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Inside this issue: Bronchiectasis.

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INTRODUCTION by Professor John Kolbe.

That this is the second APSR Respiratory Update solely on the topic of bronchiectasis, reflects the fact that this condition is, in the words of Professor Paul Torzillo, "shaking off its orphan status" (Lancet Respiratory Medicine 2016; 4:927-928). This enhanced status is further reflected in the continued expansion of publications on the condition providing an increasingly secure base for management, and in the early publications based on databases established in the US and Europe. Pleasingly the name "bronchiectasis" has been reclaimed and the the term "non-CF bronchiectasis" is being used much less frequently.

Adult Patients with Bronchiectasis. A first look at the US Bronchiectasis Research Registry.

Authors: Aksomit T R et al

Reference: Chest 2017; 151: 982-992

URL:https://doi.org/10.1016/j.chest.2016.10.055

This is the first report arising from the US Bronchiectasis Research Registry, based on 13 participating centres and the enrolment of 1826 patients between 2008 and 2014. Patients were predominantly elderly (mean age of 64 years), white (79%), female (79%), non smokers (60%) with non-tuberculous mycobacterial infection (NTM) (63%) – with mostly MAIC but about 20% were M. abcessus/chelonae. These are interesting demographic data which seemingly fit the profile of those with the so-called "Lady Windermere's Syndrome". However they may not be representative of the overall bronchiectasis population and it was acknowledged that the cohort was enrolled from tertiary institutions with an interest in NTM. The right middle lobe was the most frequently involved lobe (69%) but the more widespread nature of the disease was reflected in the fact that only 11% had single lobe involvement. Despite being the mainstay of management with proven benefit in terms of quality of life, sputum volume and exercise capacity, only 56% were using "non-pharmacologic measures to improve bronchial hygiene" with most using a Flutter device or PEP valve.

Another publication entitled "Pharmacotherapy for non-cystic fibrosis bronchiectasis" (Chest 2017; 152(6): 1120 – 1127; https://doi.org/10.1016/j.chest.2017.04.167) analysed data from this registry (but now entitled "Bronchiectasis and NTM Research Registry") and from survey responders from a non-profit NTM patient advocacy organisation. The results are noteworthy for the high rate of use of inhaled corticosteroids – 36% in those with NTM and 42% in those without. This is despite the Cochrane Systematic Review on the subject concluding that there is no convincing evidence of benefit from the use of inhaled cortico-

steroids (ICS) in this condition, and that in chronic airways disease the use of ICS seemingly increases the risk of NTM infection.

While the establishment of the US registry is a tremendous step forward, highlighting the condition and advocating on behalf of patients, the inclusion of such a selective population has the potential to distort our understanding of this condition. The challenge is now to expand the registry, to recruit from a wider range of centres, to be more geographically representative, and to include ethnic minorities – and thus be more representative of the overall bronchiectasis population and produce data that is more generalizable.

Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration.

Author: Aliberti et al

Reference: European Respiratory Journal 2016; 48: 632 – 647

URL: http://erj.ersjournals.com/content/48/3/632.long

Further demonstrating the renewed interest in bronchiectasis, the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) has been established under the auspices of the European Respiratory Society, "to promote high quality research in bronchiectasis". This publication outlines the 55(!) key research priorities in this area, established by consensus by European bronchiectasis experts, patients and their families and resulting in 22 summary recommendations. These recommendations range from the establishment of DNA biobanks to enable study of genetic susceptibility, through observational studies of large cohorts to better understand the natural history of the condition, to a number of randomised controlled trials of management strategies. This exercise to define key research priorities is an ambitious undertaking that will serve to focus much needed research in forthcoming years. One of the strengths of this endeavour is that it brought together the perspectives of "experts" and patients to produce a shared vision of research priorities.

The European Respiratory Society has also published "Guidelines for the Management of Adult Bronchiectasis". (European Respiratory Journal 2017; 50:1-22). The format of this document, developed by a multidisciplinary group, is to comprehensively address nine, clinically highly relevant questions, providing recommendations, evidence, justification and commentary on each of the specific issues. As well as being highly informative, this article provides management recommendations that could be used for audit, benchmarking and quality improvement. However, relevant to the EMBARC research priorities, was the acknowledged low quality of evidence for a number of the recommendations.

Aetiology of bronchiectasis in adults: A systematic literature review.

Author: Gao Y-H, et al

Reference: Respirology 2016; 21: 1376-1383

URL: https://onlinelibrary.wiley.com/doi/full/10.1111/resp.12832

This systematic literature review identified 56 studies of a total of 8608 adults with bronchiectasis. Reflecting the lack of a consistent definition for "idiopathic bronchiectasis" but also possibly regional differences and referral bias, the crude prevalence for identified aetiologies ranged from 18 to 95%. Overall an underlying cause could not be identified in about half (44.8%). Of the "known" aetiologies, post infection was the most frequent (29.9%), of which post-tuberculosis was most common. Identification of an etiology that led to a change in management occurred in only 18%.

However there are recognised specific aetiologies/associations of bronchiectasis and some of these have recently been reviewed; bronchiectasis-rheumatoid overlap syndrome (Chest 2017; 151(6): 1247 – 54), the yellow-nail syndrome (Respirology 2017; 22: 10177) and primary ciliary dyskinesia (Expert Review of Respiratory Medicine 2017; 11: 779 – 90).

Multi-dimensional severity assessment in bronchiectasis: an analysis of seven European cohorts.

Authors: McDonnell MJ et al

Reference: Thorax 2016:71:1110-1118

URL: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/27516225/

In a previous APSR Respiratory Update, the two composite, disease-specific, clinical prediction tools (the Bronchiectasis Severity Index (BSI) and FACED score) were reviewed. A recently published single centre cohort analysis extended these findings by demonstrating that both scores were able to predict 15-year mortality, but with the FACED score showing slightly superior predictive power (Eur Respir J 2016; 47: 482-9).

This paper describes the head-to-head comparison of the predictive utility of these two instruments in a large, combined European cohort (n=1612). As there is a considerable commonality in the factors included in these indices, it is not surprising that both scores had a good discriminatory predictive value for mortality. However the BSI demonstrated a higher sensitivity (65% vs 28%) but lower specificity (70 vs 93%) compared with the FACED score. The BSI

performed more consistently across all degrees of severity and was superior to FACED in predicting other clinically useful outcomes including hospital admissions, exacerbations, quality of life, respiratory symptoms, exercise capacity and lung function decline. This is not surprising as the FACED was developed to specifically predict mortality while the BSI was developed to predict mortality and other outcomes. While the BSI may be more useful to stratify patients on the basis of risk of future exacerbations, it needs to be borne in mind that the BSI is more complex than FACED.

In practical terms, the BSI may enable the identification of "high risk" patients in terms of current symptom burden or likely future morbidity for whom more intensive treatment would be indicated, and "low risk" patients who may require less intensive therapy and non-specialist follow-up.

These instruments have only been evaluated in European cohorts and studies validating these instruments in the Asia-Pacific populations would seem to be required.

Comorbidities and the risk of mortality in patients with bronchiectasis: an international cohort study.

Author: McDonnell MJ et al

Reference: Lancet Respiratory Medicine 2016; 4: 969 – 79

URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5369638/

The Bronchiectasis Severity Index (BSI) and the FACED score were both developed and validated in large cohorts, to predict mortality and morbidity in bronchiectasis. Understandably these indices focussed on clinical, physiological, radiologic and microbiological features of bronchiectasis. However, bronchiectasis patients frequently have comorbidities that may be "causative, synergistic or coincidental ….". These comorbidities may contribute to symptoms, functional impairment, morbidity, including hospitalisations, and mortality in patients with bronchiectasis.

In an observational cohort analysis of 986 bronchiectasis patients in four European centres, comorbidities were defined and used to develop the Bronchiectasis Aetiology Comorbidity Index (BACI). The median number of comorbidities per patient was four. Thirteen comorbidities which independently predicted mortality were integrated into the BACI. The BACI predicted five year mortality, hospitalisations, exacerbations and health-related quality of life, across all BSI risk strata. The hazard ratio (HR) for death conferred by a one point increase in the BACI was 1. 18 (95%, 1.14 – 1.23); individual comorbidities attracted a score which ranged from 12 (metastatic malignancy) to 2 (peripheral vascular disease and ischaemic heart disease). COPD, inflammatory bowel disease, connective tissue disease and asthma were also associated with a

higher risk of mortality. Even when a model was developed excluding conditions considered to be aetiologically significant, the HR was very similar (1.17). The BACI was validated in an independent cohort of 113 patients. However a prediction model incorporating both BSI and BACI was superior to either model alone for predicting five year mortality.

In summary, comorbidities are common in bronchiectasis, may be independent risk factors for morbidity and mortality and may contribute to the systemic inflammation seen in this condition. An online calculator for BACI is available at http://www.bronchiectasisseverity.com. At the very least this publication reminds us of the importance of identifying, assessing and managing comorbidities as part of the overall management of bronchiectasis.

Bronchiectasis severity is an independent risk factor for vascular disease in a bronchiectasis cohort.

Author: Evans IES et al

Reference: Chest 2017; 151: 383 – 8.

URL: https://doi.org/10.1016/j.chest.2016.09.022

Bronchiectasis is associated with systemic inflammation. A recent study, based on a retrospective database showed that bronchiectasis severity as determined by the BSI, was independently associated with the development of vascular disease (ischaemic heart disease, cerebrovascular disease, peripheral vascular disease and atrial fibrillation) after the diagnosis of bronchiectasis. Bronchiectasis severity as determined by the BSI was independently associated with the development of vascular disease.

Further, a population-based study of almost four million persons demonstrated that pre-existing diagnoses of coronary heart disease (CHD) and stroke were higher in persons with bronchiectasis than those without bronchiectasis, after adjustment for other risk factors including age, sex, smoking status and other risk factors for cardiovascular disease (Thorax 2017; 72:161 – 6). “In absolute terms our findings suggest that if a cohort of 100 people with bronchiectasis were followed up for five years, they would have three CHD events and five strokes whereas 100 people without bronchiectasis would have one CHD event and one stroke.”

Thus there is the possibility that the pro-inflammatory state of bronchiectasis may have consequences in terms of vascular diseases. This has relevance in terms of the influence of comorbidities on health care utilisation and mortality and on potential therapeutic interventions, needs further consideration (see next).

A randomised controlled trial of atorvastatin in patients with bronchiectasis infected with Pseudomonas aerigunosa. A proof of concept study.

Author: Bedi P et al

Reference: Chest 2017; 152:368 – 78

URL: https://doi.org/10.1016/j.chest.2017.05.017

Bronchiectasis is associated with system inflammation and statin drugs have anti-inflammatory (as well as other) properties. An earlier study by the same group from Edinburgh demonstrated that atorvastatin reduced cough, enhanced neutrophil apoptosis and reduced CXCL8 (also called IL8) in patients with moderately severe bronchiectasis without chronic infection with Pseudomonas aerigunosa (PA). (Lancet Respir Med 2014: 2: 455-63.)

This double-blind, cross-over, randomised trial of 32 patients with more severe bronchiectasis and chronic infection with PA, demonstrated that three month treatment with the statin atorvastatin did not improve the primary outcome of cough (as assessed by Leicester Cough Questionnaire) but did improve quality of life (assessed by St George's Respiratory Questionnaire) and reduced levels of a number of inflammatory cytokines including CXCL8, tumour necrosis factor and intercellular adhesion molecule 1.

To determine whether statins have any role in the management of bronchiectasis will require a much longer study with important patient centred outcomes.

Bronchoarterial ratio in non-smoking adults: implications for bronchial dilation definition.

Authors: Dias AA et al

Reference: Respirology 2017; 22: 108-113

URL: https://onlinelibrary.wiley.com/doi/full/10.1111/resp.12875

The defining radiologic feature of bronchiectasis is that of “airway dilation” based on the ratio of the diameter of the bronchial lumen (B) and the adjacent pulmonary artery (A). A BA ratio of >1 is the usual threshold for the radiologic diagnosis of bronchiectasis in adults. The usual assumption is that an increased BA ratio is due to an increased airway lumen, but could also be due to reduced artery calibre.

This study of the inspiratory CT scans of 106 never smokers, controls in the COPD Gene study, mean age 62 years and 70% female, examined two bronchial paths; the right upper lobe apical bronchus (RB1) and the right lower lobe posterior basal bronchus (RB10), chosen because the airway branches of these segments are usually orthogonal to the axial plane. The bronchial lumen and artery diameters were measured manually at points along the path.

Overall the BA ratio was 0.79±0.16. In the RB1, but not the RB10 path, the BA ratio decreased in peripheral airway generations. The BA ratio was >1 in 8.5% of these normal subjects. In those with BA>1, the artery diameter was smaller but bronchial lumen was not larger than those with a BA ratio <1. In other words, the increased BA ratio is a broncho-vascular process rather than solely a bronchial abnormality and in non-smokers a BA ratio > 1 is driven by small arteries rather than luminal diameter. In multivariate analysis, BA ratio was significantly associated with FEV1 and bronchial lumen size was more strongly correlated with FEV1 than pulmonary artery diameter. These findings are consistent with the concept of dysanapsis : that the bronchial tree and lung parenchyma may develop relatively independently of each other. However these findings have important implications for the diagnosis of bronchiectasis; clinically and epidemiologically.

All clinicians will be familiar with the unexpected radiologic reporting of mild thin walled bronchiectasis, usually in the basal segments of the lower lobes in elderly patients who do not have the clinical phenotype of bronchiectasis. Radiologic evidence of bronchiectasis has been reported in up to a half of patients with severe COPD, and also in patients with chronic severe asthma. In a study of the CT scans of 21 smokers with radiologic evidence of bronchiectasis and 21 non-smoking controls, the BA ratios were higher in smokers with mild bronchiectasis (as expected) but the increase was due to reduced calibre of the pulmonary artery and not due to an increase in airway lumen size. Those with an increased BA ratio had evidence of more severe airflow obstruction (Chest 2017; 151: 1255-62). Thus

smoking related increases in the BA ratio seem to be due to reductions in vascular calibre rather than bronchial dilatation – termed “mistaken identity” in the accompanying editorial.

There would seem to be the need to review the use of artery diameter as a reference to determine bronchial dilatation. The diagnosis of bronchiectasis is a clinical one and clinicians need to interpret CT scans showing a BA ratio >1 in association with the patient’s clinical features. Radiologic bronchiectasis may be common, but clinically significant bronchiectasis may be much less common, in COPD .

Pseudomonas aeruginosa adaption and diversification in the non-cystic fibrosis bronchiectasis lung.

Authors: Hilliam et al

Reference: European Respiratory Journal 2017; 49: 1602108.

URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5898933/

In cystic fibrosis, there is evidence of the coexistence of multiple divergent lineages of Pseudomonas aerigunosa (PA), and a number of transmissible strains of PA have been identified. Whether the same applies to bronchiectasis is unclear.

This study of whole genome sequencing of 189 PA isolates from 93 patients with bronchiectasis from 16 centres in England and Wales demonstrated that the distribution of the PA isolates from bronchiectasis patients were representative of the wider PA population. There was evidence of multi-lineage infections, and some sharing of PA with the same clonal lineage within the same clinic suggesting common source acquisition or cross-infection. A larger longitudinal study will be needed to determine if there is person to person transmission of PA in the bronchiectasis patient community.

As in CF, there was evidence of adaption of PA to the lung environment by the accumulation of loss of function mutations, leading to changes in phenotype, including different modes of iron acquisition, changes in twitching motility and variations in biofilm-associated polysaccharides.

FUT2 Genotype Influences lung function, exacerbation frequency and airway microbiota in non-CF bronchiectasis.

Author: Taylor SC et al

Reference: Thorax 2017; 72: 304 – 310

URL: http://dx.doi.org/10.1136/thoraxjnl-2016-208775

Disease progression in bronchiectasis is variable and difficult to predict. One factor influencing this progression is the airway microbiota; those with chronic Pseudomonas aeriguno-sa (PA) infection having faster decline in lung function, more symptoms, worse quality of life, more frequent pulmonary exacerbations and greater antibiotic requirements. Microbes use glycans on the respiratory mucosal surface to adhere. Thus variability of the expression of these glycans may affect the susceptibility to infection by certain microbes and subsequently the airway microbiome composition. The FUT2 gene encodes fucosyltranferases which act to attach fucose to disaccharide precursors and hence control the expression of ABO antigens on the epithelial mucin glycans. Homozygous loss of function mutations in the FUT2 (secretor) gene results in the inability to express a number of glycans on the mucosal surface.

Australian investigators studied the secretor genotype (the effect of loss of function mutations of the FUT2 gene, both heterozygous and homozygous) on disease severity in 112 adults with bronchiectasis. FUT2 genotype was associated with disease progress; homozygous secretors had lower lung function, greater number of exacerbations and a higher rate of PA infection than homozygous non-secretors. Patients with a heterozygous genotype demonstrated an intermediate phenotype. The authors speculated that the effect of secretor status may be through susceptibility to respiratory viral infection. There is no direct link between secretor status and PA infection.

Thus secretory genotype is a factor influencing type of chronic microbiological infection and disease severity and progression in bronchiectasis. Bronchiectasis has a complex and incompletely understood aetiology, but this may represent an early step towards the use of precision medicine for a more effective approach to patient management in this condition.

The development and validation of the Bronchiectasis Health Questionnaire (BHQ).

Authors: Spinou A et al

Reference: European Respiratory Journal 2017; 49:

URL: http://erj.ersjournals.com/content/49/5/1601532.long

The authors of the editorial accompanying this article emphasise that there are three different dimensions of any disease; severity, activity, and impact, and that the last of these is usually evaluated by quality of life questionnaires. In a previous APSR Respiratory Update, the report of the first disease -specific quality of life questionnaire for bronchiectasis (Quality of Life – Bronchiectasis (QoL-B)) was reviewed.

This paper reports on the development and validation of another disease-specific quality of life questionnaire – the Bronchiectasis Health Questionnaire (BHQ). This BHQ is simpler; it has 10 items in one domain, compared with the 37 items and eight domains of the Qol-B. The BHQ provides a single overall health status score which was shown to correlate with numbers of exacerbations and hospitalisations, radiologic severity and bacterial colonisation. The Questionnaire has been translated into a number of languages including Japanese and Mandarin and has been tested in a single center in China. However the minimally clinically significant difference has not yet been determined, nor has the instrument's responsiveness to interventions. While the BHQ meets the criteria for a good quality instrument in terms of internal consistency, validity (most items reflect a good quality clinical history) and repeatability, it does not quantify health status in the psychological, activity and social domains. Thus while the BHQ has the great advantage of brevity and simplicity, the QoL-B has advantages if a more in-depth analysis of health status is required, particularly in certain specific domains.

Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research.

Authors: Hill AT et al

Reference: Eur Respir J 2017; 49: 1700051.

URL: http://erj.ersjournals.com/content/49/6/1700051.long

This consensus definition of bronchiectasis was "unanimously approved" by a multinational, broad-based group of experts following a systematic review of the literature, a Delphi process and a round table discussion. An exacerbation for the purposes of clinical research requires at least 3 of 6 symptoms for 48 hrs and a clinician determining that a change in treat-

ment is indicated. Thus the definition includes 3 features - the development of symptoms, duration of symptoms and a management change. While there are no surprises in the definition, the development of such an agreed definition of an oft-used primary outcome is an important step forward for standardisation of clinical research in this condition.

The BRICS (Bronchiectasis Radiologically Indexed CT Score). A multicentre study score for use in idiopathic and post-infective bronchiectasis.

Authors: Bedi P et al

Reference: Chest 2018; 153: 1177-1186

URL: https://doi.org/10.1016/j.chest.2017.11.033

This paper describes the development of a simplified radiologic score (BRICS) in 184 patients. Patients who were current smokers or had a >5 pack year smoking history were excluded. The score was based on a multivariable analysis of components of the Bhalla score (Radiology 1991; 179: 783-788) and included those components that were significantly associated with the disease severity markers viz degree of bronchial dilatation and number of broncho-pulmonary segments with emphysema. The score for BRICS ranged from 0 to 5; 1 indicated mild disease, 2 – 3 indicated moderate disease and 4 – 5 indicated severe disease. The ROC curve values in the derivation cohort were 0.79 for per cent predicted FEV1, 0.71 for sputum purulence and 0.75 for hospital admissions per year. Similar ROC curve values were obtained in the validation cohort of 302 patients in six centres.

The higher levels of neutrophil elastase activity in the group with emphysema on CT scan suggested that elastase may be the cause of emphysema in this group. There was a strong correlation between the severity of the BRICS and the severity of the BSI and FACED score ($p<0.001$ for both scores). However neither the BSI or FACED scores were significantly correlated with percent predicted FEV1, sputum purulence or hospital admissions for bronchiectasis exacerbations.

The BRICS is a simple, robust scoring system based on CT features alone, that correlates significantly with important clinical parameters and predicts disease severity in patients with idiopathic and post-infective bronchiectasis.

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