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Journal Club

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Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. M. Thomsen, T.S. Ingebrigtsen, J.L. Marott, M. Dahl , P. Lange, J. Vestbo, B.G. Nordestgaard. JAMA. 2013 Jun 12;309(22):2353–61.

IMPORTANCE: Exacerbations of respiratory symptoms in chronic obstructive pulmonary disease (COPD) have profound and long-lasting adverse effects on patients.
OBJECTIVE: To test the hypothesis that elevated levels of inflammatory biomarkers in individuals with stable COPD are associated with an increased risk of having exacerbations.
DESIGN, SETTING, AND PARTICIPANTS: Prospective cohort study examining 61,650 participants with spirometry measurements from the Copenhagen City Heart Study (2001–2003) and the Copenhagen General Population Study (2003–2008). Of these, 6574 had COPD, defined as a ratio between forced expiratory volume in 1 second (FEV1) and forced vital capacity below 0.7. MAIN OUTCOMES AND MEASURES: Baseline levels of C-reactive protein (CRP) and fibrinogen and leukocyte count were measured in participants at a time when they were not experiencing symptoms of exacerbations. Exacerbations were recorded and defined as short-course treatment with oral corticosteroids alone or in combination with an antibiotic or as a hospital admission due to COPD. Levels of CRP and fibrinogen and leukocyte count were defined as high or low according to cut points of 3 mg/L, 14 μmol/L, and 9 × 10(9)/L, respectively.
RESULTS: During follow-up, 3083 exacerbations were recorded (mean, 0.5/participant). In the first year of follow-up, multivariable-adjusted odds ratios for having frequent exacerbations were 1.2 (95% CI, 0.7–2.2; 17 events/1000 person-years) for individuals with 1 high biomarker, 1.7 (95% CI, 0.9–3.2; 32 events/1000 person-years) for individuals with 2 high biomarkers, and 3.7 (95% CI, 1.9–7.4; 81 events/1000 person-years) for individuals with 3 high biomarkers compared with individuals who had no elevated biomarkers (9 events/1000 person-years; trend: P = 2 × 10(−5)). Corresponding hazard ratios using maximum follow-up time were 1.4 (95% CI, 1.1–1.8), 1.6 (95% CI, 1.3–2.2), and 2.5 (95% CI, 1.8–3.4), respectively (trend: P = 1 × 10(−8)). The addition of inflammatory biomarkers to a basic model including age, sex, FEV1 percent predicted, smoking, use of any inhaled medication, body mass index, history of previous exacerbations, and time since most recent prior exacerbation improved the C statistics from 0.71 to 0.73 (comparison: P = 9 × 10(−5)). Relative risks were consistent in those with milder COPD, in those with no history of frequent exacerbations, and in the 2 studies separately. The highest 5-year absolute risks of having frequent exacerbations in those with 3 high biomarkers (vs no high biomarkers) were 62% (vs 24%) for those with Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades C-D (n = 558), 98% (vs 64%) in those with a history of frequent exacerbations (n = 127), and 52% (vs 15%) for those with GOLD grades 3–4 (n = 465).

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CONCLUSIONS AND RELEVANCE: Simultaneously elevated levels of CRP and fibrinogen and leukocyte count in individuals with COPD were associated with increased risk of having exacerbations, even in those with milder COPD and in those without previous exacerbations. Further investigation is needed to determine the clinical value of these biomarkers for risk stratification

Comments: One of the greatest and most important challenges in management of patients with COPD is to identify individuals early on that may be part of the "frequent exacerbator" and/or "ra pid decliner" group. In theory, early detection and intervention may be particularly important in this phenotype. A very interesting finding from this study is that, even early on, in a group of patients with reportedly milder disease, a sub-group with the combination of elevated CRP, fibrinogen and leukocyte count are at risk of having frequent exacerbations. Clearly, further studies that answer whether early, more aggressive treatment of this group can impact their disease progression is one of the ultimate fruits that we hope to gather from biomarker measurements.

Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β2 agonist: observational matched cohort study (PATHOS). C.B Janson, K. Larsson, K.H. Lisspers, B. Ställberg, G. Stratelis, H. Goike, L. Jörgensen, G. Johansson. BMJ. 2013 May 29;34 6:f3306.

OBJECTIVE: To investigate the occurrence of pneumonia and pneumonia related events in patients with chronic obstructive pulmonary disease (COPD) treated with two different fixed combinations of inhaled corticosteroid/ long acting β2 agonist.
DESIGN: Observational retrospective pairwise cohort study matched (1:1) for propensity score.
SETTING: Primary care medical records data linked to Swedish hospital, drug, and cause of death registry data for years 1999–2009.
PARTICIPANTS: Patients with COPD diagnosed by a physician and prescriptions of either budesonide/ formoterol or fluticasone/salmeterol.
MAIN OUTCOME MEASURES: Yearly pneumonia event rates, admission to hospital related to pneumonia, and mortality.
RESULTS: 9893 patients were eligible for matching (2738 in the fluticasone/salmeterol group; 7155 in the budesonide/formoterol group), yielding two matched cohorts of 2734 patients each. In these patients, 2115 (39%) had at least one recorded episode of pneumonia during the study period, with 2746 episodes recorded during 19 170 patient years of follow up. Compared with budesonide/formoterol, rate of pneumonia and admission to hospital were higher in patients treated with fluticasone/salmeterol: rate ratio 1.73 (95% confidence interval 1.57 to 1.90; $P < 0.001$) and 1.74 (1.56 to 1.94; $P < 0.001$), respectively. The pneumonia event rate per 100 patient years for fluticasone/salmeterol versus budesonide/formoterol was 11.0 (10.4 to 11.8) versus 6.4 (6.0 to 6.9) and the rate of admission to hospital was 7.4 (6.9 to 8.0) versus 4.3 (3.9 to 4.6). The mean duration of admissions related to pneumonia was similar for both groups, but mortality related to pneumonia was higher in the fluticasone/salmeterol group (97 deaths) than in the budesonide/formoterol group (52 deaths) (hazard ratio 1.76, 1.22 to 2.53; $P = 0.003$). All cause mortality did not differ between the treatments (1.08, 0.93 to 1.14; $P = 0.59$).
CONCLUSIONS: There is an intra-class difference between fixed combinations of inhaled corticosteroid/long acting β2 agonist with regard to the risk of pneumonia and pneumonia related events in the treatment of patients with COPD.
TRIAL REGISTRATION: Clinical Trials.gov NCT01146392.
PMID: 23719639 [PubMed - in process] PMCID: PMC3666306

Comments: While it is acknowledged that COPD involves an inflammatory response and that exacerbations are associated with acute increased inflammation there has been evidence of a "pneumonia signal" and/ or increased "lower respiratory tract infections" in many of the prospective randomized controlled trials that examine the impact of ICS/LABA combinations in reducing exacerbations in COPD patients. This Swedish based study, funded by Astra Zeneca, is consistent with other literature in this area that has suggested that there may be an intra-class difference between these two ICS/LABA combination therapies with regard to risk of developing pneumonia. The authors provide several plausible explanations for why there may be a difference, referring to data that suggests differences in immunosuppressant potency with regard to macrophage function and differences in pharmacokinetics and pharmacodynamics leading to longer duration of fluticasone persistence in airway mucosa leading to greater impact on local immunity to pathogens. While the data certainly may cause clinicians to reflect on their choice as to which ICS/LABA combination to use, there are several points to consider with regard to the generalizability of the results. In this retrospective review of a registry there was a much higher number (7155) subjects that had been on budesonide/ formoterol versus fluticasone/ salmeterol (2738). Previous studies have shown that the pneumonia signal does trend to being dose related (i.e. higher pneumonia rates in study arms on higher doses of ICS). In this retrospective study the average dose of fluticasone was 783 μg/day (SD 338) and the average budesonide dose was 568 μg/day (SD 235). This reflects use of the fluticasone/salmeterol 500/50 formulation in a substantial proportion of the subjects. This dose is approved for use in COPD in Europe whereas only the 250/50 μg dose is approved in the United States.

Budesonide/formoterol 160/4.5 µg does not have an indication for treatment of exacerbations in the United States whereas the fluticasone 250/50 formulation does. Regardless of the combination ICS/LABA formulation that clinicians pick for their patients one must be mindful of the delicate balance of hoping to achieve optimum anti-inflammatory effects with the minimum effect on immune response to pathogens.

Use of inhaled corticosteroids and the risk of tuberculosis. C.H. Lee, K. Kim, M.K. Hyun, E.J. Jang, N.R. Lee, J.J. Yim. Thorax. 2013 Jun 8. [Epub ahead of print].

BACKGROUND: Inhaled corticosteroid (ICS) use could decrease local immunity of the lung. Concerns have been raised regarding the risk of tuberculosis (TB) development among ICS users. The aim of this study was to elucidate the association between ICS use and development of TB among patients with various respiratory diseases in South Korea, an intermediate-TB-burden country.
METHODS: A nested case-control study based on the Korean national claims database was performed. The eligible cohort consisted of 853 439 new adult users of inhaled respiratory medications between 1 January 2007 and 31 December 2010. Patients diagnosed as having TB after initiation of inhaled medication were included as cases. For each case individual, up to five control individuals matched for age, sex, diagnosis of asthma or chronic obstructive pulmonary disease (COPD) and initiation date of inhaler use were selected.
RESULTS: From the cohort population, we matched 4139 individuals diagnosed as having TB with 20 583 controls. ICS use was associated with increased rate of TB diagnosis (adjusted OR (aOR), 1.20; 95% CI 1.08 to 1.34). The association was dose dependent (p for trend <0.001). A subgroup analysis revealed that ICS use increased the risk of TB development among non-users of oral corticosteroid (OCS) but not among OCS users.
CONCLUSIONS: ICS use increases the risk of TB in an intermediate-TB-burden country. Clinicians should be aware of the possibility of TB development among patients who are long-term high-dose ICS users.
KEYWORDS: Tuberculosis

Comments: While it must be acknowledged that TB and other mycobacterial infections remain a not insignificant cause of COPD in certain parts of the world, it is certainly recognized that TB and/or atypical mycobacteria can complicate the course of patients even with COPD from cigarette smoking. Aside from their anti-inflammatory properties, inhaled corticosteroids have immunosuppressive properties that it is becoming abundantly apparent are not inconsequential and should be taken into consideration when judging the optimum therapy for the individual COPD patient.

Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. J.D. Leuppi, P. Schuetz, R. Bingisser, M. Bodmer, M. Briel, T. Drescher, U. Duerring, C. Henzen, Y. Leibbrandt, S. Maier, D. Miedinger, B. Müller, A. Scherr, C. Schindler, R. Stoeckli, S. Viatte, C. von Garnier, M. Tamm, J. Rutishauser. JAMA. 2013 Jun 5;309(21):2223–31.

IMPORTANCE: International guidelines advocate a 7- to 14-day course of systemic glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease (COPD). However, the optimal dose and duration are unknown.
OBJECTIVE: To investigate whether a short-term (5 days) systemic glucocorticoid treatment in patients with COPD exacerbation is noninferior to conventional (14 days) treatment in clinical outcome and whether it decreases the exposure to steroids.
DESIGN, SETTING, AND PATIENTS REDUCE: (Reduction in the Use of Corticosteroids in Exacerbated COPD), a randomized, noninferiority multicenter trial in 5 Swiss teaching hospitals, enrolling 314 patients presenting to the emergency department with acute COPD exacerbation, past or present smokers (≥20 pack-years) without a history of asthma, from March 2006 through February 2011.
INTERVENTIONS: Treatment with 40 mg of prednisone daily for either 5 or 14 days in a placebo-controlled, double-blind fashion. The predefined noninferiority criterion was an absolute increase in exacerbations of at most 15%, translating to a critical hazard ratio of 1.515 for a reference event rate of 50%.
MAIN OUTCOME AND MEASURE: Time to next exacerbation within 180 days.
RESULTS: Of 314 randomized patients, 289 (92%) of whom were admitted to the hospital, 311 were included in the intention-to-treat analysis and 296 in the per-protocol analysis. Hazard ratios for the short-term vs conventional treatment group were 0.95 (90% CI, 0.70 to 1.29; P = .006 for noninferiority) in the intention-to-treat analysis and 0.93 (90% CI, 0.68 to 1.26; P = .005 for noninferiority) in the per-protocol analysis, meeting our noninferiority criterion. In the short-term group, 56 patients (35.9%) reached the primary end point; 57 (36.8%) in the conventional group. Estimates of reexacerbation rates within 180 days were 37.2% (95% CI, 29.5% to 44.9%) in the short-term; 38.4% (95% CI, 30.6% to 46.3%) in the conventional, with a difference of –1.2% (95% CI, –12.2% to 9.8%) between the short-term and the conventional. Among patients with a reexacerbation, the median time to event was 43.5 days (interquartile range [IQR], 13 to 118) in the short-term and 29 days (IQR, 16 to 85) in the conventional. There was no difference between groups in time to death, the combined end point of exacerbation, death, or both and recovery of lung function. In the conventional group, mean cumulative prednisone dose was significantly higher (793 mg [95% CI, 710 to 876 mg] vs 379 mg [95% CI, 311

to 446 mg], P < .001), but treatment-associated adverse reactions, including hyperglycemia and hypertension, did not occur more frequently.

CONCLUSIONS AND RELEVANCE: In patients presenting to the emergency department with acute exacerbations of COPD, 5-day treatment with systemic glucocorticoids was noninferior to 14-day treatment with regard to reexacerbation within 6 months of follow-up but significantly reduced glucocorticoid exposure. These findings support the use of a 5-day glucocorticoid treatment in acute exacerbations of COPD.

Comments: Oral steroids are a central component of the treatment of acute exacerbations of COPD but there is ongoing controversy with regard to not only optimum dose but also duration of treatment considering the vast array of comorbidities, (diabetes, hypercholesterolemia, cardiac disease, osteopenia and cataracts to name a few), that oral steroids may adversely impact. There is also acute interest in certain juristictions to develop discharge protocols that aggressively treat COPD exacerbations to avoid readmission, as payers will not be required to pay if patients are readmitted within 30 days. While this is a relatively small study in 5 Swiss teaching hospitals the findings are intriguing and again point to the need to weigh the benefit versus risk with regard to longer more aggressive use of oral corticosteroids in patients with COPD.