



## University of Dundee

### Standardised classification of the aetiology of bronchiectasis using an objective algorithm

Araújo, David; Shteinberg, Michal; Aliberti, Stefano; Goeminne, Pieter C.; Hill, Adam T.; Fardon, Tom

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## Standardised classification of the aetiology of bronchiectasis using an objective algorithm

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Key Words:	Bronchiectasis, aetiology, COPD, diagnostic procedures

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5 **Authors:** David Araújo<sup>1</sup>, Michal Shteinberg<sup>2</sup>, Stefano Aliberti<sup>3</sup>, Pieter C. Goeminne<sup>4,5</sup>, Adam T.  
6 Hill<sup>6</sup>, Tom Fardon<sup>7</sup>, Dusanka Obradovic<sup>8</sup>, Katerina Dimakou<sup>9</sup>, Eva Polverino<sup>10</sup>, Anthony De  
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8

9 1 – Pulmonology Department of São João Hospital Center, Porto, Portugal

10 2 - Pulmonary Institute, Carmel Medical Center, Haifa, Israel

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13 Department, Respiratory Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Ca' Granda  
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43 Corresponding author: James D Chalmers, Scottish Centre for Respiratory Research, University  
44 of Dundee, Ninewells Hospital and Medical School, Dundee, DD1 9SY,  
45 jchalmers@dundee.ac.uk  
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Dear editor,

Bronchiectasis is a chronic and progressive respiratory disease with multiple possible causes(1,2). Many require a specific therapy and so a systematic aetiologic evaluation is recommended by guidelines(3). Studies have shown wide heterogeneity in the proportion of different aetiologies identified between centres(4-8), which can be partially justified because of geographical risks factors, but may also reflect variations in testing practice or in the definitions of aetiology used(9). The proportion of patients classified as idiopathic varies (26-74%) across the literature and this variability is likely to be somewhat linked to a lack of use of a standard aetiological algorithm.(4-8)

Variation in the assignment of aetiology impacts on every aspect of epidemiological research into bronchiectasis, as well as clinical trials where the inclusion of patients with post-infective or idiopathic bronchiectasis is only meaningful if we have standardised methods of assigning these aetiologies.(2) The aim of this study was to create a bronchiectasis aetiology classification algorithm that could be applied objectively to different healthcare settings. This algorithm was tested in a multicentre database of bronchiectasis patients with the goal of improving the degree of agreement and alignment between different centres.

An analysis of ten databases (Dundee, Edinburgh, Newcastle– United Kingdom; Haifa-Israel; Galway-Ireland; Leuven-Belgium; Athens-Greece; Monza-Italy; Barcelona-Spain; Serbia) of outpatients with BE was performed. Consecutive patients aged  $\geq 18$  years with a diagnosis of BE based on high-resolution computed tomographic scans were enrolled. Patients with cystic fibrosis or traction bronchiectasis due to pulmonary fibrosis were excluded. Local ethics committee approved the data collection at each site.

Demographics, previous medical history, comorbidities, as well as radiological, laboratory and microbiological findings were recorded. At each location, the aetiological diagnosis made by the clinician was also recorded. Centres all followed a standard of care that was consistent with the British Thoracic Society (BTS) 2010 guidelines in terms of testing for underlying causes.(3) The method of assignment of aetiologies and co-morbidities has been previously reported.(10)

An aetiological algorithm (figure 1-A) was generated based on the 2010 BTS guidelines. The initial assessment was required to have a documented evidence of BE in HRCT scan and a clinical history compatible with BE. All patients should then have completed a group of initial tests – complete blood count, protein electrophoresis, immunoglobulin levels (IgG, IgM, IgA, IgE), specific antibody levels (against tetanus toxoid, *S. pneumoniae* and *H. influenzae* type b), specific IgE and IgG/precipitins for *Aspergillus fumigatus*, bacterial and mycobacterial sputum culture and pulmonary function tests.(3)

A set of “definitive diagnosis” aetiologies were assembled - Congenital airway defects, bronchial obstruction (e.g due to tumour or foreign body), primary immunodeficiency, connective tissue disease (CTD) related BE. If the patient had clinical suspicion of primary ciliary dyskinesia (PCD), CF, CFTR-Related disease,  $\alpha 1$ -antitrypsin (A1AT), inflammatory bowel disease, yellow nail syndrome or diffuse pan-bronchiolitis, additional testing was performed. If all the findings were compatible with one of these aetiologies, then a definitive diagnosis was achieved. If atypical features were present (in terms of clinical manifestations, symptoms onset age, radiological findings) or other aetiology was suspected, then another group of

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3 entities would be analysed. This group was classified as “Possible diagnosis” and included  
4 allergic bronchopulmonary aspergillosis (ABPA), post nontuberculous mycobacteria infection,  
5 post tuberculosis, chronic obstructive pulmonary disease (COPD) (defined as described in (9)),  
6 asthma, gastro-oesophageal reflux disease (GORD)/aspiration, and secondary  
7 immunodeficiency. If one of these diseases was the only possible aetiology present and if there  
8 were no atypical features, we also considered this a **definitive** diagnosis. If this was not the  
9 case or if the suspected aetiology was not in this group, we had to consider a final group of  
10 “diagnosis of exclusion” where in the case of a plausible association to previous infection we  
11 have post-infective aetiology. To be considered idiopathic, all this diagnostic assessment  
12 should be performed with a negative result, otherwise we should designate the patient as “not  
13 appropriately tested”.

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16 This aetiological algorithm was then applied to the ten databases previously mentioned, and  
17 results in terms of aetiology were compared.

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20 A total of 2502 patients were accessed – 116 in Newcastle, 280 in Galway, 190 in Leuven, 113  
21 in Serbia, 494 in Dundee, 88 in Haifa, 94 in Athens, 204 in Barcelona, 608 in Edinburgh and 315  
22 in Monza. The median age was 64 years (age range – 18-97yr) with a majority of the  
23 population being over 65 years old (n=1404, 56.1%) and there was a female gender  
24 predominance (n=1539, 61.5%). Median Bronchiectasis Severity Index (BSI)(11) score was 7  
25 with a relatively homogenous distribution between the severity groups – Mild (n=744, 29.7%),  
26 Moderate (n=894, 35.7%), Severe (n=864, 34.5%).

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28 The global diagnosis made by clinicians and diagnosis after applying the algorithm, are  
29 presented on figure 1-B. A total of **1456** patients (58.2%) had an aetiological diagnosis made by  
30 the clinician. The most common aetiology, excluding idiopathic, was post-infective (n=427,  
31 17.7%) and COPD (n=235, 9.4%).

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33 After applying the aetiological algorithm, a significant reduction was seen in terms of  
34 idiopathic cases (n=1046, 41.8% vs n=726, 29.0%, **p<0.0001**). The number of patients with  
35 COPD as a BE aetiology was higher (n=373, 14.9%) and less post-infective cases were seen  
36 (n=349, 13.9%). A significantly higher number of GORD/aspiration cases were classified as  
37 probable aetiology – 109 cases (4.4%) versus only 15 cases (0.6%) considered by the clinicians.  
38 Moreover, CTD was also considered an aetiology more often – 237 cases (9.5%) versus 157  
39 (6.3%) diagnosed by the clinicians.

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42 These changes in aetiological classification were seen across all the centres. With the clinician  
43 diagnosis, we had 6 centres with more than 40% of idiopathic cases. That number went down  
44 to just one after applying the algorithm.

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46 These results show that by applying the same structured aetiological algorithm to a  
47 bronchiectasis patient group the number of idiopathic cases can be lowered substantially. We  
48 demonstrate that clinicians frequently diagnose idiopathic bronchiectasis in the presence of  
49 disease associated with bronchiectasis suggesting the need for standardized aetiological  
50 categorization. This study has some limitations, even though centres practiced the BTS 2010  
51 guideline testing algorithm, some testing particularly for CF, alpha-1 antitrypsin deficiency and  
52 PCD are still subject to “clinician suspicion” and so testing rates are highly variable between  
53 centres. In that matter, some of the patients considered as idiopathic could still be  
54 characterized as “not appropriately tested”. In some cases, the algorithm can erroneously  
55 replace the diagnostic uncertainty of the clinician, because some elements are only present in  
56 a full clinical history and not recorded in the databases.

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3 One of the major limitations is that the association between some diseases and bronchiectasis  
4 remains speculative. Particularly asthma and GORD are regarded as possible aetiologies but  
5 are very common in the general population and so cannot be regarded as definitive  
6 aetiologies. How to incorporate such diseases or phenotypes into classification algorithms is  
7 likely to require further discussion and debate over time.(12,13) **The recently published**  
8 **European Bronchiectasis Guidelines recommended testing for immunodeficiency and ABPA**  
9 **routinely in all patients but did not address aetiological diagnosis in more detail. Therefore we**  
10 **believe our study is timely and may be incorporated into future guidelines.(14)** The strengths  
11 of this study are the very large number of patients and that multiple and diverse  
12 bronchiectasis centres were included. **Our study was limited to adults only and cannot be**  
13 **applied to children under the age of 18 years.**

16 In summary, Idiopathic bronchiectasis should only be diagnosed after a thorough assessment  
17 with the exclusion of all the relevant clinical entities that could be related to bronchiectasis.  
18 The use of a standardized aetiological algorithm across all bronchiectasis centres, while  
19 imperfect, would improve the ability of reaching a diagnosis leading to a change in  
20 management in many cases and would enhance the ability to compare results of different  
21 studies from different centres.  
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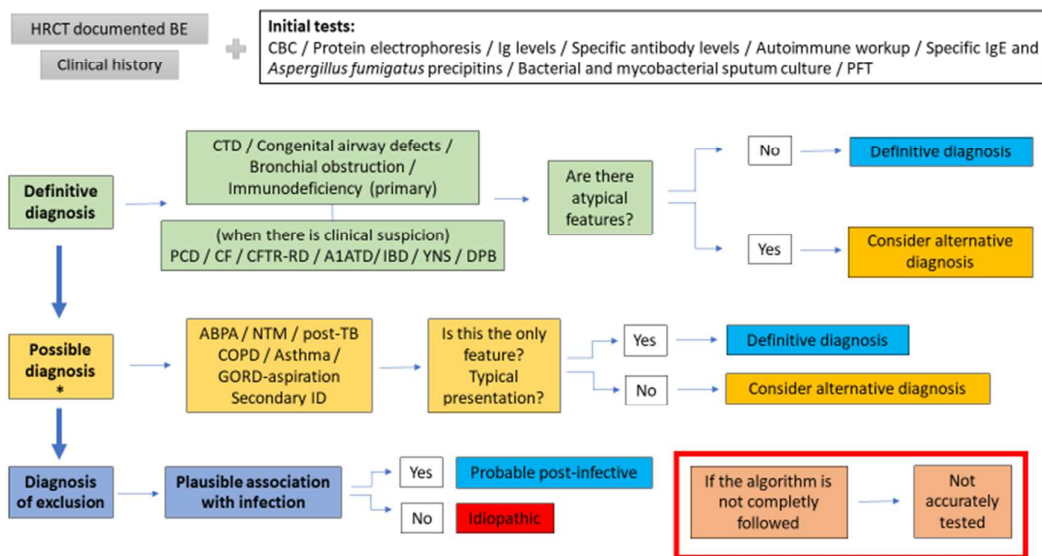
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4 remains speculative. Particularly asthma and GORD are regarded as possible aetiologies but  
5 are very common in the general population and so cannot be regarded as definitive  
6 aetiologies. How to incorporate such diseases or phenotypes into classification algorithms is  
7 likely to require further discussion and debate over time.(12,13) The recently published  
8 European Bronchiectasis Guidelines recommended testing for immunodeficiency and ABPA  
9 routinely in all patients but did not address aetiological diagnosis in more detail. Therefore we  
10 believe our study is timely and may be incorporated into future guidelines.(14) The strengths  
11 of this study are the very large number of patients and that multiple and diverse  
12 bronchiectasis centres were included. Our study was limited to adults only and cannot be  
13 applied to children under the age of 18 years.  
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16 In summary, Idiopathic bronchiectasis should only be diagnosed after a thorough assessment  
17 with the exclusion of all the relevant clinical entities that could be related to bronchiectasis.  
18 The use of a standardized aetiological algorithm across all bronchiectasis centres, while  
19 imperfect, would improve the ability of reaching a diagnosis leading to a change in  
20 management in many cases and would enhance the ability to compare results of different  
21 studies from different centres.  
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**A**



**B**

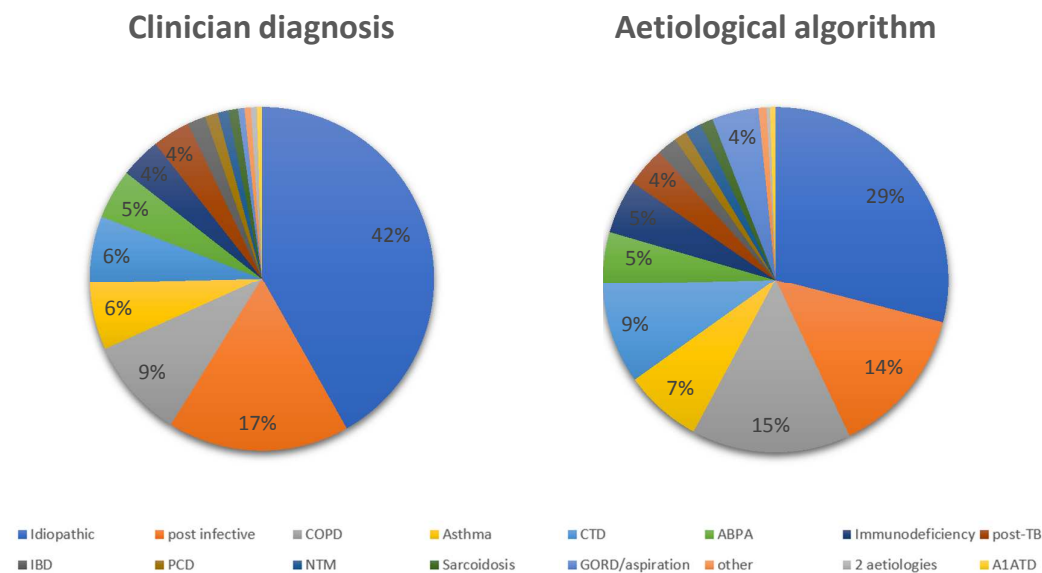


Figure 1 – A - Aetiology algorithm; B - Aetiology results, clinician diagnosis and results after aetiological algorithm. \* note these diagnoses can also be complications or co-morbidities (e.g ABPA can complicate existing bronchiectasis)