Respiratory RESEARCH REVIEW™

Making Education Easy

Issue 1 – 2019

In this issue:

Abbreviations used in this issue

CF = cystic fibrosis
CFTR = **CF** transmembrane conductance regulator
COPD = chronic obstructive pulmonary disease
CRQ = Chronic Respiratory Disease Questionnaire
FEV = forced expiratory volume
HR = hazard ratio
ICS = inhaled corticosteroid
LCI = lung clearance index
PZP = pregnancy zone protein
QOL = quality of life
RCT = randomised controlled trial
SGRQ = St. George's Respiratory Questionnaire

Welcome

to this spring issue of Respiratory Research Review with the focus on bronchiectasis and CF (cystic fibrosis). While more than enough research is published to fill this short review, many questions are still unanswered. Emily Henkle and colleagues present patient-centred research priorities based on a survey of 459 patients with bronchiectasis. These priorities cover how to prevent exacerbations, treat exacerbations, improve QOL, identify markers of poor prognosis and understand underlying conditions.

Over the year, our regional respiratory journal, Respirology, has been running an outstanding review series edited by Adam Hill and Annie Chang. The review covers topics relevant in the management of bronchiectasis like diagnosis, disease burden and prognosis, as well as inspiratory muscle training, vaccination, monitoring, cross infection and self-management plans. I enjoyed the clarity, brevity and evidence-based information on the role of airway clearance, mucoactive therapies and pulmonary rehabilitation in paediatric and adult bronchiectasis). Some take-home messages are that airway clearance techniques are effective; however, no single one has been shown to be superior to others. Airways clearance techniques can be combined with mucoactive therapy, with some promising trials ongoing. Arietta Spinou and James Chalmers provide the international perspective in their editorial on respiratory physiotherapy in bronchiectasis.

Following an updated publication by the European Respiratory Society and the Thoracic Society of Australia and New Zealand, the British Thoracic Society has published its guideline for bronchiectasis in adults. Surprisingly, it is easy to read, and facilitated by a helpful editorial, summary of recommendations and a short table 'quick summary guide'. **Whom to investigate?** Patients with symptoms, risk factors, and coexisting illnesses like COPD, rheumatoid arthritis or inflammatory bowel disease. **What radiology?** Chest x-ray, CT. **What to test?** Lung functions, immunoglobulins; for symptoms of reflux and other comorbidities. Ensure to exclude CF, primary ciliary dyskinesia and tuberculosis. **Airway clearance! Stepwise management:** antibiotics for exacerbations, manage rhinosinusitis and manage allergic bronchopulmonary aspergillosis. **The deteriorating patient.** Management plan. **Who should be followed up in secondary care?** Chronic pseudomonas infection, non-tuberculous mycobacteria or MRSA (methicillin-resistant *Staphylococcus aureus*) infection; >3 exacerbations per year, need for long-term antibiotic therapy, bronchiectasis with comorbidities of inflammatory bowel disease, immune deficiencies and rheumatoid arthritis, and patients considered for lung transplantation. The number able to be seen in secondary care is likely to be small considering that in the US, the prevalence in patients above the age of 65 years alone is 700 per 100,000 persons (Chest 2018).

Progress in CF has been so impressive that it has captured the media, like the article in the Washington Post: 'Long-awaited cystic fibrosis drug could turn deadly disease into a manageable condition'. Access to medications has been a topic in the British Parliament, which enabled access to for 90% of the about 8000 patients living with CF at a much reduced cost. Our colleagues, Scott Bell and Felix Ratjen, give an 8-minute overview in the Lancet Respiratory podcast on these new therapies (or Lancet Respir Med Commissions). The final word should go to a patient who has been lobbying parliament and describes her journey with CF in the editorial. Graciously, she gives much credit to the vibrant, positive and focussed CF community.

We hope you enjoy the selection and as always, we look forward to comments and feedback.

Kind regards,

Professor Lutz Beckert
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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 with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.

Pulmonary rehabilitation in bronchiectasis

Authors: Patel S et al.

Summary: Consecutive patients with bronchiectasis referred for a supervised pulmonary rehabilitation programme (n=213) were matched by propensity score to an equal-sized group of patients with COPD, and programme completion rates and changes in incremental shuttle walk distances and CRQ (Chronic Respiratory Disease Questionnaire) scores were compared. The programme completion rate in each group was 74%. The groups had similar improvements in incremental shuttle walk distances and most domains of the CRQ, but the COPD group had better improvements in the fatigue domain of the CRQ.

Comment: More than 65 RCTs have been performed in patients with COPD establishing pulmonary rehabilitation as a nonpharmacological treatment of COPD with good evidence that it improves walking distance and QOL. This trial managed to recruit more than 300 patients with bronchiectasis into pulmonary rehabilitation groups and matched them with COPD patients. Other than in the fatigue score, patients with bronchiectasis improved their walking distance, emotional function mastery and dyspnoea score. **Bottom line: this real-life cohort study confirms the findings on the benefit of pulmonary rehabilitation and endorses our current proactiveness to include patients with bronchiectasis in pulmonary rehabilitation programmes.**

Reference: Eur Respir J 2019;53:1801264
Abstract

Validation of the incremental shuttle walk test as a clinical end point in bronchiectasis

Authors: Cartlidge MK et al.

Summary: The reliability, validity and responsiveness of the incremental shuttle walk test as a clinical endpoint in bronchiectasis were evaluated in 30 clinically stable patients with bronchiectasis. Incremental shuttle walk distances were obtained twice, 6 months apart. Reanalysis of a 1-year gentamicin study was undertaken to assess the area under the curve (percent change of incremental shuttle walk distance with a ≥ 4-unit improvement in total SGRQ [St. George's Respiratory Questionnaire] score). Incremental shuttle walk distances were recorded before and after 14 days of antibiotics for an exacerbation (n=124) and reanalysis of the 1-year gentamicin study (n=57). There was no significant change in incremental shuttle walk distance over 6 months in clinically stable participants. Significant inverse correlations were seen between incremental shuttle walk distance and SGRQ scores and Bronchiectasis Severity Index scores, and sedentary time, and a significant positive correlation was seen with physical activity. The area under the curve for percent change in incremental shuttle walk distance with a ≥4-unit improvement in SGRQ score was 0.79 (p=0.001). At a 5% improvement threshold, the incremental shuttle walk test had a sensitivity value of 92% but a specificity value of only 50%; from responsiveness studies, it was calculated that it would detect 73% of all patients.

Comment: The next two articles address the urgent need of identifying an objective measurement to assess either progression of bronchiectasis or response to treatment. Current outcomes measured used are 24-hour sputum volume, C-reactive protein level, the 6-minute walk distance test and tools like the SGRQ. Working with a cohort of 30 patients with bronchiectasis, these Scottish authors systematically demonstrate that changes in the externally paced incremental shuttle walk test are reliable indicators of disease severity and response to treatments. **Bottom line: a 5% change in the shuttle walking test is a reliable, valid and responsive measurement of change in patients with bronchiectasis.**

Reference: Chest 2018;154:1321–9
Abstract

Pregnancy zone protein is associated with airway infection, neutrophil extracellular trap formation, and disease severity in bronchiectasis

Authors: Finch S et al.

Summary: The relationship between PZP (pregnancy zone protein) in the airways of patients with bronchiectasis and disease severity was explored in this research. Sputum samples from patients with bronchiectasis underwent label-free liquid chromatography/mass spectrometry, and the results for patients with versus without *Pseudomonas aeruginosa* infection were compared. A significant relationship was detected between elevated PZP levels and *P. aeruginosa* infection. A validation study (n=124) revealed significant associations between sputum, but not serum, PZP levels and Bronchiectasis Severity Index, frequency of exacerbations and symptoms. An association was also seen between airway infection with Proteobacteria such as *P. aeruginosa* and higher PZP levels, and there was a direct relationship between sputum PZP and airway bacterial load. *In vitro* studies showed that neutrophils that had been induced to form neutrophil extracellular traps released high PZP levels; fluorescence microscopy confirmed the presence of PZP in the neutrophil extracellular traps, whereas fluorescence and electron microscopy showed PZP localised to the cytoplasm and nuclei of neutrophils. Antibiotic therapy reduced sputum PZP levels.

Comment: These data were presented at the European Respiratory Society meeting and it is good to see it published in a high-impact respiratory journal. The name of the protein is a little distracting; however, the authors argue nicely that its role in the moderation of neutrophil function may well be involved in the pathophysiology of bronchiectasis. Combining several studies, the authors have demonstrated: i) a relationship to bacterial load; ii) decrease of the protein level to treatment; and iii) lower levels in patients with COPD. In Sanjay Chotirmall's accompanying editorial, he gives us the **bottom line: PZP may become a measurement of disease activity and response to treatment. In the future it may even become a therapeutic target itself.**

Reference: Am J Respir Crit Care Med 2019;200:992–1001
Abstract

Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4)

Authors: Haworth CS et al.

Summary: The concurrent phase 3 ORBIT-3 and ORBIT-4 trials randomised patients with non-CF bronchiectasis, who had experienced ≥2 pulmonary exacerbations treated with antibiotics in the prior 12 months and who had a history of chronic *P. aeruginosa* lung infection, to receive 3mL of liposome encapsulated ciprofloxacin 135mg and 3mL of free ciprofloxacin 54mg; evaluable n=389) or placebo (evaluable n=193). The primary endpoint of median time to first pulmonary exacerbation was significantly longer in the liposomal ciprofloxacin arm than the placebo arm in the ORBIT-4 trial (230 vs. 158 days; HR 0.72 [95% CI 0.53, 0.97]) but not in the ORBIT-3 trial (214 vs. 136 days; 0.99 [0.71, 1.38]); data pooled from both trials showed a nonsignificant difference (222 vs. 157 days; 0.82 [0.65, 1.02]). The adverse event and serious adverse event rates were similar between the trial arms in both trials.

Comment: Inhaled antibiotics for bronchiectasis, once thought to be a turning point in our treatment, were plagued by the previously mentioned lack of an objective endpoint, the development of antibiotic resistance and triggering of bronchospasm. Previous studies with aztreonam, dry powder ciprofloxacin and inhaled colistin did not reach primary endpoints. The current studies used liposomal ciprofloxacin. One study showed an effect in delaying the time to an exacerbation, and the other study didn't. The authors speculate that higher use of macrolide antibiotics may have affected the outcome. **Bottom line: in the pooled analysis, inhaled liposomal ciprofloxacin did not increase the time to an infective exacerbation.**

Reference: Lancet Respir Med 2019;7:213–26
Abstract

The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults

Authors: Laska IF et al.

Summary: This was a systematic review with meta-analysis of 16 RCTs (n=2597) investigating inhaled antibiotics for bronchiectasis and chronic respiratory tract infections in adults. Inhaled antibiotic use was associated with: i) a decrease in colony-forming units per gram of sputum of –2.32 log units (p<0.0001); ii) an increase in bacterial eradication (odds ratio 3.36 [95% CI 1.63, 6.91]); and iii) a reduction in exacerbation frequency (rate ratio 0.81 [0.67, 0.97]), with prolongation of time to first exacerbation (HR 0.83 [0.69, 0.99]), a lower proportion of patients with ≥1 exacerbation (risk ratio 0.85 [0.74, 0.97]) and a significant reduction in severe exacerbation frequency (rate ratio 0.43 [0.24, 0.78]). Neither Quality of Life Bronchiectasis questionnaire nor SGRQ score improved above the minimal clinically important difference with inhaled antibiotics, and there was no significant relative change in FEV_1. There was also no significant change in the likelihood of treatment-emergent adverse effects or bronchospasm, but bacterial resistance was evident after treatment (risk ratio 1.91 [95% CI 1.46, 2.49]).

Comment: The causes of bronchiectasis are diverse. The vicious cycle of infection, inflammation, epithelial/immune dysfunction and lung destruction is common. Inhaled antibiotic therapy is well established as standard therapy in patients with CF and *P. aeruginosa* infections. Inhaled antibiotic therapy for non-CF bronchiectasis is struggling to demonstrate efficacy. Irena Laska and colleagues present a methodologically clean meta-analysis. It doesn't make the easiest reading; however, Brian O'Sullivan summarises this meta-analysis and a sister one in his editorial. **Bottom line: inhaled antibiotics are well tolerated, reduce the bacterial load and achieve a small reduction in exacerbation frequency without improvements in QOL.**

Reference: Lancet Respir Med 2019;7:855–69
Abstract

Airway bacterial load and inhaled antibiotic response in bronchiectasis

Authors: Sibila O et al.

Summary: These researchers undertook three studies related to treatment of bronchiectasis with inhaled antibiotics to: i) evaluate the relationship between bacterial load and clinical outcomes; ii) assess bacterial load stability over time; and iii) test the hypothesis that response to inhaled antibiotics is predicted by bacterial load at baseline. The first two studies prospectively enrolled adults with bronchiectasis, whereas the third was a *post hoc* analysis of data from an RCT of inhaled aztreonam. The patients were stratified into low, moderate and high sputum bacterial loads (<105, 105–106 and ≥107 colony-forming units per gram, respectively). In all three studies, bacterial load was found to be a stable trait that was associated with worse QOL and greater airway inflammation. In the *post hoc* RCT analysis (study 3), aztreonam was associated with better Quality of Life-Bronchiectasis-Respiratory Symptoms Scores at week 4 in participants with a high bacterial load (p=0.003). The proportion of participants who achieved an increase greater than the minimum clinically important difference was higher among aztreonam recipients at weeks 4 and 12 only among those with a high bacterial load (63% vs. 37% [p=0.01] and 62% vs. 38% [p=0.01], respectively).

Comment: The starting point of these European collaborators is the lack of inhaled antibiotics to consistently reach their primary endpoints. They present three studies showing that (study 1) a higher bacterial load was associated with higher sputum neutrophil count, myeloperoxidase activity and disease activity score, and reduced QOL. In most patients, the bacterial load decreased during treatment and returned to baseline following treatment (study 2). Re-analysing data from a published study showed that QOL improves in patients with a high bacterial load (study 3). **Bottom line: high bacterial load may be a treatable trait in bronchiectasis prediction response to inhaled antibiotic therapy.**

Reference: Am J Respir Crit Care Med 2019;200:33–41
Abstract

Comparative risks of chronic inhaled corticosteroids and macrolides for bronchiectasis

Authors: Henkle E et al.

Summary: Respiratory infection risks were compared between new users of ICSs (n=83,589) and macrolide monotherapy (n=6500) for non-CF bronchiectasis in a cohort of US Medicare enrolees. The respective crude incidences of hospitalised respiratory infection for ICS and macrolide new users were 12.6 and 10.3 per 100 patient-years. Compared with new macrolide users, new ICS users had significantly higher likelihoods of hospitalisation for respiratory infections (propensity score-adjusted HRs 1.39 [95% CI 1.23, 1.57]) and acute exacerbations (1.56 [1.49, 1.64]), but not mortality (1.09 [0.95, 1.25]).

Comment: Our pharmaceutical options to treat bronchiectasis are limited. ICSs harbour an increased risk of pneumonia in patients with COPD. This group of North American authors studied more than 250,000 patients with bronchiectasis and identified a subset of 80,000 (30%) newly prescribed ICSs and 6500 (2%) prescribed new macrolide monotherapy. This retrospective study suggests that compared with macrolide use, chronic use of ICSs was associated with increased infections, admission to hospital and death. **Bottom line: the use of chronic ICSs is not supported in bronchiectasis; macrolides may be a better choice.**

Reference: Eur Respir J 2019;54:1801896
Abstract

Inhaled hypertonic saline in preschool children with cystic fibrosis (SHIP)

Authors: Ratjen F et al., for the SHIP Study Group

Summary: Patients aged 36–72 months with confirmed CF were randomised to receive inhaled 7% hypertonic saline (n=76) or 0.9% isotonic saline (n=74) nebulised twice daily (≤15 minutes per dose) for 48 weeks in the SHIP (Saline Hypertonic in Preschoolers) study; acceptable data were obtained for 89% of the nitrogen multiple breath washout tests performed to assess the primary endpoint of change in $LCI_{2.5}$ (lung clearance index; a measure of ventilation inhomogeneity). Compared with isotonic saline, hypertonic saline was associated with a significant decrease in $LCI_{2.5}$ at 48 weeks (mean treatment effect, –0.63 units [p=0.010]). None of the serious adverse events (ten in the hypertonic saline group and nine in the isotonic saline group) were deemed to be treatment-related.

Comment: The absence of a functional CFTR protein results in water depletion and impaired mucociliary clearance, leading to chronic infection and inflammation. These North American authors need to be congratulated for their study by focussing on children aged less than 6 years and by using the LCI as a primary endpoint. Kevin Southern and Ian Sinha in their accompanying editorial make a careful plug for the routine use; however, they also caution us to keep the burden of treatment in mind. **Bottom line: inhaled hypertonic saline should be considered in the treatment of children aged 3–6 years.**

Reference: Lancet Respir Med 2019;7:802–9
Abstract

Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*

Authors: Dedrick RM et al.

Summary: This was a case report of a 15-year-old patient with CF who developed a disseminated *Mycobacterium abscessus* infection that was successfully treated with a three-phage cocktail administered intravenously after bilateral lung transplantation. Genome engineering and forward genetics were used to develop lytic phage derivatives that efficiently killed the infectious *M. abscessus* strain. The treatment was well tolerated and objective clinical improvement was noted, including sternal wound closure, improved liver function and considerable resolution of infected skin nodules.

Comment: Case reports don't often make it into high-impact journals; however, sometimes they are great proofs of concept. Charles Schmidt writes the beautiful editorial, pointing out that phage therapy was first tried in 1919, so exactly 100 years ago. He also covers the other recent high-profile case of using phage therapy to treat multidrug-resistant *Acinetobacter baumannii*. More than ten preclinical or phase 1–2 trials are currently running to treat a number of infectious targets. The phage treatment was tolerated virtually without side effects; however, one cannot be sure that the patient wouldn't have improved on her own. **Bottom line: that is the first case of engineered phage therapy to treat human mycobacterial infection.**

Reference: Nat Med 2019;25:730–3
Abstract

Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele

Authors: Middleton PG et al., for the VX17-445-102 Study Group

Summary: Patients aged ≥12 years with Phe508del-minimal function genotype CF (n=403) were randomised to receive elexacaftor, tezacaftor plus ivacaftor or placebo for 24 weeks in this phase 3 trial. Compared with placebo, the combination of elexacaftor, tezacaftor and ivacaftor led to a 13.8-point increase in FEV_1 percent predicted at 4 weeks and 14.3 points higher at 24 weeks, a 63% lower pulmonary exacerbation rate, a 20.2-point higher respiratory domain score on the Cystic Fibrosis Questionnaire-Revised instrument and a 41.8 mmol/L lower sweat chloride level (p<0.001 for all). Most adverse events were mild or moderate, and the adverse event-related discontinuation rate in the active treatment arm was 1%.

Comment: This is the first time a combination of medications may address the gene mutation causing the problem in the CFTR protein in 80–90% of people affected with CF. These authors describe a 24-week RCT in 403 patients with the Phe508del *CFTR* mutation using the next-generation corrector elexacaftor plus the corrector tezacaftor and the potentiator ivacaftor. Francis Collins' N Engl J Med editorial on 'Realizing the dream of molecularly targeted therapies for cystic fibrosis' is rather emotional and she calls for a major. **Bottom line: elexacaftor-tezacaftor-ivacaftor is a highly effective therapy for Phe508del CF.**

Reference: N Engl J Med 2019;381:1809–19
Abstract