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Prognostic Value of Bronchiectasis in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease.

Authors: Martinez–Garcia et al.
URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201208-1518OC

Comment: Earlier studies from a number of groups have demonstrated a high prevalence of bronchiectasis in patients with moderate-to-severe COPD. Further, the presence of bronchiectasis is associated with bacterial colonisation by potentially pathogenic organisms and with a higher rate of exacerbations requiring hospitalisation.

This multicentre, prospective observational study from Spain of consecutive patients with moderate-to-severe COPD, of whom 57% had bronchiectasis on HRCT scans, demonstrated that the presence of bronchiectasis and its severity were associated with an increase in all-cause mortality, independent of other risk factors.

While factors such as age, Charlson Index and post-bronchodilator FEV1 had independent adverse prognostic value, the investigators did not have information on other relevant features including quantitation of emphysema on HRCT, gas transfer and quantitative microbiology. Nevertheless those with bronchiectasis were 2.5 times more likely to die that those without bronchiectasis.

This study provides further important information on the phenotype of combined bronchiectasis and moderate-severe COPD. While demonstration of bronchiectasis may often be an incidental finding, it is one with prognostic and possibly therapeutic implications. This phenotype, which resembles the “exacerbation phenotype” described by others, is a more severe form of COPD in clinical and functional terms and with a poorer outlook. Whether more intensive and comprehensive management will improve the outlook for this phenotype, will require future randomised controlled trials.

Chronic Respiratory Disease, Inhaled Corticosteroids and Risk for Non-Tuberculous Mycobacteriosis.

Authors: Andrejak et al.
Reference: Thorax, 2013; 68: 256-262
URL: http://thorax.bmj.com/content/68/3/256.abstract

Comment: This population-based case-control study encompassing all adults in Denmark with microbiologically confirmed non-tuberculous mycobacterial (NTM) pulmonary disease between 1997 and 2008, demonstrated a 16.5 fold (95%CI 12.2 – 21.5) risk associated with chronic respiratory disease (COPD, asthma, bronchiectasis and previous tuberculosis). The adjusted odds
ratio (OR) for NTM disease was 15.7 (95%CI 11.4 – 21.5) for COPD. For COPD patients on current inhaled corticosteroid therapy (ICS), the OR was 29.1 (95%CI 13.3-63.8), while the OR was 7.6 (95%CI 3.4-16.8) for those who had never received ICS therapy. A dose-response relationship was demonstrated i.e. the risk was greater in those on high dose ICS, raising the possibility of a causal relationship.

For those with bronchiectasis, the OR for NTM pulmonary disease was an extraordinary 187.5 (95%CI 24.8-1417.4) graphically illustrating the fact that bronchiectasis was a very strong risk factor for NTM disease. Relatively small numbers of bronchiectasis patients precluded further analysis based on use of ICS.

A BTS audit demonstrated that about 80% of bronchiectasis patients in the UK were taking ICS with a mean dose of beclomethasone of 1094-1252ug/day. The Cochrane Review concluded that on the basis of small, short term trials showing that high doses of ICS had limited if any clinically significant benefits, “…there is insufficient evidence to recommend the routine use of inhaled steroids in adults with stable state bronchiectasis”.

This study serves as a timely reminder that in selecting treatments for patients with non-CF bronchiectasis, we need to consider not only the efficacy of the treatment and early easily recognisable adverse effects, but also adverse effects that may be insidious in onset and have potentially greater future clinical significance.

Three studies on Azithromycin:

**Azithromycin for Prevention of Exacerbations in Non-Cystic Fibrosis Bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial.**

Authors: Wong et al  
Reference: Lancet, 2012; 380 : 660-7  

**Effect on Azithromycin Maintenance Treatment on Infectious Exacerbations Among Patients with Non-CF Bronchiectasis. The BAT Randomised Controlled Trial.**

Authors: Altenberg et al  
Reference: JAMA, 2013, 309 : 1251-9  
Comments:

While the numbers of articles published on cystic fibrosis (CF) still far exceed those published on non-CF bronchiectasis, the last few years have seen the publication of adequately powered, high quality studies to address important management issues in non-CF bronchiectasis.

Macrolides have complex immune-modulatory effects in the airways. randomised controlled trials of long term macrolide therapy in CF have demonstrated benefit in terms of improved lung function and reduced exacerbations. However there is clear evidence that some treatments that work in CF do not necessarily work in non-CF bronchiectasis and thus the role of macrolide therapy in non-CF bronchiectasis required study.

Three recent publications of randomised, double-blind, placebo-controlled trials addressed the issue of the effectiveness of long term macrolide therapy in adults with non-CF bronchiectasis who had experienced at least one exacerbation in the previous year.

EMBRACE: This New Zealand study (N=141) of 500mg azithromycin 3 times/week (vs placebo) for 6 months demonstrated a 52% reduction (0.59 per patient vs 1.57, p < 0.0001) in event-based exacerbations (a co-primary end point) but no statistically significant change in the other co-primary end points of pre-bronchodilator FEV₁ and health-related quality of life.

BAT: This Dutch study (n=83) of azithromycin 250mg/day for 12 months (vs placebo) demonstrated reduced exacerbations, increased time to first exacerbation (hazard ratio 0.29 (95% CI 0.16-0.51)) and modest improvements in FEV₁ and quality of life.

BLESS: This Australian study (n=117) of erythromycin ethyl-succinate 400mg twice daily for 12 months (vs placebo) demonstrated reduced protocol-defined pulmonary exacerbations (1.29 vs 1.97, p< 0.003), reduced 24 hour sputum production and attenuation of the lung function decline. Erythromycin was chosen because of lower cost and a reported lower risk of the induction of macrolide resistance than azithromycin.
Macrolides have well recognised adverse effects including Q-Tc prolongation and an increased risk of cardiovascular death is associated with azithromycin use. However possibly the most disturbing results were those related to the development of macrolide-resistance, although there was not the emergence of new pathogens. In the BAT study, a macrolide resistance rate of 88% was in azithromycin-treated individuals compared with 26% in the placebo group, while in the BLESS study erythromycin increased the proportion of macrolide-resistant oropharyngeal Streptococci.

Thus, despite these encouraging results, there may be a clinically significant price to play with long term macrolide therapy in non-CF bronchiectasis. Perhaps, as others have suggested, this treatment should be used for those with substantial morbidity, such as frequent exacerbations, and/or evidence of disease progression. Clinicians need to remember to exclude the presence of non-tuberculous mycobacteria before introducing long term macrolide therapy.

**Short and Long-term Antibiotic Treatment Reduces Airway and Systemic Inflammation in non-Cystic Fibrosis Bronchiectasis.**

**Authors:** Chalmers et al

**Reference:** Amer J Respir Crit Care Med, 2012; 186 : 657-65


**Comments:** This study examined the relationship between airway bacterial load and airway and systemic inflammation in different groups of subjects with non-CF bronchiectasis.

In a cohort of 385 stable patients, bacterial load was strongly associated with markers of airway inflammation measured in sputum (myeloperoxidase, neutrophil elastase, interleukin-8, tumour necrosis factor-α and interleukin -1β.) and with systemic inflammation in terms of serum levels of soluble adhesion markers. Patients with high bacterial loads had more symptoms, a higher rate of exacerbation and were more likely to require hospitalisation, independent of CT scan severity of disease. Treatment of stable patients with intravenous antibiotics or nebulised antibiotics was associated with a marked reduction in bacterial load and reduction in the markers of airway and systemic inflammation. Similarly in those with an acute exacerbation, antibiotic therapy reduced bacterial load along with makers of airway and systemic inflammation. *Pseudomonas aeruginosa* was associated with increased airway inflammation independent of bacterial load, when compared with isolation of other pathologies.

This demonstration of the relationship between clinical features (symptoms and risk of exacerbations) and airway and systemic inflammation provides support for the “vicious cycle” hypothesis of neutrophil-mediated inflammation and airway damage proposed by Professor Peter Cole almost 3 decades ago. It also provides a clear rationale for a number of therapies being used and investigated for non-CF bronchiectasis.
Risk Factors for Bronchiectasis in Children with Cystic Fibrosis.

Authors: Sly et al


Comments: Longitudinal data from the Australian-based AREST CF study, of 127 children diagnosed with CF on neonatal screening and who underwent annual CT scanning and bronchoalveolar lavage (BAL) after initial assessment aged 3 months, demonstrated that the point prevalence of bronchiectasis on CT scan increased from 29.3% at 3 months to 61.5% at 3 years. 78 children were included in the analysis at 3 years when the cumulative prevalence of bronchiectasis reached 83.7%. Risk factors for the development of bronchiectasis were meconium ileus at presentation, respiratory symptoms at time of CT or BAL, free neutrophil elastase activity in BAL fluid and gas trapping on expiratory CT scan. Persistent bronchiectasis, observed in 32.1% at 3 years of age, was associated with neutrophil elastase activity in BAL fluid at 3 months of age (OR 4.21 95%CI 1.45 – 12.21).

This study provides additional support for early lung damage in CF being associated with inflammation and infection, and for the pathogenic role for neutrophils and neutrophil elastase.

A substantial proportion of children had apparent “resolution” of bronchiectasis. This might relate to the interpretation of limited CT scans and the challenge of obtaining comparable scans in these young children. Although investigations were performed when children were clinical stable, sub-clinical acute infection causing “reversible” radiologic abnormalities is also a possibility.

As well as enhancing our understanding of the mechanism of lung damage early in CF, this study provides a rationale for treatment strategies targeting activated neutrophils or neutrophil elastase activity. It may also assist in the identification of those at greatest risk who may benefit from more proactive treatment despite a lack of respiratory symptoms.
Whole-genome Sequencing to Identify Transmission of Mycobacterium abscessus between patients with Cystic Fibrosis: a retrospective cohort study.

Authors: Bryant et al

Reference: Lancet, 2013; 381 : 1551-6

URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3664974/

Comments: Infection by non-tuberculous mycobacteria (NTM) is being increasingly identified in CF patients and infection by Mycobacterium abscessus has been reported in up to 10% of CF patients.

In this retrospective cohort study conducted on 168 consecutive isolates from 31 patients attending a single adult CF clinic, whole genome sequencing revealed two clustered outbreaks of near-identical isolates of M. abscessus. In both instances it was M abscessus subspecies massiliense, but not the other two sub-species, that was involved.

The results strongly suggested between patient transmission despite conventional infection control measures being employed. Transmission was further supported by the finding of constitutive resistance to amikacin and clarithromycin in isolates from patients never exposed to these antibiotics. Further analysis demonstrated that the patients within the clusters had numerous opportunities for within-hospital transmission from other patients. Extensive environmental sampling failed to identify a point source for the infections.

While the precise mechanism of transmission is not clear, M abscesses subspecies massiliense needs to be added to the list of organisms shown to be transmitted from person-to-person in CF and thus providing additional challenges to infection control. M abscesses is of particular concern as it is a multi-drug resistant organism which presents considerable treatment challenges, is associated with an accelerated decline in lung function and infection with this organism may have an adverse effect on the decision to proceed to lung transplantation.

Progressive Flow-to-Volume Dysanapsis in Cystic Fibrosis: A Predictor for Lung Transplantation?

Authors: Vilozmi et al

Reference: Am J Respir Crit Care Med, 2012; 186 : 82-87

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201202-0272OC#.UjhHLvxOKM8

Comments: The term “dysanapsis” describes the lack of a consistent association between lung and airway size, and is reflected in the wide variation in maximal expiratory flows between individual normal persons with similar lung size.
Vilozni and colleagues from the National Centre for Cystic Fibrosis in Israel have applied this concept to CF patients; more specifically they used this concept to examine the independence of progressive airflow obstruction and lung volume restriction longitudinally in CF patients. For this study they defined airway-to-volume dysanapsis as the ratio of forced expiratory flow between 25% and 75% of vital capacity (FEF 25-75%) and the forced vital capacity (FVC). They retrospectively analysed serial spirometry (performed at least twice per year) in 93 patients over a median period of follow-up of 8.6 years. Patients were divided into 3 groups; those with initial normal lung function (FEV₁ >80% predicted), those with initial impaired lung function but who did not progress to end stage lung disease over the period of observation, and those with initial impaired lung function and who progressed to end stage lung function (requiring transplantation or placement on a transplant waiting list). Although the 2 groups with impaired lung function did not differ in terms of baseline lung function, those progressing to end stage lung disease had much more rapid decline in FEF25-75/FVC ratio, particularly in the preceding 4 years. The rate of decline in FEF25-75/FVC was not correlated with initial FEV₁ or patient age but was related to M abscesses infection and airway hyper-responsiveness.

While it is not clear whether measurement of this parameter will facilitate more appropriate timing for the listing of patients for transplant, it does highlight the fact that the trajectory of decline of CF lung function differs between the various lung function measures and highlights the importance of disease in the peripheral small airways.

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**Re-establishment of Recipient-associated Microbiota in the Lung Allograft is Linked to Reduced Risk of Bronchiolitis Obliterans Syndrome.**

**Authors:** Willmer et al.

**Reference:** Am J Respir Crit Care Med, 2013; 187: 640-7


**Comments:** Bronchiolitis obliterans syndrome (BOS) is the major factor influencing survival after lung transplantation. The relationship between lung infection and BOS is unclear.

Using culture-independent methods based on high-throughput sequencing, this Australian group analysed, both cross-sectionally and longitudinally, the bronchoalveolar lavage (BAL) fluid from 57 lung transplant recipients with (n=17) and without BOS (n=40), and non transplant control subjects (n=18). A majority (51%) of the transplant recipients had CF.

Principal components analysis demonstrated two major microbiological communities: one dominated by *Pseudomonas* and the other dominated by *Streptococcus* and *Veillonella*. *Pseudomonas* dominated microbiota never co-existed with positive *Aspergillus* cultures.

There was a significant interaction between CF and BOS status in relation to airway microbiota that was not explicable on the basis of time post-transplant nor history of rejection. Nearly all
patients with CF and BOS had an airway microbiome dominated by organisms that would be considered atypical in adults with CF (Streptococcus, Lactobacillus, Enterococcus, Neisseria, and Haemophilus), whereas those with a high abundance of Pseudomonas, Burkholderia and Staphylococcus, organisms more usually found in CF patients with end-stage lung disease, were more likely to be BOS-free. In CF, the risk of BOS was halved in association with an abundance of Pseudomonas. Concordance of pre-transplant and post-transplant microbiota was also associated with freedom from BOS (p <0.01).

These data suggest that the de nova acquisition of respiratory pathogens post-transplant is associated with the development of BOS, whereas the re-establishment of dominant populations present pre-transplant, and particularly Pseudomonas in CF patients, was negatively correlated with BOS. It is not clear as to whether the acquisition of new organisms is associated with stimulation of the innate immune mechanisms and subsequent epithelial and airway damage or whether organisms that are long term colonisers of the airways have evolved for persistence rather than causing acute insults and consequently elicit an attenuated host response.


Authors: Mogayzel et al
URL: http://www.ncbi.nlm.nih.gov/pubmed/23540878
Comments: These updated evidence-based treatment guidelines, supported by the CF Foundation are essential reading for all those involved in the management of CF patients. The guidelines include recommendations about recently available treatments such as ivocabftor, inhaled aztreonam. The guidelines raise but do not comprehensively address important but yet unresolved issues such as “How does the burden of therapy affect self-management?” and “What is the optimal approach to administration of inhaled antibiotic therapy?”. 