Respiratory Research Review™

Making Education Easy

Issue 154 – 2018

In this issue:

Abbreviations used in this issue
ACS = acute coronary syndrome
CAP = community-acquired pneumonia
CF = cystic fibrosis
CFTR = CF transmembrane conductance regulator
COPD = chronic obstructive pulmonary disease
FEV = forced expiratory volume

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Welcome to issue 154 of Respiratory Research Review.

"This is the age of bronchiectasis." James Chalmers cites this bold statement at the beginning of his review of new therapies and perspectives on bronchiectasis in Lancet Respir Med. Time will tell if the combination of the European bronchiectasis guidelines (Respiratory Research Review, issue 142), an improved way of risk stratifying patients, and new therapeutic trials will indeed lead to a watershed moment, similar to which we as a respiratory community have been through with idiopathic pulmonary fibrosis. Certainly, James Chalmers, now the new editor of Eur Respir J, is having a huge impact for people with bronchiectasis. We will cite his research several times in this review. An ERS monograph edited by himself, Eva Polverino and Stefano Aliberti expertly summarises clinical management, models of service delivery, pathophysiology, microbiology and underlying disorders related to bronchiectasis.

Due to our focus on bronchiectasis and CF (cystic fibrosis) in this research review, we were not able to include articles debating haemoptysis, a challenging symptom accounting for around 10–15% of respiratory consultations. A group of Italian authors remind us that in their cohort of 606 patients presenting with haemoptysis, almost 20% had underlying pulmonary malignancy (Eur Respir J). That sets the stage perfectly for the pro/con debate published in Chest 'Should all initial episodes of hemoptysis be evaluated by bronchoscopy?'. The reader may enjoy this debate and both sides draw on well-published evidence. A reliable evidence base could not be detected by the Chest expert panel investigating whether nonpharmacological airway clearance methods are useful in treating chronic cough related to bronchiectasis. To give clinicians some guidance, they give a carefully worded positive recommendation to utilise clearance techniques to manage chronic cough; however, most importantly they identified significant gaps in our knowledge and make a plea to include cough as a meaningful clinical outcome in future research.

Briefly, we offer three recommendations for further readings not covered in this review. Stephen Cronin retired from running a CF clinic to write a play about his experiences in these clinics. It is called 'Cepacia' and premiered at the Edinburgh Festival Fringe in August 2018 (Lancet Respir Med). A European consortium, including James Chalmers of course, published an immunological corollary of the pulmonary mycobiome in bronchiectasis. Finally, a group of Mediterranean authors review the overlap between bronchiectasis and chronic airways disease in a state-of-the-art article, which includes helpful cartoons and ideas for future directions in research.

The world of CF research is progressing fast and currently dominated by the combination of transmembrane conduction potentiators, correctors and amplifiers. We are seeing the development of new potentiators, 'me too' drugs, which may assist to reduce treatment costs over time. New combinations are being tried and longer follow-up data are becoming available. Steve Cunningham and Susanna McColley eloquently review the current situation, including warning us of trial fatigue on the CF population.

We hope you enjoy the selection of articles and we are looking forward to feedback and comments.

Kind regards

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Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Increased risk of acute coronary syndrome in patients with bronchiectasis

Authors: Hung C-T et al.

Summary: The relationship between bronchiectasis and ACS (acute coronary syndrome) risk was explored in this population-based cohort study of 3521 patients with bronchiectasis and 14,084 randomly selected matched controls without bronchiectasis from the Taiwanese general population, followed for 17.430 and 73,639 person-years, respectively. Compared with controls, the patients with bronchiectasis had a higher likelihood of ACS (adjusted hazard ratio 1.40 [95% CI 1.20, 1.62]), and within the bronchiectasis cohort, patients with ≥3 vs. 1 respiratory infection-related emergency room visit per year had a higher likelihood of ACS (5.46 [4.29, 6.96]), as did those who required ≥3 hospitalisations due to respiratory infection per year (8.15 [6.27, 10.61]).

Comment: In this population-based study from Taiwan, researchers identified 3500 people with bronchiectasis and matched them by age, sex and index year with 14,000 people in their longitudinal health insurance database. Not surprisingly, patients with bronchiectasis had an 8-fold higher risk of admission for respiratory infection, but were also at increased risk of admission for ACS. James Geake and Scott Bell reflect in their editorial on possible biases and implications for ACS risk management and future research. Perhaps we can reduce coronary disease by treating bacterial colonisation and inflammation? Does this mean coronary disease is an infectious disease after all? **Bottom line: bronchiectasis increases the risk of suffering an ACS by 40%.**

Reference: Respirology 2018;23:828–34
Abstract

Blood neutrophils are reprogrammed in bronchiectasis

Authors: Bedi P et al.

Summary: Blood neutrophil phenotypes were assessed in eight patients with mild bronchiectasis and eight with severe bronchiectasis while stable and during exacerbations, and eight healthy volunteers. A comparison of six patients with severe bronchiectasis and six with CAP (community-acquired pneumonia) at the start and end of an exacerbation was also undertaken. Compared with the healthy volunteers, blood neutrophils from patients with stable bronchiectasis had significantly longer viability, delayed apoptosis, increased CD62L shedding, upregulated CD11b expression, increased myeloperoxidase release and impairments in neutrophil phagocytosis and *Pseudomonas aeruginosa* killing. Bacterial phagocytosis and killing by bronchiectatic airway neutrophils was significantly lower compared with matched autologous blood neutrophils. Blood and airway neutrophil phagocytosis and killing was reduced at the beginning of an exacerbation and improved after antibiotic treatment. Antibiotic treatment was also associated with significant improvements in bacterial killing and phagocytosis in patients with CAP. Compared with bronchiectasis exacerbations, there was a significant increase in bacterial killing at the start and end of CAP infections, whereas there was no significant difference in phagocytosis.

Comment: This is my favourite study in this review, and I hope the reader may wish to look up the original article and eloquent editorial 'One small step for neutrophils, one giant leap for bronchiectasis' by Sanjay Chotirmall. Using elegant biological methodology, the researchers compared neutrophil function between patients with stable bronchiectasis, patients during an exacerbation and healthy volunteers presenting with pneumonia. **Bottom line: blood neutrophils from patients with bronchiectasis had prolonged survival, delayed apoptosis and reduced bacterial phagocytosis and bacterial killing. This may explain why patients have ongoing neutrophilic inflammation with airway damage and an increased rate of infection.**

Reference: Am J Respir Crit Care Med 2018;198:880–90
Abstract

The impact of acute air pollution fluctuations on bronchiectasis pulmonary exacerbation

Authors: Goeminne PC et al.

Summary: These researchers combined a case-crossover design with distributed lag models to evaluate the effect of air pollution on pulmonary exacerbations in 432 UK patients with confirmed bronchiectasis. Their respective final models for PM_{10} (small particle concentration) and NO_2 (nitric dioxide) were based on 6741 and 6248 exacerbations from 430 and 426 patients. Each 10 $\mu g/m^3$ increase in PM_{10} and NO_2 was associated with increased risks of same-day exacerbations of 4.5% (95% CI 0.9, 8.3) and 3.2% (0.7, 5.8) respectively, and overall increased risks of 11.2% (6.0, 16.8) and 4.7% (0.1, 9.5); a subanalysis revealed that the relative exacerbation risks were significantly higher during spring and summer.

Comment: This is a case-crossover study in patients attending the regional specialist bronchiectasis clinic in Dundee, linking exacerbations with exposure to air pollution. Exacerbations are a key event in bronchiectasis and clinical guidelines suggest treatment with antibiotics. However, given the general high bacterial burden, it is important to explore other triggers for an exacerbation. Small studies have suggested a correlation between air pollution and increased inflammatory markers. In this large study, the authors explored the relationship between markers of air pollution (PM_{10} and NO_2) and exacerbations. **Bottom line: air pollution seems to be an important risk factor increasing the risk of exacerbations in bronchiectasis.**

Reference: Eur Respir J 2018;52:1702557
Abstract

Upper airway involvement in bronchiectasis is marked by early onset and allergic features

Authors: Shteinberg M et al.

Summary: These researchers searched for differential clinical and laboratory features in medical chart data from adults with bronchiectasis with upper airway symptoms (nasal discharge most days of the year, sinusitis or nasal polyps) and without primary ciliary dyskinesia (n=70) versus those without upper airway symptoms (n=127). Patients with versus without upper airway symptoms had bronchiectasis symptom onset at an earlier age (34 vs. 46 years [p=0.001]), longer median disease duration (24 vs. 12 years [p=0.027]), a higher median number of exacerbations per year (3 vs. 2 [p=0.14]), a higher median peripheral blood eosinophil count (230 vs. 200 per µL [p=0.015]) and a higher median total IgE level (100 vs. 42 IU/mL [p=0.085]). A significant independent association was seen between sinus CT score and exacerbations, with 1 point on the Lund-Mackay score increasing the number of annual exacerbations by a factor of 1.03 (p=0.004).

Comment: We know that atopy is associated with asthma and chronic rhinosinusitis, and that CF involves the upper and lower airway, but what is the link between upper airway symptoms and bronchiectasis? In this study of 214 patients with bronchiectasis from a single centre in Haifa, Israel, the authors systemically worked up patients for possible causes of bronchiectasis, which includes a careful review of sinonasal disease. Key findings include that patients with upper airway symptoms had bronchiectasis at an earlier age, have increased eosinophilia and IgE levels, more *Staphylococcus aureus* and *Haemophilus influenza* colonisation and less *P. aeruginosa* colonisation. **Bottom line: about 35% of patients with bronchiectasis have chronic sinonasal disease, which suggests a possible common allergic culprit.**

Reference: ERJ Open Res 2018;4:00115–2017
Abstract

Characterization of the 'frequent exacerbator phenotype' in bronchiectasis

Authors: Chalmers JD et al.

Summary: Data from 2572 patients with bronchiectasis across ten centres who had ≤5 years of follow-up were studied to determine if a 'frequent exacerbator phenotype' could be described, and the impact of such a phenotype on exacerbations on long-term clinical outcomes was reported. The participants were categorised according to exacerbation frequency at baseline (0, 1, 2 or ≥3 per year). The strongest predictor of future exacerbation frequency was frequent exacerbations, suggestive of a consistent phenotype, with respective incident rate ratios for future exacerbations of 1.73 (95% CI 1.47, 2.02), 3.14 (2.70, 3.66) and 5.97 (5.27, 6.78) for 1, 2 and ≥3 exacerbations per year at baseline; other independent predictors of future exacerbation frequency were *H. influenzae* infection, *P. aeruginosa* infection, FEV_1, radiological severity of disease and coexisting COPD. Patients who experienced frequent exacerbations had worse quality of life and were more likely to require hospitalisation during follow-up. There was also increased mortality during the follow-up period as exacerbation frequency increased.

Comment: Some studies seem so obvious that one wonders why nobody has done it before. This large study from ten bronchiectasis centres in Europe and Israel reviewed the clinical course of more than 2500 patients with bronchiectasis to characterise the 'frequent exacerbator phenotype'. Not surprisingly the risk of future exacerbations was related to the number of past exacerbations. In addition, colonisation with *H. influenza* or *P. aeruginosa*, radiological severity and coexisting COPD were predictive of future exacerbations. **Bottom line: the patient with frequent exacerbations has more severe disease, poorer quality of life and increased mortality.**

Reference: Am J Respir Crit Care Med 2018;197:1410–20
Abstract

Ethnicity, socioeconomic status and the severity and course of non-cystic fibrosis bronchiectasis

Authors: de Boer S et al.

Summary: In this research from Auckland, the clinical records of 437 outpatients with non-CF bronchiectasis were reviewed to explore the impact of ethnicity on disease severity and progression. The patients' median age was 65 years, their mean FEV_1 was 62.4% of predicted and 10.5% had recurrent *P. aeruginosa* growth. There was over-representation of Māori and Pacific Island patients when compared against the institution's population catchment, and they had more severe lung function impairment; mean FEV_1 values were 52.0% and 58.6% of predicted for patients of Pacific Island and Māori descent, respectively, compared with 68.6% and 64.2% for Europeans and Asians, respectively, independent of socioeconomic status. However, no overall decline in serial lung function measurements was seen for the entire cohort or for any particular ethnic group.

Comment: This is a local study published by our colleagues in Auckland focussed on Māori and Pacific Islanders assessing the prevalence of bronchiectasis and rate of pulmonary function decline over almost 10 years. Māori and Pacific Island patients came from areas of higher deprivation index and also had more severe bronchiectasis on presentation based on FEV_1 criteria. Interestingly, they remained over-represented even after correcting for the deprivation. Once in the care of our Auckland bronchiectasis clinic, ethnicity did not predict the decline in pulmonary function. **Bottom line: Māori and Pasifika patients carry a higher burden of bronchiectasis.**

Reference: Intern Med J 2018;48:845–50
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.
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Disparities in mortality of Hispanic patients with cystic fibrosis in the United States

Authors: Rho J et al.

Summary: The impact of Hispanic ethnicity and geographical dispersal of this ethnicity on outcomes in the US CF population were explored in a cohort of 29,637 CF registrants; 2493 patients identified as Hispanic. Compared with non-Hispanics, Hispanic patients died at an earlier mean age (22.4 vs. 28.1 years [p<0.0001]), and their likelihood of dying was increased 1.27-fold (95% CI 1.05, 1.53) after adjusting for covariates. Regional analyses revealed that this increased risk of death among Hispanics only affected those from the Midwest, Northeast and West US regions, and not those from southern regions.

Comment: This article is based on data from the U.S. Cystic Fibrosis Foundation Patient Registry. From a biological perspective, CF is a well-defined disease and the phenotype is determined by the type of *CFTR* gene mutation. About 18% of the US population are of Hispanic origin and they make up about 8.4% of CF patients. Patients with a Hispanic background tend to be younger at diagnosis and have similar medication usage, but die at a younger age. The accompanying editorial gives us the **bottom line: the higher mortality rates in Hispanic patients are probably related to access to services and socioeconomic status: 'tear down this wall.'**

Reference: Am J Respir Crit Care Med 2018; 198:1055–63
Abstract

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Effects of an antioxidant-enriched multivitamin in cystic fibrosis

Authors: Sagel SD et al.

Summary: Pancreatic-insufficient patients aged ≥10 years with CF and FEV_1 40–100% of predicted (n=73) were randomised to 16 weeks of an antioxidant-enriched multivitamin or control multivitamin without antioxidant enrichment in this multicentre clinical trial. Compared with the control group, recipients of the antioxidant-enriched multivitamin showed no significant difference for the primary efficacy endpoint of sputum myeloperoxidase level over 16 weeks, lung function or growth endpoints, but did have higher systemic antioxidant concentrations, lower circulating calprotectin and myeloperoxidase levels at week 4 and a lower likelihood of a first pulmonary exacerbation requiring antibiotics (adjusted hazard ratio 0.50 [p=0.04]). Adverse events and tolerability parameters did not differ significantly between the two groups.

Comment: CF is characterised by neutrophilic inflammation with increased oxidative stress, which is compounded by impaired absorption due to pancreatic insufficiency. These US researchers worked with nutritionists to generate a randomised controlled trial of a 'nutrients cocktail' versus multivitamins in CF patients. The primary endpoint, a reduction of myeloperoxidase concentration, was missed. However, the antioxidants were well tolerated, showed a transient decrease in systemic inflammation and led to a lower risk of first pulmonary exacerbation. People without CF should follow the advice by Michael Kennedy in his clinical perspective on 'the vitamin epidemic'. **Bottom line: the correction of antioxidant deficiency in CF is probably beneficial (editorial).**

Reference: Am J Respir Crit Care Med 2018; 198:639–47
Abstract

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Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a *CFTR* gating mutation (ARRIVAL)

Authors: Rosenfeld M et al., ARRIVAL study group

Summary: Children aged 12–<24 months with confirmed CF and a *CFTR* gating mutation on ≥1 allele received oral ivacaftor 50mg or 75mg according to bodyweight every 12 hours in this phase 3 study; ivacaftor was administered for 3 days plus one morning in part A (n=7), and for 24 weeks in part B (n=19). Pharmacokinetic analyses showed that exposure was similar to that reported for children aged 2–<6 years and adults. There were no discontinuations related to adverse events or new safety signals. The treatment-emergent adverse event rates were 43% and 95% in parts A and B, respectively; all in part A were mild and deemed not to be or unlikely to be related to ivacaftor, and most in part B were mild or moderate with cough the most frequent at a rate of 74%. There were four serious adverse events (all requiring hospitalisation) in part B, and five children experienced aminotransferase level increases to >3 times the upper limit of normal. The mean sweat chloride level had fallen by 73.5 mmol/L at week 24. Growth parameters remained as expected. Faecal elastase-1 level had increased and immunoreactive trypsinogen level had decreased at week 24, and mean serum lipase and amylase levels, which were elevated at baseline, fell rapidly on treatment.

Comment: Ivacaftor is a CFTR potentiator. It targets CFTR that is correctly localised but dysfunctional. It has been shown to be well tolerated by adults and children, with improvements in respiratory and pancreatic function. Since some of the lung and pancreatic damage appears to start *in utero*, these authors performed a multicentre study enrolling children aged 12–24 months with specific *CFTR* gene mutations. Although up to 95% of children reported some side effects, they were judged to be mild, and ivacaftor was generally well tolerated. **Bottom line: ivacaftor increased exocrine pancreatic function, which reduced sodium sweat test concentrations and decreased markers of pancreatic inflammation.**

Reference: Lancet Respir Med 2018;6:545–53
Abstract

VX-659-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles

Authors: Davies JC et al., for the VX16-659-101 Study Group

Summary: The effects of the next-generation CFTR corrector VX-659 in combination with tezacaftor-ivacaftor on the processing, trafficking and function of Phe508del CFTR protein was evaluated with the use of human bronchial epithelial cells, and a range of oral doses of the triple combination were evaluated in multicentre randomised controlled trials of CF patients heterozygous for the Phe508del *CFTR* mutation and a minimal-function *CFTR* mutation (Phe508del-MF genotypes) or homozygous for the Phe508del *CFTR* mutation (Phe508del-Phe508del genotype). *In vitro*, the combination was associated with significant improvements in the processing and trafficking of the Phe508del CFTR protein as well as chloride transport. In study participants, the safety and adverse-effect profile of the combination was acceptable, with most adverse events being mild or moderate. VX-659-tezacaftor-ivacaftor combination led to significant increases of ≤13.3 points in FEV_1 percent predicted out to day 29 (p<0.001) in participants with Phe508del-MF genotypes, and in those with the Phe508del-Phe508del genotype who were already receiving tezacaftor and ivacaftor, adding VX-659 increased FEV_1 percent predicted by a further 9.7 points. Both participant populations experienced improvements in sweat chloride levels and Cystic Fibrosis Questionnaire-Revised respiratory domain scores.

Comment: In October, two articles were published in N Engl J Med using combination treatment targeting CFTR. The above article combined the potentiator ivacaftor with the corrector tezacaftor and the new small molecule VX-659, which has a synergistic effect on the CFTR function. The sister trial also combines the potentiator ivacaftor with the corrector tezacaftor and the new small molecule VX-445. Both combinations were well tolerated and were associated with a significant increase in lung function. The accompanying editorial gives us the **bottom line: this is a significant breakthrough for patients with the most common gene mutation in CF.**

Reference: N Engl J Med 2018;379:1599–611
Abstract

RESEARCH REVIEW PODCAST

NEW APPROACHES IN THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): THE 2018 UPDATE

In this Breakfast Symposium, Associate Professor Rob Young addressed commonly asked questions from primary care clinicians on the best approaches to managing COPD patients in everyday practice. He also presented the latest evidence on diagnosis, management and prevention of COPD, in New Zealand and from an international perspective, in this update.

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