Welcome to this November issue of Respiratory Research Review with the focus on bronchiectasis and CF (cystic fibrosis). Bronchiectasis may be close to the tipping point of losing its orphan status – probably a function of the increasing incidence, great clinical research and up-to-date practical guidelines. Approximations of the current incidence are around 500 per 100,000 people. Bronchiectasis is commonly found in patients with a diagnosis of asthma and COPD. It is estimated that about 1 in 20 patients with COPD also have bronchiectasis. Bronchiectasis also coexists with HIV infection, rheumatoid arthritis, inflammatory bowel disease and pulmonary fibrosis. The world of CF is changing rapidly, and I am proud that many of my nursing colleagues have been acknowledged for their complex, crucial and competent work (Kai Tiaki Nursing New Zealand 2017;23[5]:14–28). New treatments and treatment combinations addressing some of the underlying pathophysiologies are entering clinical care, and when the ‘first-in-human’ trial in patients with CF is positive, we may have a viral vector to deliver the correct gene, about 100-fold more potent than nonviral, liposomal carriers.

While the aforementioned review covered essential areas of bronchiectasis in seven pages including diagrams and tables, the updated European Respiratory Society guidelines on the management of adult bronchiectasis occupies 23 pages. Still, by using the style of focusing on key clinical questions, they are surprisingly readable. I urge the reader to glance at either of these free-to-view documents; here are only the headline key clinical questions:

- Is standardised testing for the cause of bronchiectasis beneficial when compared with no standardised testing? (yes)
- Are courses of 14–21 days of systemic antibiotic therapy compared with short courses (≤14 days) beneficial for treating adult bronchiectasis patients with an acute exacerbation? (yes)
- Is eradication treatment beneficial for treating bronchiectasis patients with a new isolate of potentially pathogenic micro-organisms in comparison with no eradication treatment? (yes)
- Should long-term anti-inflammatory agents like inhaled corticosteroids be used in adult patients with bronchiectasis? (no)
- Is long-term antibiotic treatment (>3 months) compared with no treatment beneficial for adult bronchiectasis patients? (probably yes)
- Is long-term mucoactive treatment (>3 months) compared with no treatment beneficial for treating adult bronchiectasis patients? (probable yes)
- Is long-term bronchodilator treatment (>3 months) compared with no treatment beneficial for adult bronchiectasis patients? (no)
- Are surgical interventions more beneficial compared with standard (nonsurgical) treatment for adult bronchiectasis patients? (no)
- Is regular physiotherapy (airway clearance and/or pulmonary rehabilitation) more beneficial than control (no physiotherapy) in adult bronchiectasis patients? (yes)
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The Abbreviations used in this issue:

- BCSO = bronchiectasis-COPD overlap syndrome
- BROS = bronchiectasis-rheumatoid arthritis overlap syndrome
- BSI = Bronchiectasis Severity Index
- CF = cystic fibrosis
- CFTR = cystic fibrosis transmembrane conductance regulator
- COPD = chronic obstructive pulmonary disease
- FEV1 = forced expiratory volume
- QOL = quality of life

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Adult patients with bronchiectasis: a first look at the US Bronchiectasis Research Registry

Authors: Aksamit TR et al.

Summary: The characteristics of 1826 adult registry patients with bronchiectasis from the US Bronchiectasis Research Registry were reported. A history of nontuberculous mycobacterial disease or nontuberculous mycobacteria isolated at baseline evaluation was present for 63% of the patients, and such patients were older, were mainly female, had bronchiectasis diagnosed at a more advanced age and had more gastro-esophageal reflux disease than those without nontuberculous mycobacteria. Patients without nontuberculous mycobacteria had more asthma, primary immunodeficiency and primary ciliary dyskinesia. Evidence of airflow obstruction was seen on spirometry in 51% of patients, and those with nontuberculous mycobacteria were more likely to have diffusely dilated bronchiectasis diagnosed at CT in 51% of patients, and those with nontuberculous mycobacteria had more asthma, primary immunodeficiency and primary ciliary dyskinesia. Patients without nontuberculous mycobacteria used bronchial hygiene measures more often, and those without nontuberculous mycobacteria used antibiotics for exacerbations, rotating oral antibiotics, steroids and antimicrobials more often.

Comment: In other illnesses, like interstitial lung disease or pulmonary arterial hypertension, registries provide great insights, assist us to articulate the correct research questions, and act as a reservoir for patients. Here, the US authors offer insights into their registry from 13 US sites, analysing almost 2000 patients. Patients were predominantly female, white nonsmokers with a mean age of 64 years. It was not surprising 63% had co-existing nontuberculous mycobacteria; however, it was surprising that 39% used inhaled steroids despite a lack of evidence to support their use. Also surprising, the bottom line: despite good evidence, airways clearance techniques were only performed in about half of patients with bronchiectasis.


The development and validation of the Bronchiectasis Health Questionnaire

Authors: Spinou A et al.

Summary: Questionnaire data from 206 outpatients with clinically stable bronchiectasis were used to develop the BHQ (Bronchiectasis Health Questionnaire). Responses to a 65-item questionnaire were used to establish the final 10-item version of the BHQ, which displayed good internal consistency (Cronbach’s α=0.85) and high and moderate convergent validity with the St George’s Respiratory Questionnaire and percent FEV₁, predicted, respectively (r values −0.27 and −0.82 [p<0.001]). Significant associations were seen between BHQ score and number of bronchiectasis exacerbations in the prior 12 months, hospital admissions and bronchiectasis pulmonary lobe counts on CT (p<0.001 for all). Patients with spumt bacterial colonisation had significantly worse BHQ scores than noncolonised patients (p=0.048). Repeatability of the BHQ after 2 weeks was high (intraclass correlation coefficient 0.89).

Comment: Severity and prognosis of bronchiectasis can be gleaned from the BSI or FACED scores (Respiratory Research Review, issue 106). A group of European researchers developed, validated and translated a simple 10-item score to assess the QOL in patients with bronchiectasis. This new BHQ score is based on self-reported tiredness, slowness, anxiety, feeling of a clear chest, sputum production, shortness of breath, sleep disturbance, coughing fits and antibiotic treatment in the last 14 days. Bottom line: the new BHQ score is a quick, 10-item, valid score to measure the QOL of patients with bronchiectasis in the clinic.

Reference: Eur Respir J 2017;49(5):1601532

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

Authors: Hill AT et al.

Summary: Definitions used for bronchiectasis exacerbations in clinical trials between January 2000 and December 2015 were systematically reviewed by experts from Europe, North America, Australasia and South Africa, with the aim of reaching a consensus definition. The definition unanimously approved by the working group was a person with bronchiectasis with a deterioration in ≥3 key symptoms for ≥48 hours.

Comment: This article summarises the scientific process and findings of a group of international bronchiectasis experts, including our colleague Conroy Wong from Wairtemata Health, to define an exacerbation in adult patients with significant bronchiectasis. Having a clearly defined definition will assist clinical trial work, because times between exacerbations or severity of exacerbation are important clinical endpoints. Bottom line: an exacerbation of bronchiectasis is defined as three of the following key symptoms for at least 48 hours: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required.


Reference: Eur Respir J 2017;49(5):1601532

Bronchiectasis rheumatoid overlap syndrome is an independent risk factor for mortality in patients with bronchiectasis

Authors: De Soyza A et al.

Summary: This analysis examined data from six cohorts of patients (n=1716) from specialist bronchiectasis services around the world to determine if patients with BROS (bronchiectasis-rheumatoid overlap syndrome) have worse outcomes than those with bronchiectasis of other aetiologies by applying the BSI. BROS was significantly associated with mortality, although this relationship was not associated with increased bronchiectasis exacerbation or bronchiectasis-related hospitalisation rates. Over a mean 48-month follow-up, mortality rates were 9.3% for idiopathic bronchiectasis, 8.6% in patients with other causes of bronchiectasis, 18% for rheumatoid arthritis and 28.5% for BCOS (bronchiectasis-COPD overlap syndrome). BROS and BCOS were associated with significantly higher mortality than other bronchiectasis aetiologies. Compared with idiopathic bronchiectasis, BROS was associated with a statistically, but not clinically, significantly higher mean BSI score (7.7 vs 7.1 [p<0.05]). BCOS was associated with a higher mean BSI score (10.4). Pseudomonas aeruginosa colonisation rate (24%) and previous hospitalisation rate (58%).

Comment: As mentioned in the introduction, bronchiectasis can occur in patients with respiratory illnesses like COPD, or with connective tissue disorders like rheumatoid arthritis without interstitial lung disease. The authors pooled data from six databases from the UK, Ireland and Belgium and discovered an overlap with COPD in 12%; these patients are more likely to be male, older and have a lower FEV1; their mortality rate at 2 years was 28.5%.

Bottom line: a total of 8.5% of patients with bronchiectasis also had rheumatoid arthritis; their mortality at 2 years was 18%, about twice the mortality rate of idiopathic bronchiectasis.

Reference: Chest 2017;151(6):1247–54

Abstract

Bronchiectasis in yellow nail syndrome

Authors: Woodfield G et al.

Summary: These authors reported on 25 adult clinic patients with bronchiectasis who also had yellow-nail syndrome, each matched to two controls with idiopathic bronchiectasis. All patients with yellow-nail syndrome had chronic productive cough, 88% had chronic rhinosinusitis, 20% had pleural effusions and 12% had lymphoedema. In around two-thirds of patients, chest symptoms preceded yellow nails. Fourteen patients had improved nails at follow-up, although 23 had lymphoedema. In around two-thirds of patients, chest symptoms preceded yellow nails. Forty-eight percent had mild airflow obstruction and bronchiectasis sparing the upper and middle lobes. All patients were treated with physiotherapy, and 80% of patients were offered clarithromycin 250mg three times weekly as a prophylactic antibiotic. Bottom line: yellow-nail syndrome is a distinct cause of mild bronchiectasis involving mainly the lower lobes.


Abstract

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Effect of pulmonary exacerbations treated with oral antibiotics on clinical outcomes in cystic fibrosis
Authors: Stanoevic S et al.
Summary: The impact of milder pulmonary exacerbations treated with oral antibiotics (2608 events) on short-term clinical outcomes was investigated in a retrospective cohort of 570 patients with CF. Lung function was already ≥90% of baseline FEV1 at the start of oral antibiotic therapy for 53.4% of events, and it was ≥90% of baseline at follow-up for 82% of events. Compared with no oral antibiotic-treated milder pulmonary exacerbation events in the prior 12 months, the occurrence of ≥1 such event was associated with a decreased rate of FEV1 exacerbation events had the steepest rate of FEV1 decline. Oral antibiotic-treated milder pulmonary exacerbations were not associated with changes in body mass index.

Comment: Infective exacerbations in patients with CF are important events leading to a loss of FEV1. In up to a third of patients. Severe exacerbations are defined as a hospital admission for intravenous antibiotics. Clinicians often treat milder exacerbations with oral antibiotics. This Canadian group from Toronto used a cohort of 570 children and 2600 exacerbations to explore the effect of milder exacerbations on lung function. The authors found a dose-response like relationship between the number of exacerbations treated with oral antibiotics and the loss of FEV1. Bottom line: exacerbations treated with oral antibiotics have a negative short-term and cumulative effect on lung function.

Abstract

Independent commentary by Professor Lutz Beckert.
Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board.
FOR FULL BIO CLICK HERE

Variation in lung function as a marker of adherence to oral and inhaled medication in cystic fibrosis
Authors: White H et al.
Summary: Adherence to CF treatment was evaluated in 249 patients aged ≥16 years with the disease to determine if lung function variability predicts adherence. The patients were categorised as <50%, 50–<80% or ≥80% adherent according to composite medication possession score ratios. Mean adherence according to medication possession ratio was 63%. An inverse relationship was seen between the coefficient of variation for FEV1, and adherence at 6 and 12 months on univariate analysis (respective odds ratios 0.92 [95% CI 0.87, 0.98] and 0.94 [0.93, 0.99]; significance persisted in the final models. Neither bodyweight nor C-reactive protein level variability predicted adherence.

Comment: Poor adherence remains a significant challenge in the management of chronic diseases, including CF, where it may lead to pulmonary exacerbations, loss of QOL or hospital admissions. Here the research unit in Leeds enrolled 250 of their 400 CF patients to explore whether the variability in FEV1, rather than the loss in FEV1, could be a sensitive marker to reflect treatment adherence. The researchers compared the variability of FEV1, with traditional measures like pill retrieval or self-reported adherence. Bottom line: the variability in FEV1, measurements is a significant predictor of adherence to treatment.

Reference: Eur Respir J 2017;49(3):1600987
Abstract

Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR
Authors: Ratjen F et al., on behalf of the show VX14-809-109 investigator group
Summary: Patients aged 6–11 years with CF (percent predicted FEV1 ≥70 and lung clearance indexCV≤17.5) and the F508del-CFTR (cystic fibrosis transmembrane conductance regulator) mutation on both alleles were stratified by bodyweight and percent predicted FEV1, and randomised to receive lumacaftor 200mg and ivacaftor 250mg (evaluable n=103) or placebo (evaluable n=101) every 12 hours for 24 weeks in this phase 3 trial. For the lumacaftor plus ivacaftor versus placebo arms, there was a significant difference for least squares mean difference in average absolute change in: i) lung clearance indexCV≤17.5 between baseline and week 24 (primary endpoint: −1.09 units [p<0.0001]); ii) sweat chloride level at day 15/week 4 (−20.8 mmol/L [p<0.0001]); and iii) percent predicted FEV1, out to week 24 (2.4 [p=0.0182]). Safety data were consistent with those in previous phase 3 trials of lumacaftor and ivacaftor.

Comment: Ivacaftor, a CFTR potentiator, is effective in class III channel abnormalities, where CFTR reaches the cell membrane but is not fully functional. In the 5% of the CF population with the CFTR mutation Gly551Asp, ivacaftor improves lung function, nutritional status and symptoms. Ivacaftor is not active in the most common homozygous class II mutation (Phe508del) with minimal or nonfunctional CFTR. The combination of ivacaftor with the potentiator lumacaftor led to mild/moderate side effects in almost half the group. Bottom line: the combination of ivacaftor and lumacaftor is associated with a small improvement in lung function.

Abstract

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Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del

Authors: Taylor-Cousar JL et al.

Summary: Patients aged ≥12 years with CF who were homozygous for the Phe508del CFTR mutation were randomised to receive tezacaftor 100mg once daily and ivacaftor 150mg twice daily or matched placebo for 24 weeks in this phase 3 trial; 475 participants completed treatment. Compared with placebo recipients, tezacaftor plus ivacaftor recipients experienced a significant difference for the absolute and relative changes in percent predicted FEV₁ (4.0 and 6.8, respectively [P<0.001 for both]) and a 35% lower rate of pulmonary exacerbations (P=0.005). Adverse events were similar between the two groups, and most were of mild or moderate severity. There were fewer adverse respiratory events in the tezacaftor plus ivacaftor arm than in the placebo arm, and none led to discontinuation.

Comment: Ivacaftor alone is not active in patients with the common class II (Phe508del) CFTR mutation. The combination of lumacaftor and ivacaftor has only a modest benefit with side effects of cough, rhinorrhea, nasal congestion and possible liver damage. Researchers here reported on the combination of a new corrector, tezacaftor, with ivacaftor. The active treatment group had improved FEV₁, reduced exacerbations and improved QOL. However, Hartmut Gressmann gives a great view in this accompanying editorial of gene defects, treatment options and our bottom line: the current therapies for the most common CF mutation are still suboptimal.

Reference: N Engl J Med; Published online Nov 3, 2017

Preparation for a first-in-man lentivirus trial in patients with cystic fibrosis

Authors: Alton EWFW et al.

Summary: This paper reported on key translational, preclinical studies in preparation for a first-in-human trial using a lentiviral vector for CFTR gene delivery in patients with CF. The lead candidate was selected by assessing regulatory-compliant vectors that carried a range of promoter/enhancer elements in mice and human air-liquid interface cultures. It was assessed for CFTR expression and function in CF models, and its toxicity was assessed and 'benchmarked' against a leading nonviral formulation used in a recent phase 2b clinical trial. Clinical trial dose ranging was determined, and assessment of the impact of pre-existing and acquired immunity against the vector and vector stability in several clinically relevant delivery devices was performed. The lead candidate lentiviral vector was found to express functional CFTR and retained 90–100% transduction efficiency in relevant delivery devices. The authors commented that the efficacy (≥14% of airway cells transduced), toxicity and integration-site profile findings support progression to clinical trials.

Comment: One of the rate-limiting steps of gene therapy in the management of CF is the search for a suitable vector to ‘inject’ respiratory epithelial cells with the corrected CFTR gene to express appropriate function. Adenovirus infections cause significant respiratory comorbidities, while nonviral formulations have a low targeted infection rate. In this paper, UK researchers detail the rationale and animal experiments exploring the safety and efficacy of lentivirus regional vector delivery to the airways. Bottom line: the combination of viral vector production methods with mouse and ex vivo human data suggests first-in-human studies in CF could start.

Reference: Thorax 2017;72(2):137–47