

Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation



Journal Club

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Abbreviations: asthma-COPD overlap syndrome, **ACOS**; Type 2 helper T cell, **Th2**; inhaled corticosteroids, **ICS**; long-acting beta-agonists, **LABA**; interleukin 6, **IL-6**; airway hyper-responsiveness, **AHR**; bronchodilator response, **BDR**; forced expiratory volume in 1 second, **FEV1**; forced vital capacity, **FVC**; immunoglobulin E, **IgE**; Global Initiative for Asthma, **GINA**; Global initiative for obstructive Lung Disease, **GOLD**; interleukin-1 beta, **IL-1B**; interleukin-8, **IL-8**; interleukin-10, **IL-10**; tumor necrosis factor-alpha, **TNF α** ; Th2 signature, **T2S**; interleukin-13, **IL-13**; serine peptidase inhibitor B2, **SERPINB2**; interleukin-5, **IL-5**

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Introduction: The Asthma-COPD Overlap Syndrome: What Do We Mean by It? What is the Significance?

This Journal Club presents articles that have addressed the challenges and various approaches in differentiating COPD from asthma, and the rationale for doing so with regard to primary and secondary prevention, pharmacological and non-pharmacological management, assessing comorbidities, monitoring and prognosis. This collection of articles takes us from bedside to bench showing an evolution in understanding of asthma-COPD overlap syndrome (ACOS) from classic clinical characterization to biomarkers and genetic phenotyping. The absence of a clear universal definition of what is meant by ACOS undoubtedly indicates that there are further sub-phenotypes within the ACOS group. What is most important is the fact that for both asthma and COPD it is a relatively small subgroup (perhaps a third in COPD and even less in asthma) of severe and very severe patients that do not respond to conventional therapies and who incur the majority of the burden of illness, morbidity, mortality and both direct and indirect health care costs. It is this group in which the underlying, biological heterogeneity is perhaps the

most enriched and important to decipher to determine if combined treatment, earlier treatment and/or which new biologic targeted treatments will have an impact on control, progression of disease and mortality.

Abstract 1 Distinguishing adult-onset asthma from COPD: a review and a new approach

Abramson MJ, Perret JL, Dharmage SC, McDonald VM, McDonald CF. *Int J Chron Obstruct Pulmon Dis.* 2014;9(1):945-962.

doi: <http://dx.doi.org/10.2147/COPD.S46761>

Adult-onset asthma and chronic obstructive pulmonary disease (COPD) are major public health burdens. This review presents a comprehensive synopsis of their epidemiology, pathophysiology, and clinical presentations; describes how they can be distinguished; and considers both established and proposed new approaches to their management. Both adult-onset asthma and COPD are complex diseases arising from gene-environment interactions. Early life exposures such as childhood infections, smoke, obesity, and allergy influence adult-onset asthma. While the established environmental risk factors for COPD are adult tobacco and biomass smoke, there is emerging evidence that some childhood exposures such as maternal smoking and infections may cause COPD. Asthma has been characterized predominantly by Type 2 helper T cell (Th2) cytokine-mediated eosinophilic airway inflammation associated with airway hyperresponsiveness. In

established COPD, the inflammatory cell infiltrate in small airways comprises predominantly neutrophils and cytotoxic T cells (CD8 positive lymphocytes). Parenchymal destruction (emphysema) in COPD is associated with loss of lung tissue elasticity, and small airways collapse during exhalation. The precise definition of chronic airflow limitation is affected by age; a fixed cut-off of forced expiratory volume in 1 second/forced vital capacity leads to overdiagnosis of COPD in the elderly. Traditional approaches to distinguishing between asthma and COPD have highlighted age of onset, variability of symptoms, reversibility of airflow limitation, and atopy. Each of these is associated with error due to overlap and convergence of clinical characteristics. The management of chronic stable asthma and COPD is similarly convergent. New approaches to the management of obstructive airway diseases in adults have been proposed based on inflammometry and also multi-dimensional assessment, which focuses on the four domains of the airways, comorbidity, self-management, and risk factors. Short-acting beta-agonists provide effective symptom relief in airway diseases. Inhalers combining a long-acting beta-agonist and corticosteroid are now widely used for both asthma and COPD. Written action plans are a cornerstone of asthma management although evidence for self-management in COPD is less compelling. The current management of chronic asthma in adults is based on achieving and maintaining control through step-up and step-down approaches, but further trials of back-titration in COPD are required before a similar approach can be endorsed. Long-acting inhaled anticholinergic medications are particularly useful in COPD. Other distinctive features of management include pulmonary rehabilitation, home oxygen, and end of life care.

Comments

Abramson and colleagues present a comprehensive up-to-date overview of conventional clinical metrics used in the assessment of patients with obstructive airway disease. They also discuss the reasons why it does make a difference whether or not a patient is considered to have asthma or COPD with regard to medication choices, as well as non-pharmacological interventions, monitoring and prognosis. While ACOS is not the main focus, the authors present a cogent treatise as to why we should not simply clump everyone together and treat them all the same and in turn, why ACOS may be a distinct

group with its own unique features warranting special considerations in evaluation and treatment options.

Abstract 2 The asthma-COPD overlap syndrome (ACOS)

Bujarski S, Parulekar AD, Sharafkhaneh A, Hanania NA. *Curr Allergy Asthma Rep*. 2015; 15(3):509. doi: <http://dx.doi.org/10.1007/s11882-014-0509-6>

Asthma and chronic obstructive pulmonary disease (COPD) have traditionally been viewed as distinct clinical entities. Recently, however, much attention has been focused on patients with overlapping features of both asthma and COPD: those with asthma-COPD overlap syndrome (ACOS). Although no universal definition criteria exist, recent publications attempted to define patients with ACOS based on differences in clinical features, radiographic findings, and diagnostic tests. Patients with ACOS make up a large percentage of those with obstructive lung disease and have a higher overall health care burden. Identifying patients with ACOS has significant therapeutic implications particularly with the need for early use of inhaled corticosteroids (ICS) and the avoidance of use of long-acting bronchodilators alone in such patients. However, unlike asthma and COPD, no evidence-based guidelines for the management of ACOS currently exist. Future research is needed to improve our understanding of ACOS and to achieve the best management strategies.

Comments

Buiarski and colleagues provide a review of the state of our current concepts regarding ACOS. They provide a review of the literature from bench to bedside as well as discuss the implications of identification of this group at an early stage and the potential impact of early intervention with ICS and avoidance of use of long-acting beta-agonists (LABA) alone in this group. While this may be the immediate clinical impetus for improving our understanding of ACOS, it is becoming apparent that we are learning a great deal about the biological heterogeneity of severe obstructive airway disease and insights into why this group of patients presents the greatest challenges to treat with conventional therapies. This has implications for prevention strategies and the development and patient selection for future *biologics*

and other agents that are currently under study.

Abstract 3 Systemic inflammation in older adults with asthma-COPD overlap syndrome

Fu JJ, McDonald VM, Gibson PG, Simpson JL. *Allergy Asthma Immunol Res.* 2014;6(4):316-324.

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Purpose: The role of systemic inflammation on asthma-COPD overlap syndrome is unknown. This study aimed to examine systemic inflammation in asthma-COPD overlap syndrome, and to identify associations between clinical characteristics and inflammatory mediators in asthma-COPD overlap syndrome.

Methods: In 108 adults older than 55 years comprising healthy controls (n=29), asthma (n=16), COPD (n=21) and asthma-COPD overlap syndrome (n=42), serum high sensitivity C-reactive protein and interleukin 6 (IL-6) were assayed. Spirometry, induced sputum, quality of life, comorbidities and medications were assessed, and their associations with asthma-COPD overlap syndrome were analyzed using logistic regression. Associations between systemic inflammatory mediators and clinical characteristics were tested in multivariate linear regression models.

Results: Patients with asthma-COPD overlap syndrome had significantly elevated IL-6 levels compared with healthy controls and asthmatics. Age, comorbidity index and IL-6 level were independently associated with asthma-COPD overlap syndrome. FEV₁% predicted was inversely associated with IL-6 level, and cardiovascular disease was associated with an increased IL-6 level. Systemic markers were not associated with airway inflammation.

Conclusions: Systemic inflammation is commonly present in asthma-COPD overlap syndrome, and asthma-COPD overlap syndrome resembled COPD in terms of systemic inflammation. IL-6 is a pivotal inflammatory mediator that may be involved in airflow obstruction and cardiovascular disease and may be an independent treatment target.

Keywords: Ageing; C-reactive protein; asthma; comorbidity; interleukin-6; obstructive airway disease

Comments

This study determined a COPD/asthma overlap group

on clinical grounds as a group with a history of asthma or evidence of airway hyper-responsiveness (AHR) (positive methacholine) or significant bronchodilator response (BDR) but without return to normal lung function (forced expiratory volume in 1 second to forced vital capacity [FEV₁/FVC] ratio <70% and FEV₁ <80% predicted). In this study the COPD definition excluded any patients with BDR and/or AHR. Interestingly in this cohort of consecutively recruited patients in a tertiary care setting, the overlap group constituted 53.2% of the patients with any evidence of obstructive airway disease. There were 20.3% who were asthmatic and 26.6% who had COPD. The overlap group had a post bronchodilator FEV₁ (54.6% predicted) much closer to the COPD group (52.1% predicted) and interestingly a higher rate of airway hyper-responsiveness than the asthma group (92.7% versus 75%). It is interesting that apparently 4 of the asthma patients did not show AHR (criteria were AHR and/or BDR). The overlap group also had the highest pack year history and 54% were atopic versus 43% of the asthma group and 61.9% of the COPD group. With regard to smoking status, the overlap group had 12 never smokers and 30 ex-smokers compared to 5 never and 16 ex-smokers in the COPD group and 11 never and 5 ex-smokers in the asthma group. There were no significant differences in inhaled corticosteroid use between the groups. Sputum indices for the COPD and the overlap group showed high neutrophils (>61%) and low eosinophils (<3%) whereas the asthma group was the reverse. In this cohort, the overlap group seems to be enriched by a group of asthma patients that smoked and developed COPD and perhaps not surprisingly, have more severe disease and an enhanced inflammatory response and greater comorbidity. It would have been interesting to know the proportion of patients in the overlap group that had an early onset asthma history and to see other measures associated with asthma such as peripheral blood eosinophils, exhaled nitric oxide, immunoglobulin E (IgE), and how these compared between the groups.

Abstract 4 Biological clustering supports both “Dutch” and “British” hypotheses of asthma and chronic obstructive pulmonary disease

Ghebre MA, Bafadhel M, Desai D, et al. *J Allergy Clin*

Immunol. 2015;135(1):63-72.

doi: <http://dx.doi.org/10.1016/j.jaci.2014.06.035>

Background: Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous diseases. Objective: We sought to determine, in terms of their sputum cellular and mediator profiles, the extent to which they represent distinct or overlapping conditions supporting either the “British” or “Dutch” hypotheses of airway disease pathogenesis.

Methods: We compared the clinical and physiological characteristics and sputum mediators between 86 subjects with severe asthma and 75 with moderate-to-severe COPD. Biological subgroups were determined using factor and cluster analyses on 18 sputum cytokines. The subgroups were validated on independent severe asthma (n=166) and COPD (n=58) cohorts. Two techniques were used to assign the validation subjects to subgroups: linear discriminant analysis, or the best identified discriminator (single cytokine) in combination with subject disease status (asthma or COPD).

Results: Discriminant analysis distinguished severe asthma from COPD completely using a combination of clinical and biological variables. Factor and cluster analyses of the sputum cytokine profiles revealed 3 biological clusters: cluster 1: asthma predominant, eosinophilic, high TH2 cytokines; cluster 2: asthma and COPD overlap, neutrophilic; cluster 3: COPD predominant, mixed eosinophilic and neutrophilic. Validation subjects were classified into 3 subgroups using discriminant analysis, or disease status with a binary assessment of sputum IL-1 β expression. Sputum cellular and cytokine profiles of the validation subgroups were similar to the subgroups from the test study.

Conclusions: Sputum cytokine profiling can determine distinct and overlapping groups of subjects with asthma and COPD, supporting both the British and Dutch hypotheses. These findings may contribute to improved patient classification to enable stratified medicine.

Comments

Ghebre and colleagues clinically characterized their patients as having asthma or COPD based on Global Initiative for Asthma (GINA) and Global initiative for obstructive Lung Disease (GOLD) clinical guidelines. They then assessed patients with a combination of clinical and sputum inflammatory mediators and

performed cluster analysis to identify the 3 clusters: asthma predominant (55 asthma, 3 COPD), asthma/COPD overlap (28 asthma, 19 COPD) and COPD predominant (2 asthma, 39 COPD). Clinical data included pre and post bronchodilator FEV₁, FVC and symptoms' scores. There was no difference in atopic status across the asthma patients in the different clusters. Methacholine challenges were not performed. Immunoglobulin E levels were not measured. Sputum samples were analyzed for cell count and differential and bacteriology and cell free supernatant was assessed for 18 cytokines that have been implicated in airway disease. Eosinophilic high was defined as sputum eosinophils >3% with neutrophils <61%, mixed granulocytic was eosinophils >3% with neutrophils >61%, neutrophilic was eosinophils <3% with neutrophils >61% and paucigranulocytic was eosinophils <3% with neutrophils <61%. They found elevated TH2 cytokines (IL-5, IL13 and CCL26) and TH1 mediators (CXCL10 and 11) in severe asthma whereas COPD patients had increased IL-6, CCL2, CCL3, and CCL4. The overlap group showed sputum neutrophil predominance in 75% of asthmatics and 95% of COPD patients and eosinophilic predominance in 11% and 5% respectively. The overlap group also had elevated levels of interleukin-1 beta (IL-1B), interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF α) and an increased rate of bacterial colonization (>10⁷CFU/ml sputum or positive culture). Somewhat surprisingly, the predominantly COPD cohort had 28% pure neutrophilic, 21% pure eosinophilic, 23% mixed and 28% paucigranulocytic. The overlap group also had the highest sputum total inflammatory cell count suggesting that it was a chronic bronchitis group. The authors point out that the findings of this study are not necessarily generalizable because of the referral bias to this secondary care setting (highly specialized center where only more severe patients are seen). Indeed it may well be that the overlap group is enriched in the group of more difficult to manage patients that end up in specialty clinics. It is also important to note that the Leicester group, where all patients were seen, is particularly skilled in the acquisition of viable sputum samples and this remains a challenge for many clinical centers. Nonetheless, the work of these authors further establishes the heterogeneity of asthma and COPD and the importance of characterizing the more difficult to treat patients (in both groups) according to their underlying biology and their basic clinical characteristics. As newer agents become available it

will be instructive to see if there is a selective benefit of treating this particular subgroup earlier and whether it protects lung function over time.

Abstract 5 Asthma-COPD overlap: clinical relevance of genomic signatures of type 2 inflammation in COPD

Christenson SA, Steiling K, van den Berge M, et al. *Am J Respir Crit Care Med*. 2015;191(7):758-766.

doi: <http://dx.doi.org/10.1164/rccm.201408-14580C>

Rationale: COPD is a heterogeneous disease, and likely includes a subgroup that is biologically comparable to asthma. Studying asthma-associated gene expression changes in COPD could add insight into COPD pathogenesis and reveal biomarkers that predict a favorable response to corticosteroids.

Objective: To determine whether asthma-associated gene signatures are increased in COPD and associated with asthma-related features.

Methods: We compared disease-associated airway epithelial gene expression alterations in an asthma cohort (n=105) and two COPD cohorts (n=237, 171). The Th2 Signature (T2S) score, a gene expression metric induced in Th2-high asthma, was evaluated in these COPD cohorts. The T2S score was correlated with asthma-related features and response to corticosteroids in COPD in a randomized, placebo-controlled trial (GLUCOLD, n=89).

Measurements and main results: The 200 genes most differentially expressed in asthma versus healthy controls were enriched among genes associated with more severe airflow obstruction in these COPD cohorts ($p < 0.001$), suggesting significant gene expression overlap. A higher T2S score was associated with decreased lung function ($p < 0.001$), but not asthma history, in both COPD cohorts. Higher T2S scores correlated with increased airway wall eosinophil counts ($p = 0.003$), blood eosinophil percentage ($p = 0.03$), bronchodilator reversibility ($p = 0.01$), and improvement in hyperinflation following corticosteroid treatment ($p = 0.019$) in GLUCOLD.

Conclusion: These data identify airway gene expression alterations that can co-occur in asthma and COPD. The association of the Th2 signature with increased severity and asthma-like features (including

a favorable corticosteroid response) in COPD suggests Th2 inflammation is important in a COPD subset that cannot be identified by clinical history of asthma.

Comments

Christenson and colleagues have demonstrated in a very elegant study the very reason it is important to discuss the COPD/asthma overlap as a phenotype distinct from known asthma patients that smoke and develop COPD. These investigators had previously determined a Th2-high gene expression signature in a group of asthma patients using an array of variables including elevated airway epithelial expression levels of 3 interleukin-13 (IL-13) inducible genes, periostin, chloride channel, Ca²⁺ activated 1 and serine peptidase inhibitor B2 (SERPINB2). These were correlated with high levels of interleukin-5 (IL-5), IL 13 in bronchial biopsies, increased serum total IgE levels, greater blood and lung eosinophilia, increased airway hyper-responsiveness and better lung function (FEV₁) response to ICS. This Th2 signature score (and a revised version of it using a 100 gene set) was then evaluated in 2 COPD cohorts and shown to be associated with more severe airflow obstruction, bronchodilator responsiveness, eosinophilia and steroid responsiveness. This study suggests that there are certain underlying TH-2-associated genetic and biological characteristics that may increase the likelihood of developing COPD even in the absence of a clear clinical history of asthma. It is also quite compelling that this group of patients also appears to have more severe airflow obstruction and steroid responsiveness in the absence of an asthma history. Interestingly, the authors also found that the COPD gene sets correlated with an asthma diagnosis. They also found that the up-regulated genes in the COPD/asthma overlap group were enriched amongst genes that are down-regulated by ICS+/- LABA compared to placebo and the down-regulated overlap genes were enriched amongst genes up-regulated with ICS+/- LABA compared to placebo. With renewed questions about the role of ICS in the treatment of COPD, given comorbidities and concerns about increased incidence and severity of pneumonia, this study provides compelling evidence that there is indeed a role of ICS treatment for at least a subset of COPD patients. Perhaps even more important, it may also point to a group of COPD patients where earlier intervention with ICS may actually prevent or at least impede more

severe progression of disease. Furthermore this may also define a group of COPD patients for whom new biologics being considered for asthma, (such as anti-Il-5 agents), should also be studied for their efficacy.