Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations

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Bronchiectasis refers to both a clinical disease and a radiological appearance that has multiple causes and can be associated with a range of conditions. Disease heterogeneity and the absence of standardised definitions have hampered clinical trials of treatments for bronchiectasis and are important challenges in clinical practice. In view of the need for new therapies for non-cystic fibrosis bronchiectasis to reduce the disease burden, we established an international taskforce of experts to develop recommendations and definitions for clinically significant bronchiectasis in adults to facilitate the standardisation of terminology for clinical trials. Systematic reviews were used to inform discussions, and Delphi processes were used to achieve expert consensus. We prioritised criteria for the radiological diagnosis of bronchiectasis and suggest recommendations on the use and central reading of chest CT scans to confirm the presence of bronchiectasis for clinical trials. Furthermore, we developed a set of consensus statements concerning the definitions of clinical bronchiectasis and its specific signs and symptoms, as well as definitions for chronic bacterial infection and sustained culture conversion. The diagnosis of clinically significant bronchiectasis requires both clinical and radiological criteria, and these expert recommendations and proposals should help to optimise patient recruitment into clinical trials and allow reliable comparisons of treatment effects among different interventions for bronchiectasis. Our consensus proposals should also provide a framework for future research to further refine definitions and establish definitive guidance on the diagnosis of bronchiectasis.

Introduction

Bronchiectasis is both the name of a disease and a single radiological appearance that might or might not be associated with disease.[1] Bronchiectasis can be a feature of many diverse clinical entities, including cystic fibrosis, chronic obstructive pulmonary disease (COPD) or asthma, and traction associated with interstitial lung disease or tuberculous-associated lung destruction.[2,3] In some cases, bronchiectasis might be asymptomatic, and radiological bronchiectasis has been documented in up to 20% of healthy adults older than 65 years.[4,5]

The prevalence and incidence of non-cystic fibrosis bronchiectasis (hereafter referred to as bronchiectasis) are rising in adults, and the condition places a considerable burden on health care with an effect on patients' quality of life and survival.[6–9] There is no licensed treatment for bronchiectasis, although physical and drug treatments that are effective in other diseases have been repurposed on the basis of variable evidence. Experts agree that the most important reasons for the scarcity of positive findings in randomised controlled trials (RCTs) of treatments for bronchiectasis, as well as two of the most notable challenges encountered in clinical practice, are disease heterogeneity and the absence of standardised clinical and radiological definitions. In clinical research, the heterogeneity of bronchiectasis is illustrated by the different characteristics of study populations enrolled in observational and interventional studies, as highlighted in studies involving bronchiectasis phenotypes, endotypes, and treatable traits.[10–14]

From a radiological perspective, international societies have suggested definitions of bronchiectasis according to chest CT findings.[15] However, these criteria are, to some degree, subjective, and the extent to which they are applied in clinical practice is unclear. Clinical trials and research studies on bronchiectasis generally require a radiological diagnosis of bronchiectasis made by a clinician. Therefore, a consensus among bronchiectasis experts on how to apply these criteria (eg, an absence of tapering of the airways, the ratio of an airway diameter to its adjacent artery diameter [airway–artery diameter ratio], and visibility of airways in the periphery) to make a radiological diagnosis of bronchiectasis is needed. An alternative approach to standardise clinical trials would be to require central reading of chest CT scans to confirm the presence of bronchiectasis.

From a clinical perspective, there is no consensus on what encompasses clinically relevant bronchiectasis in adults. This absence of consensus definitions might, in part, explain the heterogeneity of the enrolled study populations and the unexpected absence of significant treatment effects in large international clinical trials.[16,17]

Many other aspects of bronchiectasis as a disease are poorly defined, such as the terms idiopathic, post-infectious bronchiectasis, and coexisting comorbidities. Bacterial infection is a key treatable trait in bronchiectasis and consequently most clinical trials in bronchiectasis

have tested new or existing antibiotics, targeting patients with chronic bacterial infection or attempting to achieve microbial eradication.[18] However, there is no accepted definition of the often-used term bacterial colonisation or of important microbiological outcomes such as eradication. The published methods of RCTs on bronchiectasis have either not reported these definitions or, when they have been reported, the criteria for the definitions have differed between studies.[11] A key pathway to reproducibility in clinical research is the use of objective standardised inclusion and exclusion criteria and outcome measures, which are absent in bronchiectasis.

Motivated by the need to develop new therapies for bronchiectasis and reduce the burden of disease, an international taskforce of experts, including members of the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and the US Bronchiectasis and non-tuberculous mycobacteria Research Registry (BRR), was established to prioritise currently used criteria for the diagnosis of radiological bronchiectasis and to develop a consensus on definitions of clinically significant bronchiectasis in adults, as well as definitions for the terms bacterial colonisation and eradication.[19] Our consensus proposals are primarily intended to optimise patient recruitment into clinical trials, but could also be useful in daily clinical practice.

Methods

The process followed by this international group of experts was modelled on methods previously used to achieve a definition of bronchiectasis exacerbations.[20] SA, JDC, PCG, TRA, and AEO'D oversaw the project and invited individuals with expertise in bronchiectasis to participate in this project on behalf of EMBARC and the BRR.[19] This resulted in a taskforce of 34 bronchiectasis experts from Europe (representing EMBARC), North America (representing the BRR), the Middle East, Australasia, and South Africa (appendix p 2).

Two systematic reviews of radiological findings and clinical definitions of bronchiectasis used in RCTs from 2000 to 2020 and involving adults with non-cystic fibrosis bronchiectasis were done. The radiological findings from studies up to July 11, 2018, were based partly on a published systematic review,[10] and the clinical definitions from studies up to July 31, 2018, were previously published in a systematic review;[11] these were supplemented by updated radiological and clinical literature reviews done in June, 2020. The complete methods of the two systematic reviews are reported in the appendix (pp 4, 28). Chest CT definitions and the clinical signs and symptoms of bronchiectasis were identified, and individual criteria were extracted. JJM, SA, HT, PCG, JDC, MLC, and TV did the systematic review analyses and all authors participated in the discussion of the results.

Between May, 2017, and September, 2018, 31 taskforce members took part in four online surveys and four face-to-face meetings in Europe and the USA, at the second and third World Bronchiectasis Conferences (Milan, Italy, July, 2017; Washington, DC, USA, July, 2018) and two European Respiratory Society International Congresses (Milan, Italy, September, 2017; Paris, France, September, 2018), to facilitate grading of the criteria and Delphi processes to establish which radiological criteria and clinical signs and symptoms identified by the systematic searches should be included in the consensus criteria and definitions. Final consensus statements were then shaped by a core writing group (SA, JDC, PCG, TRA, and AEO'D). During the different stages of the phrasing and writing of these statements, checkpoint votes among all participants took place between meetings, and a minimum of 80% agreement was needed to proceed.

Radiological definitions

According to the results of the previously published systematic review[10] and updated literature review, experts were asked to grade each of the published radiological signs of bronchiectasis on chest CT as follows: (1) its presence does not make me confident in making the radiological diagnosis of bronchiectasis; (2) its presence makes me partially confident in making the radiological diagnosis of bronchiectasis; (3) its presence makes me confident in making the radiological diagnosis of bronchiectasis; or (4) its presence makes me highly confident in making the radiological diagnosis of bronchiectasis. The grading process was anonymous. For each of the criteria, a mean score was obtained from the average of grades across all participants. Criteria with mean scores of more than the overall mean value for all criteria together were taken to represent the criteria that were considered by clinicians to be the most discriminating for the diagnosis of radiological bronchiectasis. Furthermore, experts expressed their opinion through a Delphi process on the need for central reading of chest CT scans to confirm the presence of bronchiectasis as follows: (1) for all trials on bronchiectasis; (2) for all multicentre RCTs; (3) only for regulatory phase 3 RCTs; (4) only for very few studies (ie, specific RCTs that have a special focus on interventions that affect radiological endpoints, such as the radiological progression of bronchiectasis); or (5) central reading was not needed. On the basis of those results, statements about the role of radiological confirmation in patient recruitment for clinical trials were developed by the core writing group and voted upon by the experts.

Clinical definitions

The clinical criteria extracted from the previously published systematic review[11] and updated literature review provided a comprehensive list of signs and symptoms that were used to inform the experts about currently used definitions of clinical bronchiectasis. The experts were then asked to discuss each sign and symptom and a separate Delphi process was launched to

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See Online for appendix

	Mean scores
Inner airway–artery diameter ratio ≥1·5	3·50/4·00
Outer airway–artery diameter ratio ≥1·5	3·21/4·00
Lack of tapering	3·00/4·00
Visibility of airways in the periphery	2·89/4·00
Inner airway–artery diameter ratio ≥1·1	2·75/4·00
Inner airway–artery diameter ratio ≥1·0	2·71/4·00
Outer airway–artery diameter ratio ≥1·1	2·13/4·00
Outer airway–artery diameter ratio ≥1·0	1·88/4·00

Scores for radiological signs are presented as means of grades across all experts out of a possible total mean score of 4·00. The ratios of airway diameters to their adjacent artery diameters (airway–artery diameter ratios) were based on cutoff values from a published systematic review[10] and our updated literature search (appendix pp 6–27). Experts graded each of the criteria separately. An inner or outer airway–artery diameter ratio of ≥1·0 is still considered diagnostic for bronchiectasis, although use of criteria with higher gradings increases the likelihood of identifying true bronchiectasis. Notably, the first four criteria (inner or outer airway–artery diameter ratio of ≥1·5, lack of tapering of the airways, and visibility of airways in periphery) had scores of more than the mean value of all criteria together (2·76) and their presence provides the greatest confidence for making a diagnosis of radiological bronchiectasis.

Table 1: **Radiological criteria for the diagnosis of bronchiectasis in adults graded by the taskforce**

grade these signs and symptoms. Experts were able to add signs or symptoms that they deemed important, which were then graded in further Delphi rounds. Experts graded signs or symptoms regardless of the number of papers they were cited in. Signs and symptoms were graded as follows: (1) its presence does not define bronchiectasis as a clinical syndrome; (2) its presence makes the definition of bronchiectasis as a clinical syndrome more probable; (3) its presence is highly relevant for the definition of bronchiectasis as a clinical syndrome; or (4) its presence is mandatory to define bronchiectasis as a clinical syndrome. The grading process was anonymous. For each of the criteria, a mean score was obtained from the average of grades across all participants. Individual signs and symptoms with mean scores of more than the overall mean value for all criteria together were then discussed by the taskforce during the face-to-face meetings and a series of statements concerning the definition of bronchiectasis was developed by the core writing group and voted upon by the experts.

With regard to the definitions of chronic bacterial infection (formerly bacterial colonisation) and sustained culture conversion (formerly eradication), a condensed approach was followed, using all relevant papers from the first process to search for and list these definitions. Because some identified definitions were more concise than others, a Delphi process was not used and all relevant papers were summarised and directly used as a basis for discussion during face-to-face meetings, eventually leading to several draft consensus statements developed by the core writing group and again voted upon by the experts.

Results

Radiological definitions

We identified eight criteria for the radiological diagnosis of bronchiectasis in adults from 165 studies (122 studies from the previously published systematic review[10] and 43 from the updated literature review; see appendix p 5 for the study screening and selection process, and appendix pp 6–27 for the full results), which were graded by the taskforce (table 1). In the grading process, the following four criteria had a score of more than the mean value of all scores together (2·76): an inner airway–artery diameter ratio of 1·5 or more, an outer airway–artery diameter ratio of 1·5 or more, a lack of tapering of the airways, and visibility of airways in the periphery (table 1). In a Delphi process (three rounds, with a 100% response rate among all experts in each round), central reading of chest CT scans to confirm the presence of bronchiectasis was considered to have value by 91·7% of the taskforce members: 12·5% of the members thought it was necessary for all trials, 25% for all multicentre RCTs, 37·5% only for regulatory phase 3 RCTs, and 16·7% thought it was necessary only in very few studies. Two statements concerning recommendations for the use and central reading of chest CT scans to confirm bronchiectasis in clinical trials were developed on the basis of these results, both of which had 100% agreement among experts (table 2).

Clinical definitions

We identified 74 articles that reported definitions of bronchiectasis in adults (54 studies from the previously published systematic review[11] and 20 from the updated literature review; see appendix p 29 for the study screening and selection process, and appendix pp 30–34 for the full results). All possible criteria to define clinically significant bronchiectasis were considered in a Delphi process. After four Delphi rounds (with a 100% response rate among all experts in each round), 27 signs and symptoms were evaluated with a consensus of 80% or more reached for 22 of them. In the grading process, the following signs and symptoms had a score of more than the mean value of all scores together (≥1·9): a daily cough, chronic mucopurulent or purulent sputum, a history of exacerbations, daily sputum production, a daily productive cough, sputum production most days of the week, intermittent production of purulent sputum, a history of recurrent haemoptysis, and a cough sometimes during the week (figure 1).

A list of statements concerning the definitions of bronchiectasis, chronic bacterial infection, and sustained culture conversion with regard to the adult population was developed and discussed during the four face-to-face meetings. All statements that were developed are reported in table 2. A 100% consensus was obtained for all statements concerning the clinical definition of bronchiectasis (statements 1 to 4), and a consensus of more than 90% was obtained for the statements

	Consensus statements	Level of consensus among experts
General statement		
Statement 1	Bronchiectasis is a chronic respiratory disease that has multiple causes and is associated with different conditions, although in some patients, a cause cannot be identified (idiopathic disease); the diagnosis of clinically significant bronchiectasis as a disease requires both clinical and radiological criteria	100%
Radiological statements		
Statement 1	Confirmation of the presence of bronchiectasis on chest CT scans on the basis of an a priori accepted definition (table 1) is recommended for all clinical trials in adults and this could be done either at a local level or through central reading	100%
Statement 2	Central reading to confirm the presence of bronchiectasis on chest CT scans on the basis of an a priori accepted definition (table 1) could improve accuracy and should be strongly considered in clinical trials, especially for regulatory phase 3 trials	100%
Clinical statements		
Statement 1	Although there is a wide spectrum of signs and symptoms of bronchiectasis, most patients who meet a definition of clinically significant bronchiectasis will have at least two of the following: (1) a cough most days of the week; (2) sputum production most days of the week; (3) a history of exacerbations	100%
Statement 2	Some patients with radiological bronchiectasis are asymptomatic; the long-term prognostic significance of asymptomatic radiological bronchiectasis is unknown and requires additional investigations with longitudinal studies	100%
Statement 3	Underlying causes or conditions associated with bronchiectasis should be investigated; we caution against use of the terms idiopathic or post-infectious bronchiectasis unless other potential causes or conditions have been excluded	100%
Statement 4	Bronchiectasis can coexist with other common chronic airway diseases including asthma and COPD; the identification of treatable traits in this complex group of patients is important for management, appropriate enrolment in clinical trials, and new drug registration purposes	100%
Statement 5	Chronic bacterial infection* can be clinically defined as evidence of positive respiratory tract cultures of the same microorganism, by standard microbiology, on two or more occasions at least 3 months apart over 1 year while in a stable state, in the context of clinically significant bronchiectasis; cultures should be tested in accredited laboratories dealing with high-quality samples	94%
Statement 6	Sustained culture conversion† can be pragmatically defined as evidence of negative respiratory tract cultures for the targeted microorganism, by standard microbiology, on two or more consecutive occasions at least 3 months apart over 1 year; cultures should be tested in accredited laboratories dealing with high-quality samples	94%

COPD=chronic obstructive pulmonary disease. *During discussions, the taskforce agreed that the term chronic bacterial infection is preferable to bacterial colonisation. †During discussions, the taskforce agreed that the term sustained culture conversion is preferable to eradication.

Table 2: **Consensus statements on radiological criteria and clinical definitions for the diagnosis of bronchiectasis in adults in clinical trials**

regarding chronic bacterial infection (statement 5) and sustained culture conversion (statement 6). During discussions, the terms chronic bacterial infection and sustained culture conversion were preferred over the terms bacterial colonisation and eradication.

Discussion

The published RCTs to date that have tested interventions for adults with bronchiectasis have generally not specified radiological or clinical criteria to define the disease for patient enrolment. The heterogeneity of these study populations might be one of the possible causes for RCTs not meeting their primary endpoints and the resulting absence of licensed treatments.

The recognition of bronchiectasis as a chronic respiratory disease, as proposed here by the taskforce of international experts, is the first step to giving bronchiectasis the same recognition as other chronic respiratory conditions, such as COPD or asthma, and has important implications on many levels: (1) for health-care professionals to implement dedicated standard of practice initiatives as recommended by international treatment guidelines[1] and to improve patient outcomes; (2) for patients to be able to organise and associate themselves for advocacy purposes; (3) for pharmaceutical and device industries to develop evidence-based therapies; and (4) for researchers and regulatory entities to be able to better design, undertake, and interpret results from RCTs to improve health care and support patients with bronchiectasis.

From a radiological point of view, the taskforce, which was mainly composed of clinicians, decided not to pursue a stringent radiological definition of bronchiectasis, which would be a more appropriate task for an international society of radiology. However, the results of the prioritisation exercise indicated that among the different criteria for the radiological diagnosis of bronchiectasis reported in the literature, an inner or outer airway–artery diameter ratio of 1·5 or more, a lack of tapering of the airways, and visibility of airways in the periphery were the four criteria that made the taskforce experts most confident in making a radiological diagnosis of bronchiectasis on chest CT scans. It is not surprising that these criteria, representing more severe bronchiectasis radiologically, would be considered more likely to support a diagnosis of radiological bronchiectasis. The currently used diagnostic criteria require an inner or outer airway–artery diameter ratio of 1·0 or more.[10] The

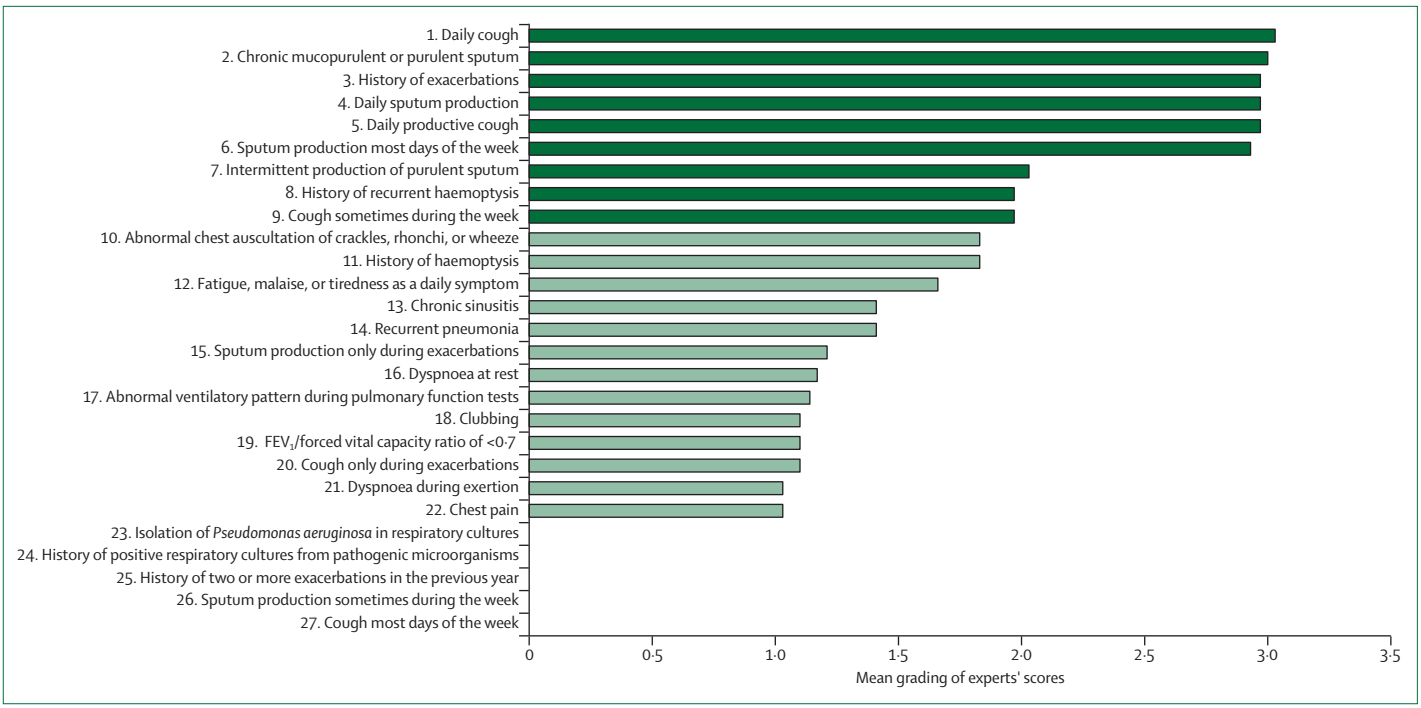

Figure 1: **Clinical signs and symptoms of bronchiectasis in adults graded by the taskforce**

Scores for clinical signs and symptoms are presented as means of grades across all experts out of a possible total mean score of 4·00. Experts graded each of the criteria separately. Dark green bars indicate signs or symptoms with mean scores of more than the overall mean value for all criteria together (≥1·9). Light green bars indicate signs or symptoms with mean scores of less than the overall mean value for all criteria together (<1·9). Criteria with mean scores of more than the overall mean cutoff value were further considered in the development of consensus clinical statements. Criteria 23–27 did not receive any expert votes and thus had a mean score of 0.

implications of the panel vote, whereby ratios of 1·0 or more had mean scores of less than 3·00 out of 4·00, indicates that a high proportion of clinicians found this only suggestive of a diagnosis. This result might reflect the increasing awareness of the frequency with which modest increases in the ratio are seen in asymptomatic older individuals or the artificial elevation of the ratio observed with changes in vascular size in COPD.[21] We therefore propose that the diagnosis of bronchiectasis should require at least one of the currently recognised diagnostic radiological criteria in combination with the clinical syndrome (figure 2).[10]

Concerning the inner versus the outer airway diameter, some caveats should be noted. On the one hand, the inner airway diameter of a widened airway can be reduced because of the presence of mucus attached to the airway wall, and is related to a patient's lung volumes during high-resolution CT scan acquisition. On the other hand, the outer airway diameter might be affected by bronchial wall thickening, which is common in inflammatory lung diseases such as bronchiectasis, potentially giving a false indication of bronchiectasis and leading to overdiagnosis of this disease.

The availability of central reading of chest CT scans to confirm the presence of bronchiectasis was considered of high value for clinical trials by the panel of experts. Confirmation of the presence of radiological bronchiectasis on chest CT scans on the basis of an a priori accepted definition was recommended for all clinical trials in adults, and this could be done either at a local level or through central reading. The grading of radiological signs of bronchiectasis and the radiological statements proposed here corroborate the clinical recommendations of the latest British Thoracic Society guidelines on bronchiectasis and integrate those with the importance of central reading from a research perspective.[22]

From a clinical point of view, the taskforce recognised that although there is a wide spectrum of signs and symptoms of bronchiectasis, most patients who meet a definition of clinically significant bronchiectasis will have at least two of the following: (1) a cough most days of the week; (2) sputum production most days of the week; or (3) a history of exacerbations. These criteria define bronchiectasis as a chronic respiratory disease for RCTs and for daily clinical practice. No sign or symptom was graded an overall mean score of 4·00 (ie, mandatory to define bronchiectasis as a clinical syndrome) by the panel of experts, with the highest mean score being 3·03 (figure 1). Thus, no single sign or symptom was considered to be 100% sensitive or specific for bronchiectasis. Crucially, the taskforce also agreed that the history of exacerbations criterion should be based on a standard definition of exacerbations, as proposed elsewhere.[20]

Notably, the clinical characteristics of patients to be included in RCTs can vary substantially depending on

the tested interventions and the study endpoints. The scientific community should benefit from an international agreement on the different and specific characteristics of patients to be enrolled in RCTs for comparisons of airway clearance therapy, inhaled antibiotic treatment, immunomodulatory or anti-inflammatory agents, and other interventions. Trial investigators should also consider patients who have clinically significant bronchiectasis (chronic respiratory disease) and have responded to treatment interventions that have reduced the severity of their signs and symptoms. Just as a patient with well controlled asthma still has asthma on the basis of their history of symptoms, there should also be recognition of the concept of clinically significant bronchiectasis that is well controlled from a symptomatic perspective. These patients with well controlled bronchiectasis who are asymptomatic should not be considered for RCTs enrolling patients with signs and symptoms of disease.

The relevance of radiological bronchiectasis in the absence of clinical symptoms is unknown given the incomplete understanding of the natural course of the disease process. Patients with signs of bronchiectasis on CT but without clinical symptoms should not be considered to have clinically significant bronchiectasis as a disease, and should not be included in clinical trials of bronchiectasis interventions except as part of natural history studies, possibly testing interventions that could prevent the appearance of signs and symptoms.

The taskforce cautioned against using the terms idiopathic or post-infectious bronchiectasis unless appropriate efforts have been made to identify other potential causes or conditions associated with bronchiectasis. The identification of an associated condition that underlies bronchiectasis is one of the most important steps to target treatable traits of the disease.[12] Data suggest that many patients with bronchiectasis do not receive basic testing for immunoglobulins, cystic fibrosis, or allergic bronchopulmonary aspergillosis, or culture studies for non-tuberculous mycobacteria.[23,24] When the association of bronchiectasis with other conditions is unknown despite appropriate testing, idiopathic is an appropriate term.[1] When the associations have not been investigated, however, this term should be avoided. An improvement in the understanding of bronchiectasis pathophysiology, microbiology, genetics, and inflammatory mediators, the potential development of an animal model, and the possible implementation of extensive clinical investigations are strategies that might increase the identification of causes of bronchiectasis and reduce the proportion of patients classified as having idiopathic disease.[25,26] The taskforce likewise advised against labelling bronchiectasis as post-infectious without testing for treatable traits given that the history of suspected pulmonary infection that initiates bronchiectasis is often remote and inaccurate, and several causes might coexist in the same individual.

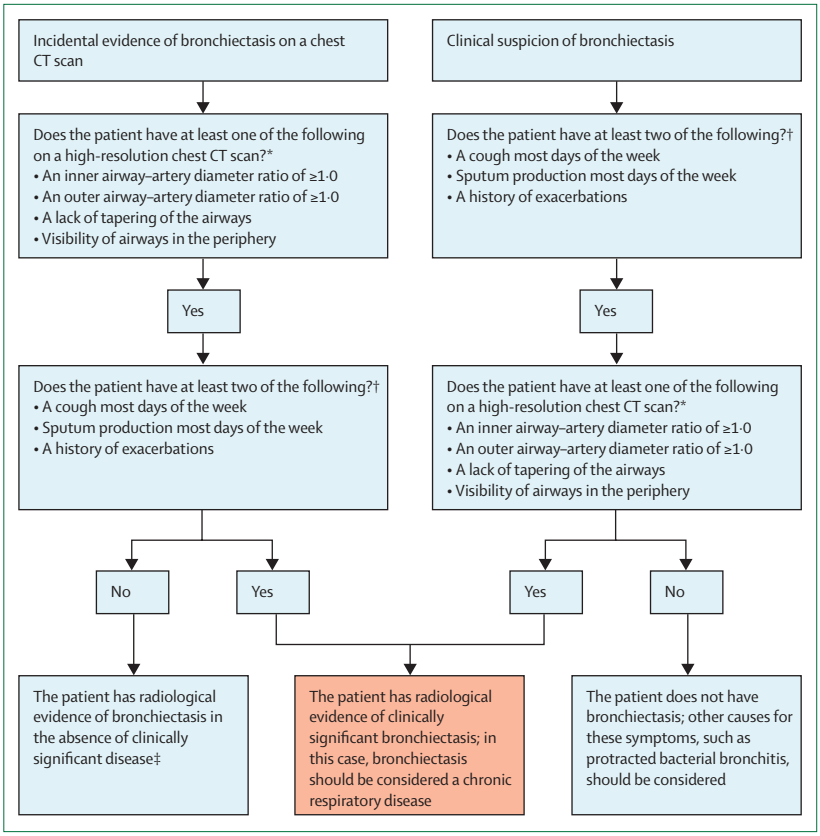

Figure 2: **Flow chart to define clinically significant bronchiectasis**
*The currently used diagnostic criteria require a ratio of the inner or outer airway diameter to its adjacent artery diameter (airway–artery diameter ratio) of 1·0 or more to define bronchiectasis;[10] a ratio of 1·5 or more, a lack of tapering of the airways, and visibility of airways in the periphery increase physicians' confidence in making a radiological diagnosis of bronchiectasis on chest CT, according to the grading process by the taskforce (table 1). †See clinical statement 1 in table 2; identification of at least two of the three criteria is intended for clinical trials, whereas the presence of even one of the three criteria might be sufficient in daily clinical practice to identify a patient with clinically significant bronchiectasis. ‡See clinical statement 2 in table 2.

The coexistence of bronchiectasis and other chronic respiratory diseases, such as COPD or asthma, is a debated issue. Bronchiectasis has been found in up to 72% of patients with severe COPD and 68% of patients with severe or uncontrolled asthma.[27] Most published studies suggest that the coexistence of bronchiectasis and chronic obstructive diseases is associated with increased airway inflammation, a higher number of exacerbations, worse lung function, and higher mortality than bronchiectasis alone.[28] Future clinical trials, according to the tested intervention and endpoints used, should exclude individuals with COPD. However, if the clinical trial investigators wish to include patients with COPD, a subgroup of patients with both diseases could be identified (eg, with COPD defined by a FEV_1/forced vital capacity ratio of <0·7 and at least ten packs-years of cigarettes or other substantial smoke exposure).[29] The prevalence of asthma in bronchiectasis reported so far is not based on a standard definition, and different criteria have been used to define the association between bronchiectasis and asthma.[27] A complete investigation of

the clinical, biological, and functional characteristics of asthma in bronchiectasis is therefore needed.

Infection is unanimously considered to be one of the key components of bronchiectasis pathophysiology, and assessment for the presence and type of chronic bacterial infection (formerly known as bacterial colonisation) is crucial for identifying appropriate antibiotic interventions. Studies have confirmed the negative effects of a chronic *Pseudomonas aeruginosa* infection, especially in patients with frequent exacerbations, on clinically meaningful outcomes such as quality of life, hospital admissions, and mortality.[30,31] The presence of a chronic bacterial infection has been reported as one of the key inclusion criteria in several published RCTs.[32] During the discussion process, the taskforce agreed that the term chronic infection should be preferred to bacterial colonisation, because the term colonisation implies that the presence of the bacteria is directly associated with tissue damage and inflammation. Additionally, in view of the heterogeneity of definitions for chronic bacterial infection in the literature, the panel of experts agreed that the clinical definition for chronic bacterial infection should be as follows: evidence of positive respiratory tract cultures of the same microorganism, by standard microbiology, on two or more occasions at least 3 months apart over 1 year while in a stable state, in the context of clinically significant bronchiectasis. This definition is pragmatic, balancing the need to demonstrate that the infection is sustained over time with the reality that most patients with bronchiectasis do not have sputum cultures taken more than two times per year in clinical practice. It is evident from this definition that meeting the microbiological criteria for trials might require multiple cultures of respiratory secretions, long-term follow-up, or both, and the experts agreed that cultures should be tested in accredited laboratories dealing with high-quality samples.

Notably, patients already prescribed long-term suppressive antibiotic treatment because of a chronic bacterial infection and with negative cultures during treatment should not be precluded from being classified as having a chronic infection. Chronic infection with other pathogens, such as viruses, non-tuberculous mycobacteria, or even fungi, might require different criteria, and this issue should be addressed in future studies. The experts also understood that the term intermittent infection is frequently used in clinical practice and in the cystic fibrosis literature.[33] However, in contrast to cystic fibrosis, there is little evidence for the usefulness of this term in bronchiectasis and thus it should be avoided in RCTs and clinical practice. As further knowledge is gained regarding the lung microbiome, which shows remarkable within-patient consistency over time,[34] it is possible that such terms will become obsolete. However, an incomplete understanding of the lung microbiome's effect on bronchiectasis means that the microbiome cannot be considered in the definition of clinically significant bronchiectasis at present.

A pragmatic definition for sustained culture conversion (previously referred to as eradication) has been proposed here as follows: evidence of negative respiratory tract cultures for the targeted microorganism, by standard microbiology, on two or more consecutive occasions at least 3 months apart over 1 year. The taskforce advocated against the use of the term eradication, which would ideally require demonstration of the sustained disappearance of the target organism (not only with standard microbiology but also with molecular techniques), which has not yet been shown. The term sustained culture conversion is consistent with the terminology used in the management of non-tuberculous mycobacteria and includes the possibility that actual eradication of the microorganism, or suppression of the organism to the extent that cultures are no longer positive, might be possible. The term also makes no assumptions regarding the nature of chronic infection. Some patients who apparently become negative for *P aeruginosa* in cultures will subsequently become culture-positive again. Whether this indicates a reinfection or re-emergence of the previous infection is not known. The term culture conversion is preferred, therefore, because it can be applied regardless of whether eradication of the microorganism was originally achieved. As for chronic bacterial infection, the definition of sustained culture conversion requires multiple cultures over time to establish the presence or absence of the microorganism. Notably, the level of certainty regarding its presence or absence depends on the number of cultures tested over a long period of time, and culture surveillance should follow international guidelines.[1] Finally, some patients with bronchiectasis and a first episode of infection who subsequently receive a targeted treatment might not expectorate further. Some experts suggest that this is indicative of sustained culture conversion.

We acknowledge that the statements presented here are based on expert opinion and the process did not follow formal guideline methods. We tried to mitigate this limitation by including a large representation of 34 international experts in bronchiectasis from 15 countries in five continents (appendix p 2) and by having the grading processes anonymised. The taskforce recognises that these statements might undergo changes in the near future, but they are necessary to raise awareness of bronchiectasis as a chronic respiratory disease in the clinical and scientific communities and to start optimising patient inclusion in trials.

More research is needed to narrow these statements to more specific subgroups of patients with bronchiectasis. Different directions and implications for future research can be identified according to the results of this project, including the following needs: (1) to investigate the long-term follow-up of asymptomatic patients with radiological bronchiectasis; (2) to elucidate the causes of idiopathic bronchiectasis and search for other treatable traits and specific treatments; (3) to evaluate not only comorbid conditions but also the interplay of different comorbid

Search strategy and selection criteria

References for this manuscript were identified through searches of PubMed for articles published from Jan 1, 2000, to Jan 31, 2021, using the search terms "bronchiectasis" and "definition". Articles published in English resulting from this search, and relevant references cited in those articles, were reviewed. The final list of cited articles was selected on the basis of their relevance to the aims of this Health-care Development paper. In addition, a reference list of papers retrieved from two systematic reviews, which were used to inform discussions and Delphi and grading processes for the development of the consensus proposals and recommendations reported here, is presented in the appendix (p 35), along with the full search criteria for the systematic reviews (appendix pp 4, 28).

conditions, and their effect on treatment response and clinical outcomes; (4) to explore the effect of chronic infection (according to different microbiological techniques used) and the evolution of infection over time in patients receiving or not receiving specific treatments; (5) to evaluate the concept of sustained culture conversion in light of the presence of new microbiological techniques; and (6) to work on standardisation of other definitions in the field of bronchiectasis.

Conclusions

This initiative by a taskforce of international experts in bronchiectasis has led to the prioritisation of currently used criteria for the radiological diagnosis of bronchiectasis and the development of definitions for clinically significant bronchiectasis in adults as a chronic respiratory disease with specific signs and symptoms, as well as definitions for chronic bacterial infection and sustained culture conversion. These definitions might help to standardise some key aspects of clinical trials in bronchiectasis and enable solid comparisons of treatment effects between different interventions. Although the objective of this taskforce was to develop definitions for clinical trials, these definitions could also be applicable to patients and clinicians in clinical practice (figure 2). However, the purpose of these definitions is not to override clinical judgement but to improve patient recruitment for clinical trials and help researchers to compare results from international studies. These proposals should now pave the way for the scientific community to reach a consensus on additional criteria to optimise methods for RCTs testing specific interventions for bronchiectasis to improve the likelihood of identifying effective treatments and reduce the burden of bronchiectasis for patients.

Contributors

SA, JDC, PCG, TRA, and AEO'D oversaw the project and invited the bronchiectasis experts to participate in this project on behalf of the European Multicentre Bronchiectasis Audit and Research Collaboration and the US Bronchiectasis and non-tuberculous mycobacteria Research Registry. JJM, SA, HT, PCG, JDC, TV, and MLC did the systematic review analysis and all authors participated in the discussion of the results. SA, JDC, PCG, TRA, and AEO'D drafted the initial series of statements concerning the definition of bronchiectasis. All authors, except for MLC, JJM, and TV, participated in the Delphi processes and the face-to-face meetings. SA drafted the manuscript. All authors contributed equally to the revision and final drafting of the manuscript. SA and JDC have accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SA reports personal fees from AstraZeneca, Bayer Healthcare, Chiesi, GlaxoSmithKline, Grifols, Insmed, Menarini, Zambon, and ZetaCube; and grants from Chiesi, Fisher & Paykel, and Insmed, outside of the submitted work. AFB reports personal fees from Wolters Kluwer and UpToDate, during the conduct of the study. FB reports personal fees from AstraZeneca, Chiesi, GlaxoSmithKline, Grifols, Guidotti, Insmed, Menarini, Novartis, Pfizer, Vertex, and Zambon; and grants from AstraZeneca, Bayer, Chiesi, GlaxoSmithKline, Menarini, and Pfizer, outside of the submitted work. JDC reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Insmed, Janssen, Novartis, and Zambon; and grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Gilead Science, Insmed, and Novartis, outside of the submitted work. MLC reports personal fees from AstraZeneca, outside of the submitted work. ADS reports grants and personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, Forest Labs, GlaxoSmithKline, Grifols, Insmed, Teva, and Zambon, outside of the submitted work. PCG reports personal fees from AstraZeneca and GlaxoSmithKline; and grants and non-financial support from Chiesi, outside of the submitted work. CSH reports personal fees from Aradigm, CSL Behring, GlaxoSmithKline, Grifols, Insmed, International Biophysics, Janssen, Meiji, Mylan, Novartis, Teva, and Zambon; and grants from Insmed, International Biophysics, and Teva, outside of the submitted work. MSM reports non-financial support from Boehringer Ingelheim, Insmed, and Zambon; and personal fees from Zambon, outside of the submitted work. MRL reports personal fees from AstraZeneca, Grifols, and Insmed, outside of the submitted work. AEO'D reports personal fees from Electromed, Insmed, and Zambon; and grants from AstraZeneca, Insmed, Janssen, and Zambon, outside of the submitted work. EP reports grants from Chiesi and Grifols; and personal fees from CSL Behring, Chiesi, Shionogi, Insmed, Shire, Teva, and Zambon, during the conduct of the study. FCR reports personal fees from AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Celtaxsys, Chiesi, Corbus, Grifols, InfectoPharm, Insmed, Novartis, PARI, Parion, Polyphor, Vertex, and Zambon; grants from Bayer Healthcare, Grifols, InfectoPharm, Insmed, Novartis, and PARI; and non-financial support from PARI, outside of the submitted work. MS reports personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kamada, Novartis, Teva, Vertex, and Zambon; grants from GlaxoSmithKline and Novartis; and non-financial support from Actelion, GlaxoSmithKline, and Rafa, outside of the submitted work. HT reports personal fees from Insmed, Novartis, Thirona, and Vertex; and grants from the Cystic Fibrosis Foundation, Insmed, and Novartis, outside of the submitted work. In addition, HT's institution, Erasmus MC, receives license fees for the chest CT image analysis PRAGMA-CF software developed by Thirona (Nijmegen, Netherlands) and by Resonance Health (Perth, Australia) and for the chest CT image analysis AA-method software co-developed by Erasmus MC and Thirona (Nijmegen, Netherlands). HT contributed to the development and validation of this software. GT reports grants from the US Bronchiectasis and non-tuberculous mycobacteria Research Registry (which is funded by the COPD Foundation); and personal fees from AstraZeneca and Cipla, outside of the submitted work. MV reports non-financial support from Chiesi, GlaxoSmithKline, Novartis, and Zambon; and personal fees from Insmed, outside of the submitted work. All other authors declare no competing interests.

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