Standardised classification of the aetiology of bronchiectasis using an objective algorithm

To the Editor:

Bronchiectasis (BE) is a chronic and progressive respiratory disease with multiple possible causes [1, 2]. Many require a specific therapy and thus, a systematic aetiologic evaluation is recommended by guidelines [3]. Studies have shown wide heterogeneity in the proportion of different aetiologies identified among 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 influences every aspect of epidemiological research into BE, 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 BE aetiology classification algorithm that could be applied objectively to different healthcare settings. This algorithm was tested in a multicentre database of BE patients with the goal of improving the degree of agreement and alignment among different centres.

An analysis of 10 databases (Dundee, Edinburgh, Newcastle: United Kingdom; Haifa: Israel; Galway: Ireland; Leuven: Belgium; Athens: Greece; Monza: Italy; Barcelona: Spain; and Vojvodina: Serbia) of outpatients with BE was performed. Consecutive patients aged ⩾18 years with a diagnosis of BE based on high-resolution computed tomography (HRCT) scans were enrolled. Patients with cystic fibrosis or traction BE due to pulmonary fibrosis were excluded. The local ethics committee at each site approved the data collection.

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. All centres followed a standard of care that was consistent with the 2010 British Thoracic Society (BTS) 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 1a) was generated based on the 2010 BTS guidelines. The initial assessment was required to have documented evidence of BE in an 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* and 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 and connective tissue disease (CTD)-related BE. If the patient had clinical suspicion of primary ciliary dyskinesia (PCD), CF, CFTR-related disease, α1-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
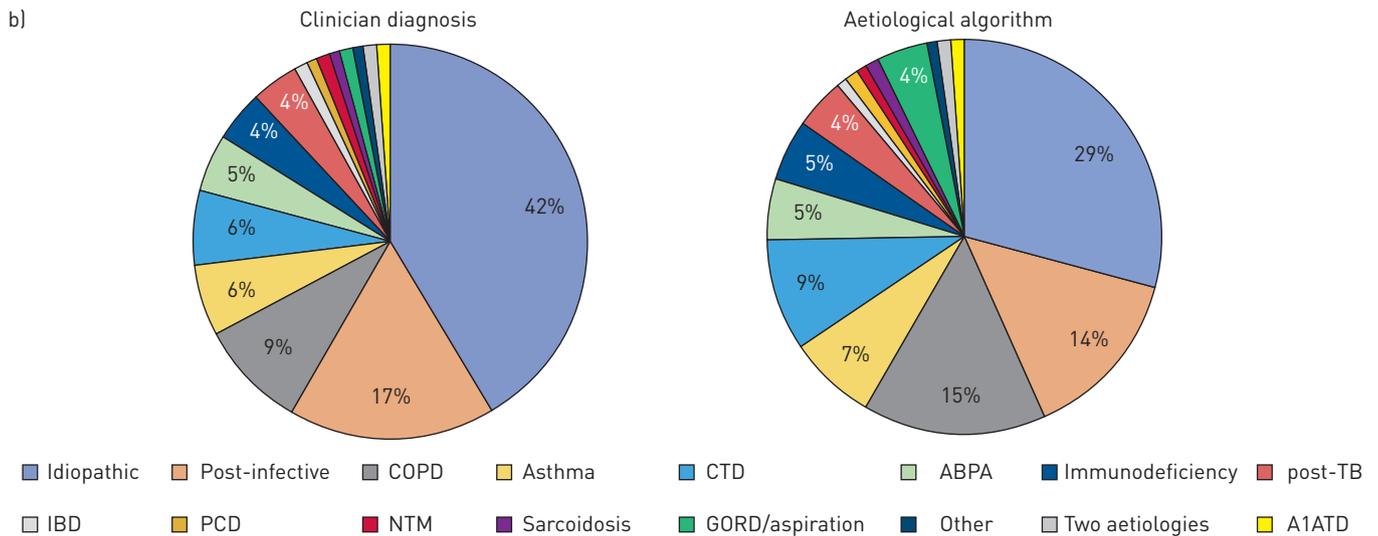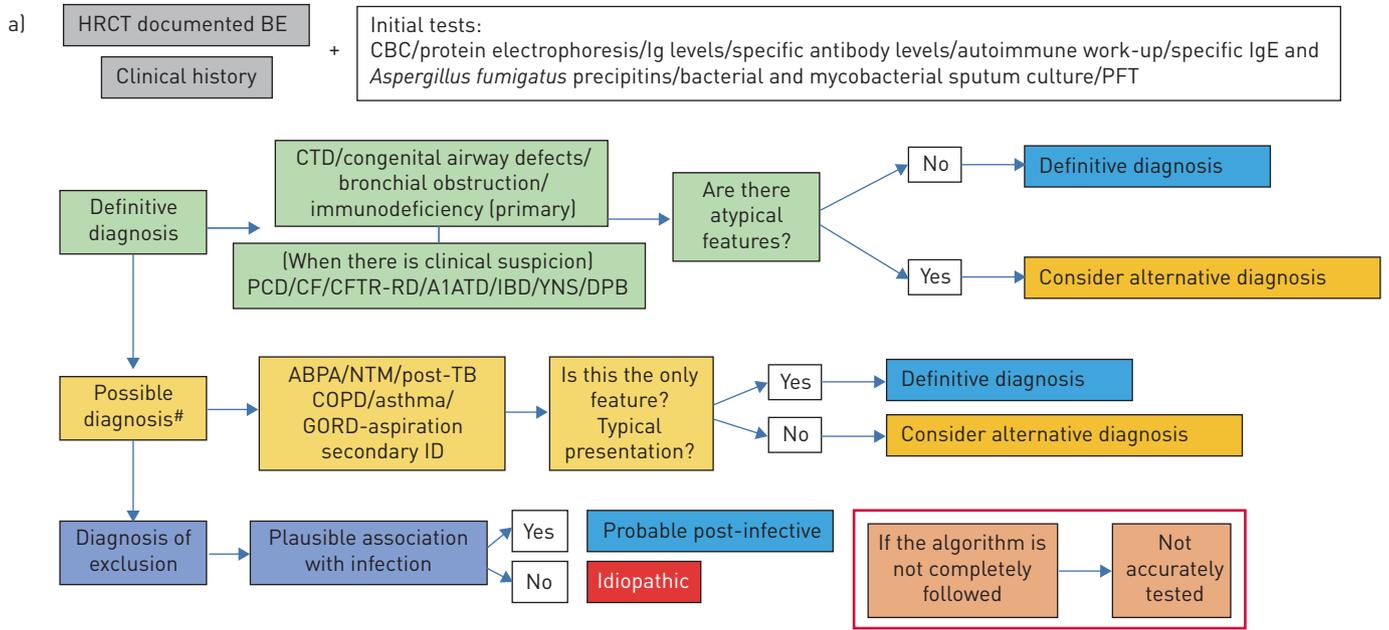
FIGURE 1 a) Aetiology algorithm; b) aetiology results, clinician diagnosis and results after aetiological algorithm. #: Note these diagnoses can also be complications or co-morbidities (e.g. allergic bronchopulmonary aspergillosis (ABPA) can complicate existing bronchiectasis). HRCT: high-resolution computed tomography; BE: bronchiectasis; CBC: complete blood count; PFT: pulmonary function test; CTD: connective tissue disease; PCD: primary ciliary dyskinesia; CF: cystic fibrosis; CFTR-RD: cystic fibrosis transmembrane conductance regulator-related disease; A1ATD: α_1-antitrypsin deficiency; IBD: inflammatory bowel disease; YNS: yellow nail syndrome; DPB: diffuse panbronchiolitis; NTM: nontuberculous mycobacteria; TB: tuberculosis; COPD: chronic obstructive pulmonary disease; GORD: gastro-oesophageal reflux disease; ID: immunodeficiency.

group of entities would be analysed. This group was classified as 'Possible diagnosis' and included allergic bronchopulmonary aspergillosis (ABPA), post nontuberculous *Mycobacteria* infection, post tuberculosis, chronic obstructive pulmonary disease (COPD) (defined as described in [9]), asthma, gastro-oesophageal reflux disease (GORD)/aspiration and secondary immunodeficiency. If one of these diseases was the only possible aetiology present and if there were no atypical features, we also considered this a definitive diagnosis. If this was not the case or if the suspected aetiology was not in this group, we had to consider a final group of 'diagnosis of exclusion' where in the case of a plausible association to previous infection, we had confirmation of post-infective aetiology. To be considered idiopathic, all this diagnostic assessment should have yielded negative results, otherwise the patient would be designated as 'not appropriately tested'.

This aetiological algorithm was then applied to the 10 databases previously mentioned, and results in terms of aetiology were compared.

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

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

After applying the aetiological algorithm, a significant reduction was seen in terms of idiopathic cases (n=1046, 41.8% *versus* n=726, 29.0%, p<0.0001). The number of patients with COPD as a BE aetiology was higher (n=373, 14.9%), and less post-infective cases were seen (n=349, 13.9%). A significantly higher number of GORD/aspiration cases were classified as probable aetiology: 109 cases (4.4%) *versus* only 15 cases (0.6%) considered by the clinicians. Moreover, CTD was also considered to have a higher frequency (237 cases [9.5%]) than that diagnosed by the clinicians 157 (6.3%).

These changes in aetiological classification were seen across all the centres. With the clinician diagnosis, we had six centres with more than 40% of idiopathic cases; this number reduced to just one after applying the algorithm.

Our results show that by applying the same structured aetiological algorithm to a BE patient group, the number of idiopathic cases can be substantially lowered. We have shown that clinicians frequently diagnose idiopathic BE in the presence of disease associated with BE, suggesting the need for standardised aetiological categorisation. This study has some limitations. Although centres practised the BTS 2010 guideline testing algorithm, some testing particularly for CF, alpha-1 antitrypsin deficiency and PCD are still subject to 'clinician suspicion' and thus, testing rates are highly variable among centres. Hence, some of the patients considered as idiopathic could still be characterised as 'not appropriately tested'. In some cases, the algorithm can erroneously replace the diagnostic uncertainty of the clinician, because some elements are only present in a full clinical history and not recorded in the databases.

One of the major limitations is that the association between some diseases and BE remains speculative; in particular, asthma and GORD are regarded as possible aetiologies but are very common in the general population and so cannot be regarded as definitive aetiologies. How to incorporate such diseases or phenotypes into classification algorithms is likely to require further discussion and debate [12, 13]. The recently published European Bronchiectasis Guidelines recommends testing for immunodeficiency and ABPA routinely in all patients but does not address aetiological diagnosis in more detail. Therefore, we believe our study is timely and may be incorporated into future guidelines [14]. The strengths of this study are the very large number of patients and that multiple and diverse BE centres were included. Our study was limited to adults only and cannot be applied to children under the age of 18 years.

In summary, idiopathic BE should only be diagnosed after a thorough assessment with the exclusion of all the relevant and related clinical entities. The use of a standardised aetiological algorithm across all BE centres, albeit imperfect, would improve the ability to diagnose BE and lead to a change in management, thereby enhancing the ability to compare results of different studies from different centres.

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