# Blood eosinophils in COPD and the future risk of pneumonia

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**There is an increase in pneumonia risk in COPD patients who have higher blood eosinophil counts at baseline** http://ow.ly/XPVh30kvOpZ

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The eosinophil, whether in the blood or sputum, has been receiving increasing attention as a measure of treatment response or failure in patients with chronic obstructive pulmonary disease (COPD). A recent review by Bafadhel *et al.* [1] summarises the biology of the eosinophil, its role in airway disease, as well as the clinical data supporting the use of blood eosinophils as a biomarker in airway disease, and more specifically, COPD. To paraphrase their conclusions: while the role of eosinophils in COPD needs clarification, there is now the realisation that blood eosinophils may be a useful guide to therapy. There is, however, substantial within-person variation in blood eosinophil counts [2]. Despite this, there is a significant proportion of patients with COPD in whom blood eosinophil counts are consistently high or low: 65% consistently above or below $0.40\times10^9$ per L over a 1-year period in the Leicester cohort [1] and 51% at the 2% cut-off over a 3-year period in the ECLIPSE study [3]. Consistency also appears better when using absolute counts and at lower counts. For example, using a cut-off value of $<0.15\times10^9$ per L, Southworth *et al.* [4] found 87% to be in the same category at 6 months and a similar proportion at >2 years of follow-up. It has further been suggested that higher blood eosinophil counts are predictive of future eosinophilic exacerbations [5] and this is supported by the better response to oral corticosteroids in patients with exacerbations characterised by higher blood eosinophils at presentation [1]. The broader importance of the eosinophil in the natural history of airway disease at an early stage is suggested by the predictive value of blood eosinophil counts on decline in forced expiratory volume in 1 s ($FEV_1$) and $FEV_1$/forced vital capacity in young adults from the New Zealand birth cohort, an effect that is independent of asthma and cigarette smoking [6].

In the May issue of the *European Respiratory Journal*, Vedel-Krogh *et al.* [7] described the relationship between blood eosinophil count at levels of $\geqslant0.34\times10^9$ per L and risk of severe pneumonia requiring hospitalisation from the Copenhagen General Population Study, a prospective cohort study with spirometry and complete blood counts obtained at recruitment. There were 7180 individuals with airway obstruction by spirometry and without self-reported asthma, of whom 4832 had smoked >10 pack-years.

Overall, among these 4832 subjects, there was no relationship between blood eosinophil count and pneumonia. When stratifying individuals according to $FEV_1$, among subjects with an $FEV_1$ $\geqslant$50% predicted, there was a trend toward a protective effect of higher eosinophils (incidence rate ratio (IRR) 0.69, 95% CI 0.47–1.00). In subjects with severe airway obstruction and $\geqslant$10 pack-years of smoking (553 subjects), the risk of pneumonia was increased (IRR 1.82, 95% CI 1.10–3.02) after adjustment for various confounders including prior pneumonia events, use of inhaled corticosteroids (ICS) and number of

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inflammatory markers. When not counting multiple pneumonias in the same individual or when excluding those with a pneumonia event prior to cohort entry, the risk was further diminished and no longer statistically significant. The effect was stronger in a population with "clinical COPD" (⩾10 pack-years of smoking, an exacerbation in the prior year and $FEV_1$ <70% predicted; IRR 3.14, 95% CI 1.42–6.91). However, we are not provided with an analysis not counting multiple pneumonias in the same individual or when excluding those with pneumonia prior to cohort entry, which to me are the most valid analyses.

The results of this study appear to contradict a patient level meta-analysis of clinical trials reported by Pavord *et al.* [8]. Among 3065 subjects who were fairly typical of COPD clinical trial populations, although 41% were without prior exacerbation in previous 12 months, and who did not receive ICS in their treatment arm, the hazard ratio of pneumonia was 1.53 (95% CI 1.01–2.31) for subjects with peripheral blood eosinophil counts at baseline of <2% as compared to those with higher values. While the differences in results may reflect differences in study populations (one carried out in the general population, the other in a highly selected clinical trial population; differences in the definition of pneumonia; and the Copenhagen study examined only severe pneumonia leading to hospitalisation, the clinical trial looking at all pneumonia events), the results are still hard to reconcile. One has to wonder whether severe exacerbations of COPD might have been mislabelled as pneumonia in a general population cohort, especially since higher eosinophil counts were also a risk factor for severe COPD exacerbations leading to hospitalisation in the same subgroups of patients [9]. This might have been less likely to happen in clinical trials where exacerbations of COPD are a principal outcome. Of note, other retrospective re-analyses of clinical trials did not find differences in risk of pneumonia according to blood eosinophil count [10, 11].

From the point of view of biological plausibility, eosinopenia is the more obvious choice as a risk factor for pneumonia. Eosinophils appear to have potent antibacterial properties in a mouse model [12]. Major basic protein and eosinophilic cationic protein contained in the cytoplasmic granules of eosinophils are bactericidal [13]. In a prospective clinical cohort of fairly typical COPD patients, 32% of whom were current smokers and 86% receiving ICS, high bacterial load of potentially pathogenic organisms at baseline was inversely related to sputum eosinophils (but not blood eosinophils), while at the onset of a COPD exacerbation, blood eosinophils had decreased significantly in those with increased bacterial load [14].

Pneumonia is a common complication of COPD. Advancing age, current smoking, severity of airway obstruction, low body weight, prior pneumonia, recent exacerbations, use of high-dose ICS [15], especially fluticasone [16], are well recognised and important risk factors [17–21]. The additional predictive value of blood eosinophils, whether high or low, is uncertain. While the relationship between blood eosinophils and response to therapy in COPD is changing clinical practice, it is less clear how the relationship of eosinophils to pneumonia risk might change our approach. For the moment, it appears prudent to target ICS therapy to patients with COPD who have higher blood eosinophil counts since they derive the most benefit in order to balance the increase in risk of pneumonia which appears to be present at all levels of blood eosinophils [22].

Conflict of interest: None declared.

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