Until recently, research in bronchiectasis has been inhibited by the lack of a severity index incorporating clinical, physiologic, microbiologic and radiologic parameters, as well as a lack of a disease-specific quality of life (QoL) instrument. With the publication of two validated severity indices and a validated disease-specific quality of life (QoL) instrument since the last APSR Respiratory Update on bronchiectasis (and Cystic Fibrosis) in October 2013, these deficiencies have been comprehensively addressed.
The Bronchiectasis Severity Index (BSI). An international derivation and validation study.

Authors: Chalmers JD et al
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3977711/

This index to identify independent predictors of mortality and hospitalisation during 4 year follow-up was derived from an Edinburgh cohort of 608 consecutive patients. It was then validated in 4 European cohorts totaling 702 patients. Patients with non-tuberculous mycobacterial (NTM) disease were excluded. The derivation cohort also excluded patients receiving long-term antibiotic therapy, although such patients were included in the validation cohorts.

Independent predictors for future (both short and long term) hospitalisation for exacerbation of bronchiectasis were prior hospitalisation, Medical Research Council (MRC) dyspnea score >4, FEV₁ <30% predicted, chronic Pseudomonas aeruginosa infection, “colonization with other pathogenic organisms” and involvement of >3 lobes on HRCT scan. Independent predictors of mortality were older age, low FEV₁, low body mass index (BMI), prior hospitalisations and >= 3 exacerbations in the year before. The predictors were dichotomised and points were awarded for each of the predictors. Area under the receiver operator characteristics curve (AUC) was 0.80 for mortality and 0.88 for hospitalization in the derivation cohort and 0.81 – 0.84 and 0.80-0.88 respectively in the validation cohorts.

Multi-dimensional approach to non-cystic fibrosis bronchiectasis: the FACED score.

Authors: Martinez-Garcia MA et al
URL: http://erj.ersjournals.com/content/43/5/1357.long

This study involving 7 Spanish centers enrolled 839 consecutive patients with bronchiectasis who were randomly allocated to construction (derivation) and validation cohorts. Independent predictors of 5 year all-cause mortality were identified and used to construct a 7 point score. Independent predictors were FEV₁ % predicted, Age, Chronic infection by Pseudomonas aeruginosa, radiologic Extent of disease on CT scan, and Dyspnoea based on MRC scale (the FACED score). The AUC was 0.87 for the construction cohort and 0.83 for the validation cohort. FEV₁ had the greatest predictive power for mortality. In this study the presence of chronic infection by other organisms including NTM, was not predictive of mortality.
Thus there are now 2 multi-dimensional clinical predictor instruments for bronchiectasis. While FACED is simpler, the more complex BSI predicts annual risk of mortality and also the risk of hospitalisation. That there is so much commonality in the predictors provides reassurance about the generalizability of these indices. The predictors are clinically intuitive and there is the advantage that all are routinely collected clinical parameters. These severity indices will allow better comparison of cohorts, allow stratification for severity of disease in clinical trials and the identification of sub-groups in whom individual management strategies may be most effective. They may also impact clinical decision-making by identifying those at highest risk of adverse outcomes and thus candidates for intensification of treatment.

**Quality of Life Questionnaire – Bronchiectasis (QoL-B): final psychometric analysis and determination of minimal important difference scores.**

Authors: Quittner AL et al  
Reference: Thorax 2015; 70: 12-30  
URL: [http://thorax.bmj.com/content/70/1/12.long](http://thorax.bmj.com/content/70/1/12.long)

An earlier publication (Chest 2014; 146: 437-448) described the development of this self-administered, patient-reported, outcome measure assessing symptoms, functioning and health-related quality of life (QoL) in patients with bronchiectasis. QoL-B contains 37 items on 8 scales (respiratory symptoms, physical, role, emotional and social functioning, vitality, health perceptions and treatment burden), and is based on recall over the past week. It had been shown to have strong internal consistency, excellent test-retest reliability and there was strong convergent validity of QoL-B Respiratory Symptoms with the St George’s Respiratory Questionnaire.

This paper described QoL-B’s performance in terms of psychometric properties in two double-blind, multi-centre, randomised, placebo-controlled trials of nebulised aztreonam. The instrument showed excellent internal consistency and good two week test-retest reliability. There were no floor or ceiling effects for the Respiratory Symptoms scale i.e. patients had room on the scale to both improve and worsen. The minimal important difference (MID) score for this scale was 8.0 points. The QoL-B also demonstrated responsiveness to changes in health status in association with exacerbations when the change in score exceeded the MID.

Hence there is now a disease-specific QoL instrument for bronchiectasis that has demonstrated excellent psychometric properties in field testing. No longer will researchers of bronchiectasis be dependent on generic instruments or instruments developed for other conditions. There seems little doubt that this instrument will be used to provide a well-validated patient-centred outcome in future clinical trials. Indeed, a subsequent study from Belfast (BMC Pulmonary Medicine 2014; 14: 107) has demonstrated that adherence to airway clearance, but not other therapies, was associated with lower QoL-B respiratory symptoms and treatment burden domains scores.
National BTS bronchiectasis audit 2012: is the quality standard being adhered to in adult secondary care?

Authors: Hill AT et al
Reference: Thorax 2014; 69: 292-4
URL: http://thorax.bmj.com/content/69/3/292.long

This 2012 audit was conducted in 98 institutions providing secondary care for 3147 patients with bronchiectasis in the United Kingdom. Patient care was audited against the 11 quality statements in British Thoracic Society (BTS) guidelines and demonstrated the “variable adoption” of these standards. While compliance with some standards was good (91% adherence with the standard for the diagnosis based on HRCT) and some surprisingly good (94% adherence with the standard that patients in secondary care be managed by a multidisciplinary team lead by a respiratory physician), this was not the case for all the standards. There was only 62% adherence with the standard requiring sputum culture on an annual basis when clinically stable, and only 32% adherence with pulmonary rehabilitation for those with breathlessness affecting activities of daily living.

While there may not be universal agreement with these standards and some lack an adequate evidence base, the standards are a useful basis for audit of clinical performance. It is in this area that we could well take a leaf out of the CF book: the audit and review component of Port CF provides an excellent example of the improvements in patient outcomes that occur as a consequence of audit as part of a continuous quality improvement program (See Supplement of BMJ Quality and Safety, Volume 23, 2014). While a bronchiectasis equivalent of Port CF may be quite some time away, all respiratory physicians looking after bronchiectasis patients are encouraged to audit their performance against these (or other validated) standards, identify areas for improvement and ensure that the quality improvement cycle is completed.

Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised controlled trial.

Authors: Bilton et al
Reference: Thorax 2014; 69: 1073-1074
URL: http://thorax.bmj.com/content/69/12/1073.long

This 52 week double-blind, randomised, controlled trial of inhaled mannitol (400mg BD) versus control (mannitol 50mg BD) was conducted in 461 bronchiectasis patients with chronic sputum production and at least 2 exacerbations in the last year. The primary outcome, exacerbation rate, was not significantly reduced in the mannitol group (1.69 vs 1.84, rate ratio 0.92, p=0.31). However secondary outcomes of time to first exacerbation (165 vs 124 days, HR 0.78, p= 0.0225), number of days on antibiotics to trial exacerbations and QoL based on St George’s Respiratory Questionnaire were significantly better in the mannitol group.
Inhaled Colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection.

Authors: Haworth et al
Reference: Am J Respir Crit Care Med 2014; 189: 975-982
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4098097/

This randomised, placebo-controlled study of inhaled colistin (1 million IU per day) versus placebo for one year in 144 patients with bronchiectasis and Pseudomonas aeruginosa chronic infection was conducted in 35 centers in several countries. Colistin was administered by an aerosol delivery device designed to maximize aerosol deposition in the airways. Patients were recruited within 21 days of completing a course of anti-Pseudomonal antibiotics for an exacerbation. In the intention to treat analysis there was no statistically significant difference in the primary endpoint of time to exacerbation; 165 vs 111 days in the colistin vs placebo groups respectively (p=0.11). In the analysis of adherent patients, the median times to exacerbation were 168 and 103 days respectively (p=0.038), suggesting that the failure to meet the primary endpoint was due to the greater number of exacerbations in poorly adherent patients. The Pseudomonas density reduced and QoL, as assessed by the St George’s Respiratory Questionnaire, improved in the colistin group.

Patients with chronic Pseudomonas aeruginosa infection are an important group of patients in whom to study “new” treatments; they have worse QoL, increased rate of exacerbations, and increased risk of hospitalisation and death. As the accompanying editorial states, there is a sense of de ja vu about the results; previous studies of nebulised aztreonam and of mannitol (see above) also failed to achieve their primary endpoints, although there were improvements in a number of secondary endpoints. To what extent these negative results may be due to failure to stratify for severity in those heterogenous populations, the use of inappropriate and/or non-patient-centred primary endpoints, or a more fundamental lack of understanding of the pathogenic process involved (including the respiratory microbiome) is not clear.

Lung resection improves the quality of life of patients with symptomatic bronchiectasis.

Authors: Vallilo CC et al
URL: http://www.sciencedirect.com/science/article/pii/S0003497514008340

This paper describes a prospective cohort study of surgical resection in consecutive patients with symptomatic bronchiectasis in whom medical treatment was unsuccessful. Medical therapy was considered to have failed if after a year of treatment the patient had ongoing features which included “… frequent infectious exacerbations, chronic cough or purulent sputum interfering significantly with their daily activities. Haemoptysis and fungus ball were also considered to represent failure”. QoL was measured by generic instruments (SF-36 and WHO QOL) before, and 9 months after surgery. Limited details were provided about the surgical procedure but this “was aimed at primary resection of the affected area …. in the case of multiple lesions, the resected region showed the most exuberant change, major bleeding or presence of fungus ball”. Most (83%) underwent lobectomy and 17% underwent pneumonectomy. Before and after surgery QoL results were available for 44 of the 53 patients who underwent surgery. QoL was low at baseline but improved considerably after surgery, including in the physical and mental components of the SF-36. The benefit appeared greatest in those with the poorest pre-operative QoL.
However the decision to proceed to lung resection is not one to be taken lightly. The post-operative 30 day mortality in this study was 1.8%, and 24.5% had post-operative adverse events including prolonged air leak, empyema, and bronchial stump fistula.

The pendulum against surgical resection for bronchiectasis may have swung too far. This study reminds us that surgery still does have a role in selected patients with symptomatic bronchiectasis, including those with poor QoL. It would be important to follow-up these patients to determine whether the improvements in QoL are maintained in the longer term.

**Long term azithromycin for Indigenous children with non-cystic fibrosis bronchiectasis or chronic suppurative lung disease (CSLD) (Bronchiectasis Intervention Study): a multicenter, double-blind, randomised controlled trial.**

Authors: Valery PC

In an earlier study (Paed Pulmonal 2014; 49: 189-200) by this group, indigenous children with CSLD/bronchiectasis attending specialist clinics in 3 developed countries (Australia, New Zealand and USA (Alaska)) were found to have poverty indices similar to those reported for their respective local populations. However the CSLD/bronchiectasis children were more often born prematurely and had earlier and more frequent lower respiratory tract symptoms. These investigators also reported the morbidity associated with CSLD/bronchiectasis in indigenous Australian and Alaskan children, with a mean age of 3yrs. These 93 children experienced 280 acute respiratory exacerbations (median =2) and 15% of these resulted in hospitalisation over a period of 3 years (Chest 2014; 146: 762-764). Thus, there is the need for therapeutic interventions to reduce the high level of morbidity in these children.

This group undertook a multi-centre, double-blind, randomised, parallel group, placebo-controlled trial of azithromycin (30mg/kg once a week) for a mean of 20.7 months in clinically stable indigenous children aged 1-8 years in Australia and New Zealand (Indigenous Australian, Maori and Pacifica children) who had CSLD/bronchiectasis. In those on azithromycin, there was a 50% reduction in the primary outcome of exacerbation rate (incidence rate ratio 0.50, 90% CI 0.35-0.71; p<0.0001) as well as a significant increase in weight-for-age Z scores. Children in the azithromycin group were less likely to have needed hospital admission. However they were 7 times more likely to carry azithromycin-resistant bacteria than the control group.

This is the first long-term RCT of macrolide therapy in children in bronchiectasis and it was conducted in a group with high morbidity. The results, both in terms of reduced exacerbation rate and increased rate of resistant organisms, are similar to those of the 3 RCTs of macrolide therapy conducted in adults with bronchiectasis. (See APSR Respiratory Review October 2013).

**Read the Editorial by Prof. Kolbe in the current issue of Respirology:**

Does failed chronic wet cough response to antibiotics predict bronchiectasis?

Authors: Goyal V et al  
Reference: Arch Dis Child 2014; 99: 522-25  
URL: http://adc.bmj.com/content/99/6/522.long

Chronic suppurative lung disease (CSLD) is a term used to describe a condition in children with symptoms and signs of bronchiectasis but without HRCT confirmation. This designation is often required because the social, economic and other circumstances of these children inhibit their access to radiologic investigations. Such children have substantial morbidity, especially in terms of infective respiratory exacerbations and the need for hospitalisation, and tend to be managed as if they have bronchiectasis. Whether such an approach is justified has not been previously addressed.

In this study from a single tertiary paediatric centre which had a standardised approach to the investigation of children with “wet cough”, a retrospective review of CT scans was undertaken. In the 105 children with persistent cough despite 4 weeks of antibiotics (the current recommendation for clinical review), 84% had bronchiectasis on CT scans. Poor clinical response to antibiotic therapy had a sensitivity of 94% and specificity of 51% for radiologically confirmed bronchiectasis. Of the 24 children whose cough resolved after antibiotics, 25% were found to have bronchiectasis—highlighting the fact that some children who seem to respond to antibiotics may still have bronchiectasis.

However this study does provide support for the pragmatic approach to treat children with a persisting wet cough after 4 weeks of antibiotics as if they have bronchiectasis. This should allow earlier appropriate management of children who are disproportionately disadvantaged.

Atorvastatin as a stable treatment in bronchiectasis: a randomised trial.

Authors: Mandal P et al  
URL: http://www.sciencedirect.com/science/article/pii/S2213260014700505

The pleotrophic effects of statins could reduce the neutrophil-driven, “vicious cycle” of inflammation, chronic infection and airway damage in bronchiectasis. Sixty patients, mean age of 60yrs, with radiologically proven bronchiectasis, recruited from a secondary care clinic, were randomised to receive atorvastatin (80mg/d) or placebo. Those with chronic Pseudomonas infection were excluded. The primary outcome, cough as measured by the Leicester Cough Questionnaire, was reduced in the atorvastatin group. The atorvastatin group showed evidence of reduced systemic inflammation (in terms of CRP and IL8 levels) and airway inflammation (in terms of fewer viable neutrophils and more apoptotic neutrophils in sputum). However there was no reduction in sputum myeloperoxidase or elastase. Not surprisingly because of the high dose used, 6 of 30 patients in the atorvastatin group withdrew because of side effects.

This study provided “proof of concept” for a role for atorvastatin in reducing the neutrophilic inflammation in bronchiectasis. Future studies using more tolerable doses of atorvastatin in a wider spectrum of bronchiectasis patients and powered for more robust clinically relevant outcomes are awaited.