moment, one specific treatment).

Various studies have shown that there are probably several clinical phenotypes in bronchiectasis[22-24] (Fig. 2). Of these, three appear to have been most widely investigated and accepted by the scientific community: the phenotype of chronic bronchial infection by PA, the exacerbator phenotype and the phenotype associated with COPD.

Phenotype 1. Chronic bronchial infection (CBI) by PA

The most fully characterized of these phenotypes is probably chronic bronchial infection by PA. Various studies have shown that the presence of PA in the respiratory secretions (particularly in the form of CBI) of bronchiectasis patients is associated with greater severity of the disease, as well as higher mortality, lower quality of life, more symptoms and poorer lung function[25,27]. Accordingly, it is a variable that has not been overlooked by any of the multidimensional scores that mark the severity of the disease[6-8]. At the moment, however, no effective biomarker has been found to predict or diagnose those patients who are carriers of a CBI by PA. Another important issue is whether PA itself is a marker of severity (i.e., PA infects the most severely affected patients), or whether there is a causal relationship (i.e., it is infection by PA that increases the severity of bronchiectasis). The answer to this question may be that both are true, but that an individual patient can be affected by one or the other, depending on his or her characteristics.

Phenotype 2. Exacerbator or multiple exacerbations

In recent years, the role played by exacerbations (especially when they are severe) in the prognosis and management of bronchiectasis has become increasingly clear[28-30]. In fact, like CBI by PA, exacerbations also appear in all the multidimensional scores for severity[7-9], and they have an even greater weight (especially in severe forms of bronchiectasis and cases that require hospitalization). Furthermore, a profile has emerged, as in the case of COPD patients, of a phenotype of a patient with multiple exacerbations, characterized by greater disease severity and, consequently, significant expenditure[31-32]. No cut-off point has been established to define the exacerbator phenotype, but it does seem that this phenotype remains stable over time as the main risk factor for presenting a severe exacerbation is having already suffered one on a previous occasion[33].

Phenotype 3. Overlap with COPD

This phenotype has also been fairly well characterized, and its existence has been supported

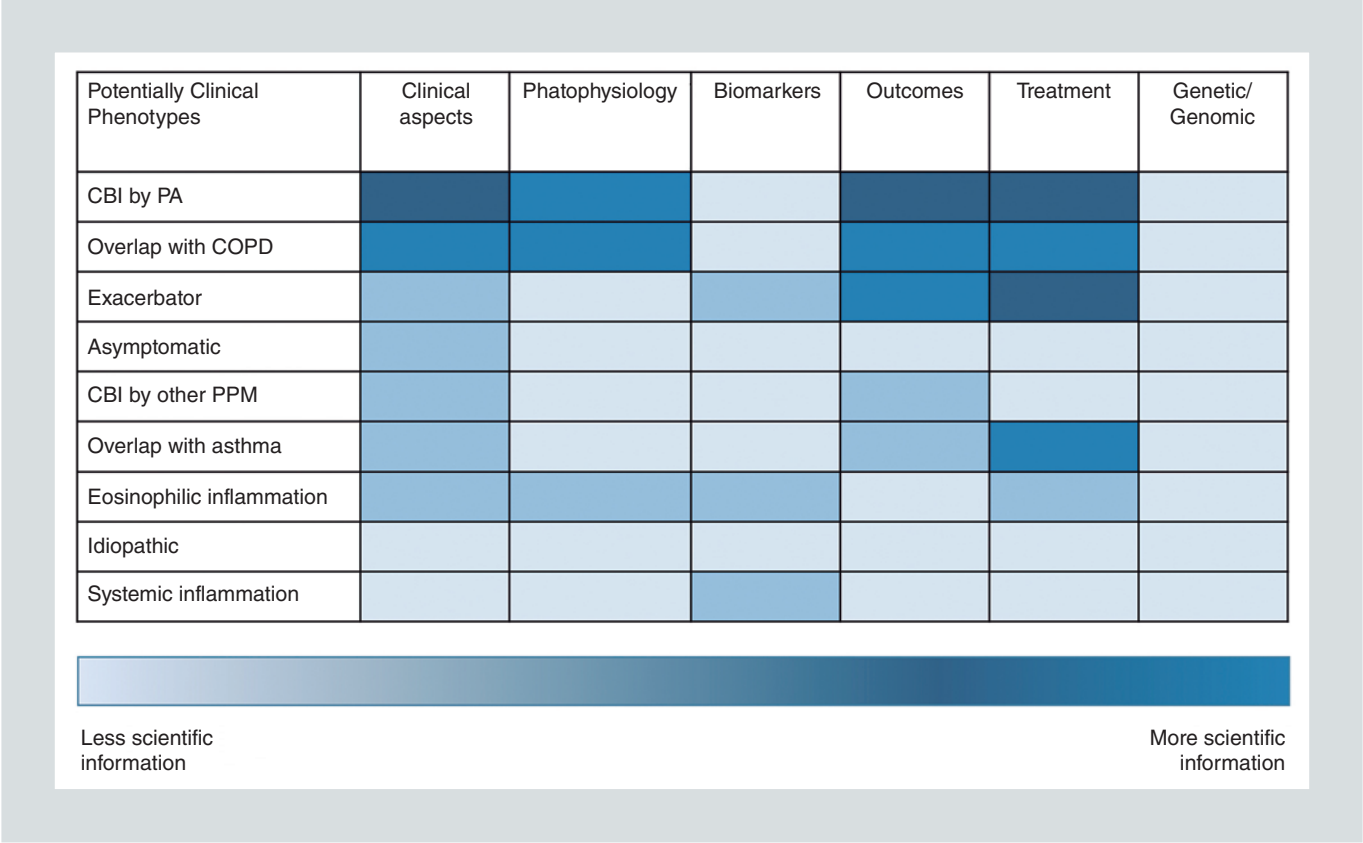

Figure 2. Potential clinical phenotypes in bronchiectasis and its relative scientific evidence.
CBI: chronic bronchial infection; COPD: chronic obstructive pulmonary disease; PA: *Pseudomonas aeuginosa*; PPM: potentially pathogenic microorganisms.

by various studies. COPD, in its natural history, can give rise to bronchiectasis in its later stages, with greater severity and a poorer prognosis as a result[34-36]. The international guidelines for both COPD and bronchiectasis agree on the need to rule out the presence of bronchiectasis (via computed tomography [CT]) in some groups of COPD patients[37-41].

One important aspect of these three types of phenotypes is that they need to be identified because each one requires specific treatment. In the case of CBI by PA, an early and powerful antibiotic treatment is recommended[39-41]; in that of the exacerbator phenotype, drugs such as macrolides take on an important role[39-42], while, in the COPD overlap phenotype, both diseases must be treated in accordance with the corresponding guidelines[37-41]. Furthermore, it is important to take into account that these phenotypes can coexist within a single patient and can also alter over time, either spontaneously or after treatment. It is not uncommon, for example, to find that a patient in the advanced stages of COPD develops bronchiectasis, which is then infected by PA, thereby triggering an increase in exacerbations.

There are other potential candidates for clinical phenotypes that are still being studied: a bronchiectasis-asthma overlap (bronchiectasis increases the risk of asthma becoming more difficult to control and of exacerbations)[42]; bronchiectasis with eosinophilia (which could be a target phenotype for treatment with steroids or biological anti-Th2 medication)[21]; idiopathic bronchiectasis (some authors have observed a lower degree of severity in this case)[43]; and bronchiectasis with systemic inflammation (associated with greater disease severity), although the evidence here is still scarce and no treatment has been clearly established[17,18].

Finally, there are some variables (known as modifying variables) that can affect the clinical expression of these phenotypes: age, gender, comorbidities, aetiology and socio-economic status[44].

ENDOTYPES IN BRONCHIECTASIS

The term endotype refers to the pathophysiological characteristics (associated with a person's genetic factors) presented by different individuals. This field has been much less studied. The endotype linked to the type of inflammation is probably the best characterized. Although the majority of bronchiectasis cases present predominantly neutrophilic inflammation[45-47], there is increasing evidence that eosinophilic inflammation can be substantial, and even predominant, in some patients, even in the absence of asthma and underlying diseases associated with a greater degree of eosinophilia. It is also important not to overlook the role played by T cells in the inflammatory picture of bronchiectasis[48-49].

Endotype 1. Neutrophilic inflammation

Neutrophils play a crucial role in the pathophysiology of most bronchiectasis patients, particularly those with bronchial infection by pathogenic microorganisms. Neutrophils are capable of inducing and producing a large amount of pro-inflammatory molecules with proteolytic and elastolytic characteristics that, along with bacterial products, cause damage in the bronchial wall and the local defence mechanisms[45-47]. Of all these molecules, neutrophil elastase is one of the most significant and, moreover, it has proved to be a promising biomarker of inflammatory activity at a bronchial level, as confirmed by several studies that have observed its relationship with the severity of bronchiectasis. In fact, studies with various neutrophile elastase (NE) inhibitors are currently underway, with good results[50-52].

Endotype 2. Eosinophilic inflammation

Beyond the presence of asthma and other aetiologies of bronchiectasis associated with eosinophilia, up to 30% of bronchiectasis patients present a high T2 phenotype (understood as at least 300 eos/µL and/or oral fractional exhaled nitric oxide [FeNO] of at least 25 ppb), with 15-20% presenting > 300 eosinophils/uL and more than 20% oral FeNO levels of at least 25 ppb. However, few studies have analyzed the clinical characteristics or prognostic and therapeutic impact of this finding[53-54]. Orinao et al.[55] observed that those patients with bronchiectasis and a Th2 profile present greater disease severity (poorer lung function,

greater dyspnoea, and a higher bronchiectasis severity index (BSI) score (6 [4-11.5] versus 5 [3-8]; p = 0.042). However, the presence of peripheral eosinophilia seems to improve the response to corticoids and reduce the number of exacerbations, opening the door to the use of various biological agents (especially anti-Interleukin [IL]-5 drugs like benralizumab and mepolizumab)[56]. It may therefore be important to investigate whether the presence of eosinophilia could be a treatable trait in bronchiectasis.

BEYOND PHENOTYPES AND ENDOTYPES IN BRONCHIECTASIS. TOWARDS A PRECISION MEDICINE

All in all, the knowledge of bronchiectasis that has been acquired in recent years has encouraged efforts to take a step beyond phenotypes as a means to distinguish between individuals with bronchiectasis and move closer to what is known as personalized or precision medicine. Various formulas associated with clinical and therapeutic aspects of bronchiectasis have been used in this respect. In the following sections, we shall examine two of these formulas, one with a more clinical approach (the concept of "fingerprinting" in bronchiectasis) and the other more closely related to therapeutic aspects (the concept of "treatable traits" in bronchiectasis).

CLINICAL FINGERPRINTING IN BRONCHIECTASIS

"Clinical fingerprinting" refers to the graphic representation of the presence and degree of impact of a series of variables involved in the definition of bronchiectasis, in a way that allows them to be evaluated together. This graphic representation (which comes in various models) is the result of an analysis of the three key domains (the "control panel") of bronchiectasis (Fig. 3): **Severity** (defined as functional impairment and its spread to target organs); **Activity** (level of activation of the biological process driving the progression of the disease or its consequences) and **Impact** (patients' perception of the severity and activity of the disease). Each of these three elements can be modified or modulated by untreatable variables such as age, gender and race[44,57].

- *Severity*. Four variables are evaluated in the severity domain: forced expiratory volume in one second (FEV_1), representing lung function; radiological extension (number of pulmonary lobes affected); comorbidities (through the Bronchiectasis Aetiology Comorbidity Index [BACI] classification system) and aetiology[44].
- *Activity*. This is the most complicated dimension to measure due to the lack of biomarkers with a good diagnostic, prognostic or therapeutic capacity. It embraces the purulence of the sputum (which indicates the inflammation and/or infection present, as measured on the Murray scale); the presence of bronchial infection (particularly by PA); the number and severity of exacerbations and, lastly, the body mass index (BMI), the most disputed variable, although it is related to a certain degree of low-level systemic inflammation. Other future candidates for this dimension would be those markers that have been accumulating scientific evidence, such as elastase neutrophil[44].

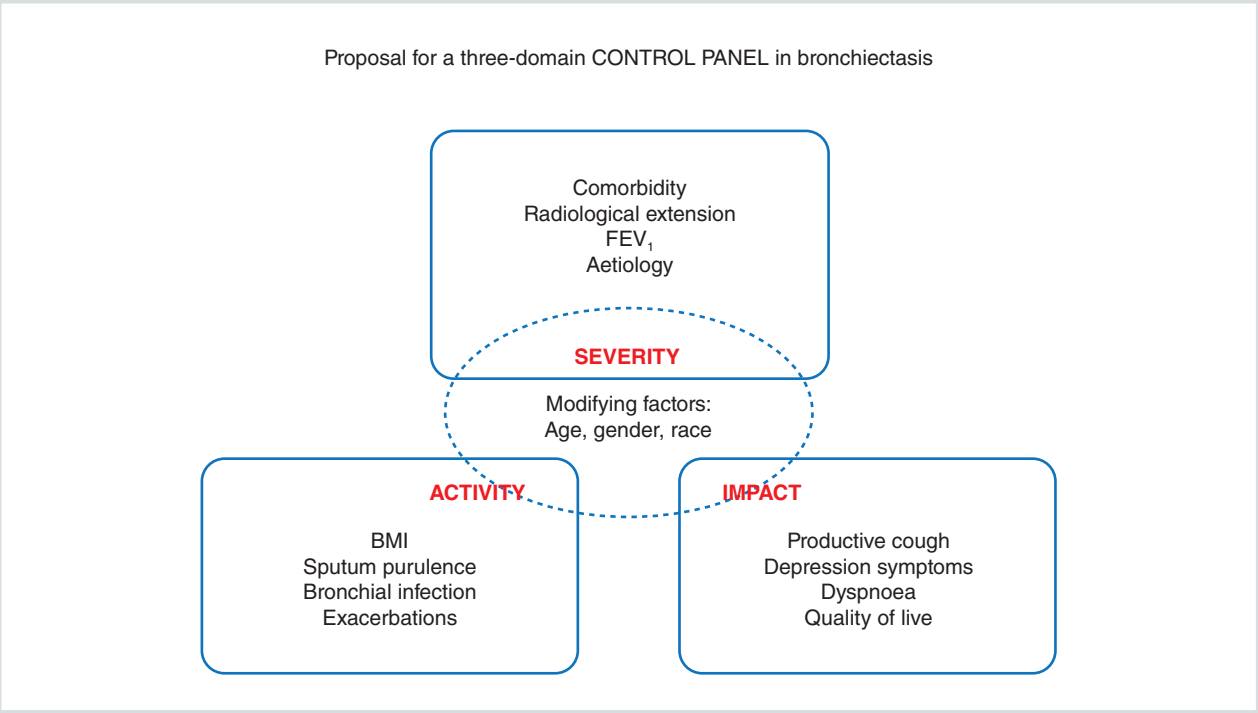

Figure 3. Proposal of a new tool in bronchiectasis: The control panel.
BMI: body mass index; FEV_1: forced expiratory volumen in one second.

– *Impact*. The impact of bronchiectasis on an individual is generally evaluated by means of questionnaires or subjective instruments. This dimension includes dyspnoea (usually measured by the modified Medical Research Council [mMRC]), symptoms of depression or anxiety (almost always undervalued in individuals with chronic airway diseases), the quantity of sputum produced per day and the quality of life (for which some short, specific and easy-to-use questionnaires, such as the COPD Assessment Test (CAT), are being developed or validated)[44].

The availability of all this quantified information allows to create a graphic image which represents, in a multidimensional manner, a curve whose form and area will be different for every patient, based on the quantification of each of the variables analyzed as part of the three dimensions (see Fig. 4). Moreover, this area can change over time or be modified by treatment, which would make it possible to calculate the overall efficacy of the treatments foreseen for each aspect of the disease – which will be different for each patient (reflecting his or her "fingerprint")[44].

TREATABLE TRAITS IN BRONCHIECTASIS

Treatable traits (TT) can be defined as those characteristics of bronchiectasis that are treatable

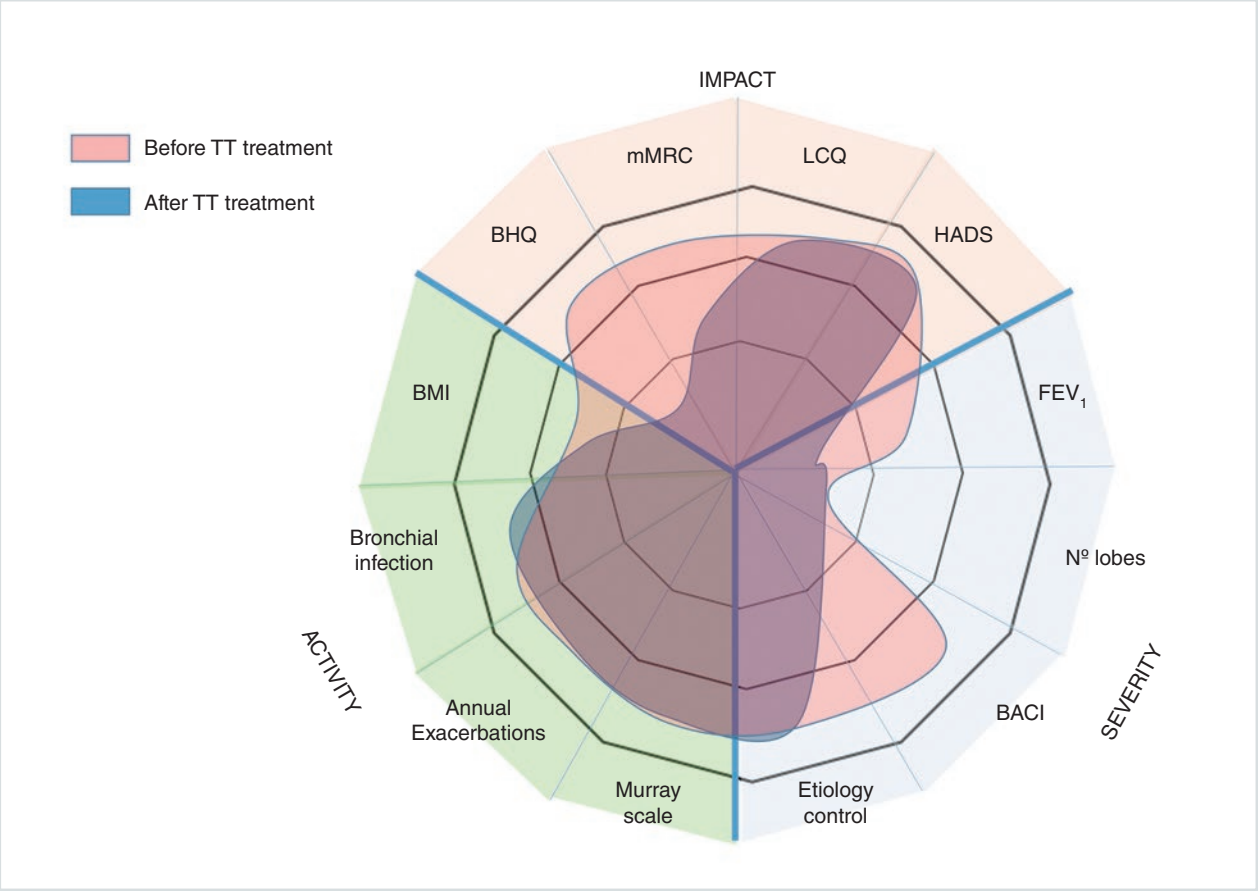

Figure 4. Changes in the fingerprinting (area under the curve) of patient with bronchiectasis before treatment of different treatable traits (dark and smaller area) an after treatment of treatable traits (light and larger area).
BACI: Bronchiectasis Aetiology and Comorbidity Index; BHQ: Bronchiectasis Health Questionnaire; BMI: body mass index; HADS: Hospital Anxiety and Depression Symptoms; LCQ: Leicester Cough Questionnaire; mMRC: modified Medical Research Council; TT: treatable trait.

(or potentially treatable)[58]. These TT refer not only to pulmonary characteristics but also to extra-pulmonary ones that also require treatment, as well as those related to a patient's lifestyle. It has been postulated that many of these TT are shared with other airway diseases such as COPD and asthma. Some authors have gone even further and suggested that, in future, the nomenclature for the various diseases should disappear and that we should talk in terms of a single disease (inflammatory airway disease) in which all the treatable traits appearing in each patient should be identified and treated. This approach would help to adapt the clinical practice to a more personalized form of medicine[44,59].

Going back to bronchiectasis in particular, several TT have been proposed, as shown in figure 5.

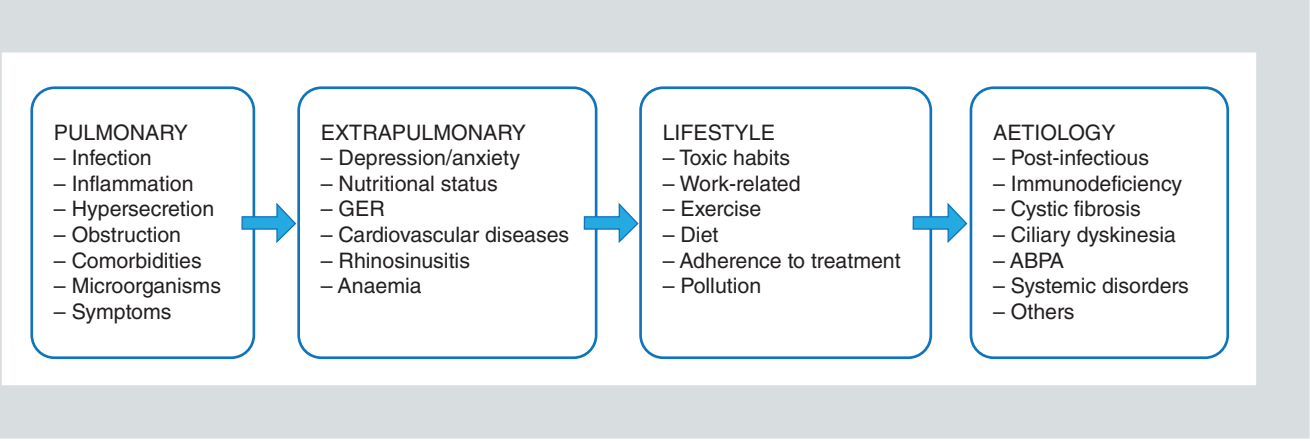

Figure 5. Treatable traits in bronchiectasis.
ABPA: allergic bronchopulmonary aspergillosis; GER: gastroesophageal reflux.

DISCLOSURES

Dr. Oscullo, Dr. García-Ortega, Dr. Gómez-Olivas, Dr. Beauperthuy, Dr. Bekki, and Dr. Martinez-Garcia have nothing to disclose.

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