Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Journal Club

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Abbreviations: potentially pathogenic microorganisms, **PPMs**; computed tomography, **CT**; tuberculosis, **TB**; pulmonary function test, **PFT**; pulmonary nontuberculous mycobacterial, **pNTM**; American Thoracic Society, **ATS**; diffusion capacity of carbon monoxide, **DLCO**; residual volume, **RV**; inhaled corticosteroids, **ICS**; pulmonary Mycobacterium avium complex, **MAC**; Methicillin-sensitve Staphylococcus aureus, **MSSA**

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Introduction: Bronchiectasis/ COPD Overlap-- A Distinct COPD Phenotype?

COPD patients with frequent exacerbations continue to be major sources of cost, morbidity and mortality, particularly COPD patients who are prone to develop pneumonia. The heightened interest in microbiome research utilizing techniques such as pyrosequencing of bacterial DNA in sputum samples of COPD and asthmatic airways reveals that many species of pathogenic microbes are present that are not detectable by conventional culture techniques. Current studies of the microbiome of COPD airways are improving our understanding of the complex relationship between the alterations in the microbial flora and the chronic inflammation and structural changes that occur in COPD patients. In this issue we present 4 recent articles that examine characteristics of COPD patients that have bronchiectasis and/or the presence of mycobacterial organisms in their sputum. The authors discuss the implications not only for predicting outcomes but also important therapeutic considerations and the rationale for considering this as a possible distinct sub-phenotype of COPD.

Abstract 1
Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis

Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. *Int J Chron Obstruct Pulmon Dis.* 2015;10:1465-1475. doi: http://dx.doi.org/10.2147/COPD.S83910

Background:
In the 2014 Global initiative for chronic Obstructive Lung Disease guidelines, bronchiectasis was for the first time defined as a comorbidity of chronic obstructive pulmonary disease (COPD), and this change has been retained in the 2015 update, which emphasizes the influence of bronchiectasis in the natural history of COPD. The present meta-analysis was aimed at summarizing the impact of bronchiectasis on patients with COPD.

Methods:
Databases including Embase, PubMed, and the Cochrane Central Register of Controlled Trials were searched comprehensively to identify all relevant human clinical studies published until August 2014. Bronchiectasis was confirmed either by computed tomography or high-resolution computed tomography.

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One or more clinicopathological or demographical characteristics, including age, sex, smoking history, daily sputum production, exacerbations, inflammatory biomarkers, lung function, and colonization by potentially pathogenic microorganisms (PPMs), were compared between COPD patients with and without bronchiectasis.

Results:
Six observational studies with 881 patients were included in the meta-analysis. The mean prevalence of bronchiectasis in patients with COPD was 54.3%, ranging from 25.6% to 69%. Coexistence of bronchiectasis and COPD occurred more often in male patients with longer smoking history. Patients with COPD and comorbid bronchiectasis had greater daily sputum production, more frequent exacerbation, poorer lung function, higher level of inflammatory biomarkers, more chronic colonization by PPMs, and higher rate of Pseudomonas aeruginosa isolation.

Conclusion:
In spite of the heterogeneity between included studies and detectable publication bias, this meta-analysis demonstrated the impact of bronchiectasis in patients with COPD in all directions, indicating that coexistence of bronchiectasis should be considered a pathological phenotype of COPD, which may have a predictive value.

Keywords: bronchiectasis; chronic obstructive pulmonary disease; meta-analysis; phenotype

Comments:

This meta-analysis and systematic review is instructive in pointing out that there actually is a surprisingly high prevalence of bronchiectasis in the various cohorts studied. Patients with frequent exacerbations warrant computed tomography (CT) scan assessment to identify bronchiectasis as plain chest radiographs are less sensitive. Identification of bronchiectasis should give pause as to the relative risks and benefits of inhaled corticosteroids given the evidence for chronic colonization/chronic infection with pseudomonas and other pathogens. Certainly the challenges of management, particularly the concern about the use of inhaled corticosteroids in this patient population, are reasonable grounds to consider this group as a distinct pathological phenotype as the authors suggest.

Abstract 2
TB meets COPD: An emerging global comorbidity in human lung disease

O'Toole RF, Shukla SD, Walters EH. *Tuberculosis (Edinb)*. 2015; pii: S1472-9792(15)30091-30093.

Chronic obstructive pulmonary disease (COPD) is emerging as the third largest cause of human mortality worldwide after heart disease and stroke. There is growing evidence of a comorbidity between COPD and tuberculosis (TB), the leading cause of death globally due to respiratory infection. Thus, the increase in the burden of COPD over the coming decades, as predicted by the World Health Organization, is of concern with respect to the control of TB. A better understanding of the interactions between these 2 diseases is essential for the design of complementary preventive and control strategies. In this review, some of the known risk factors that are common to both diseases are discussed. Furthermore, we examine how impairment of the innate immune system, and corticosteroid therapy, in COPD patients may increase the risk of TB manifestation. Conversely, we review how TB lung pathology may heighten susceptibility to subsequent development of COPD, even after completion of effective TB treatment. Growing evidence appears to point towards a bidirectional relationship between these 2 lung diseases where each may act as an independent risk factor for the other. This has important implications for the respective long-term management of TB and COPD.

Comments:

In this review article the authors provide a very nice overview of the relationship between COPD and TB with the premise that the interaction is indeed bidirectional. Bronchiectasis is a common feature of many of the patients with TB. As the authors discuss, the impairment of the innate immune system and use of inhaled corticosteroids likely increase the susceptibility of COPD patients to development and persistence of not only mycobacterium tuberculosis but also non-tuberculous mycobacterial infections. Conversely the inflammatory and immune responses to mycobacterial infections likely cause structural changes that contribute to obstructive physiology.

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Abstract 3
Impact of pulmonary non-tuberculous mycobacterial treatment on pulmonary function tests in patients with and without established obstructive lung disease

Mehta M, Chapman KR, Heffer M, Marras TK. *Respirology*. 2015 ;20(6):987-993. doi: http://dx.doi.org/10.1111/resp.12565

Background and Objective:
There is relatively little data regarding pulmonary function test (PFT) findings and impact of treatment on PFT in pulmonary nontuberculous mycobacterial (pNTM) disease.

Methods:
We performed a retrospective study on pNTM patients. Clinical, radiographical, microbiological and PFT data were reviewed. Patients were divided into 3 groups based on pre-existing obstructive lung disease: (i) normal (no chronic obstructive pulmonary disease [COPD] or asthma); (ii) asthma; and (iii) COPD. We studied pre-treatment PFT and assessed for PFT changes after anti-mycobacterial therapy.

Results:
A total of 96 patients fulfilled American Thoracic Society (ATS) disease criteria and had pre-treatment PFT (54 'normal', 18 asthma, 24 COPD). Most common causative NTM was Mycobacterium avium complex (76%), and radiographical disease type was nodular bronchiectasis (71%). Before therapy, all groups had PFT abnormalities, including obstruction, gas trapping and at least mildly low diffusion capacity of carbon monoxide (DLCO). Pre-treatment PFT abnormalities were more pronounced among patients with asthma and COPD. A total of 44 patients had >12 months anti-mycobacterial therapy and post-treatment PFT. There tended to be small and generally not statistically significant reductions in spirometry and DLCO in most groups. Among the nine asthmatic patients, there was a small reduction in residual volume (RV) (1.5% predicted, P=0.01) and RV/total lung capacity (by 7% predicted, P=0.06).

Conclusions:
Patients with pNTM have abnormal PFT, and treatment was not associated with substantial changes therein. Asthmatics may experience some improvements in gas trapping after NTM therapy, but because the sample size and the observed change were both small, this requires further investigation.
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Keywords: infections atypical; mycobacterial infections atypical; nontuberculous mycobacterial infection; obstructive lung disease; pulmonary function test

Comments:

This is a relatively small study. Larger studies should be conducted to identify patients with non-tuberculous mycobacterial infections with underlying COPD and/or asthma, as the use of inhaled corticosteroids (ICS) presents challenges for these individuals to clear such infections. Studies have demonstrated the potential effects of ICS on local immunity and macrophage function. It is worth noting that many patients had bronchiectasis and it is not surprising that there were no significant improvements in lung function for COPD patients. The improvements in gas trapping in the asthmatic cohort may very well reflect resolution of a bronchiolitis that can occur with infections, including mycobacterial disease.

Abstract 4
Prevalence and risk factors for chronic co-infection in pulmonary Mycobacterium avium complex disease

Fujita K, Ito Y, Hirai T, et al. *BMJ Open Respir Res*. 2014;1(1): e000050. doi: http://dx.doi.org/10.1136/bmjresp-2014-000050

Background:
Patients with pulmonary Mycobacterium avium complex (MAC) disease are often co-infected with various pathogenic microorganisms. This study aimed to determine the prevalence of co-infection with non-MAC pathogens and the risk factors associated with co-infection in patients with pulmonary MAC disease.

Methods: We retrospectively reviewed the patient characteristics, microbiological results and chest CT findings in 275 patients with pulmonary MAC who

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visited the Kyoto University Hospital from January 2001 to May 2013. We defined chronic pathogenic co-infection as the isolation of non-MAC pathogens from sputum samples taken on more than 2 visits that occurred at least 3 months apart.

Results:
The participants were predominantly female (74.5%) and infected with M. avium (75.6%). Chronic co-infection with any pathogen was observed in 124 patients (45.1%). Methicillin-sensitive Staphylococcus aureus (MSSA; n=64), Pseudomonas aeruginosa (n=35) and Aspergillus spp (n=18) were the most prevalent pathogens. The adjusted factors were chronic obstructive pulmonary disease (COPD; OR=4.2, 95% CI 1.6 to 13.1) and pulmonary M. intracellulare disease (OR=2.2, 95% CI 1.1 to 4.4) in chronic co-infections; COPD (OR=4.2, 95% CI 2.1 to 31.4), long duration of MAC disease (OR=2.2, 95% CI 1.2 to 4.4) and nodules (OR=3.5, 95% CI 1.2 to 13.2) in chronic MSSA co-infection; COPD (OR=7.5, 95% CI 2.1 to 31.4) and lower lobe involvement (OR=9.9, 95% CI 2.0 to 90.6) in chronic P. aeruginosa co-infection; and use of systemic corticosteroids (OR=7.1, 95% CI 1.2 to 50.9) and pulmonary M. intracellulare disease (OR=4.0, 95% CI 1.1 to 14.5) in chronic Aspergillus spp co-infection.

Conclusions:
Patients with pulmonary MAC disease frequently had chronic co-infections with pathogenic microorganisms such as MSSA, P. aeruginosa and Aspergillus. The risk factors for chronic co-infection were COPD and pulmonary M. intracellulare disease.

Keywords: Atypical Mycobacterial infection; bacterial infection; bronchiectasis; respiratory infection

Comments:

This study is a rather small cohort, however, the findings are instructive with regard to the frequency of co-infection with other organisms for those patients that have positive cultures for MAC. Of the 275 patients, 234 had bronchiectasis and only 24 had COPD and 19 of the 24 were on inhaled corticosteroids. Interestingly, of the many conditions ranging from bronchiectasis, pneumonia, diabetes, autoimmune disease, rheumatoid arthritis and malignancy, COPD was the only condition associated with an increased risk of MSSA. Patients with COPD that have evidence of infection typically have structural changes, bronchiectasis and altered innate immunity in addition to the use of ICS. It is likely these factors predispose them to having multiple pathogenic organisms present. Interestingly COPD, Mycobacterium intracellulare and lower lobe bronchiectasis were at increased risk for having Psuedomonas aeruginosa. Findings of this study and others lay the foundation for some investigators to suggest they constitute a sub-phenotype *bronchiectasis/COPD overlap* with distinct features and treatment considerations, particularly with regard to the use of inhaled corticosteroids.

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