# Predicting Pneumonia in Chronic Obstructive Pulmonary Disease

## Have We Unraveled the Network of Risks?

Inhaled corticosteroids (ICS) reduce exacerbation rates in patients with chronic obstructive pulmonary disease (COPD) but may also cause adverse effects, including pneumonia (1, 2). Blood eosinophil counts can predict the clinical response to ICS and <100 eosinophils/μl is associated with a low probability of a reduction in exacerbation rates (3). Based in part on these data, the use of ICS in clinical practice is becoming more personalized, weighing the possibility of benefit (using exacerbation history and blood eosinophil counts) against the risk of adverse events, including pneumonia (4, 5).

In this issue of the *Journal*, Martinez-Garcia and colleagues (pp. 1078–1085) report the relationships between pneumonia risk and ICS use, blood eosinophil counts, and chronic bacterial infection (CBI) of the airways (assessed using sputum samples) from a cohort of 201 patients with COPD followed for a median of 84 months (6). Previous studies have shown that pneumonia risk factors in COPD include ICS use, older age, lower $FEV_1$, lower body mass index, and previous pneumonia (7–9). An important novel aspect of this study is that bacterial infection data is included in the analysis of pneumonia risk. Bacterial isolates were detected in 42.3% of patients on at least one occasion, whereas CBI was present in 22.4%.

Univariate analysis showed that older age, lower $FEV_1$, presence of bronchiectasis, exacerbation rates, and <100 eosinophils/μl were associated with CBI. These risk factors were also associated with pneumonia risk, as was CBI and ICS treatment. A multivariate Cox proportional hazard regression model showed that age, $FEV_1$, CBI, and <100 eosinophils/μl were all independently associated with pneumonia. Of note, ICS use itself was not associated with pneumonia in the overall population, although ICS further increased the risk of pneumonia in those with CBI and <100 eosinophils/μl.

Few studies of pneumonia in COPD have included blood eosinophil counts as a risk factor, mostly showing either a weak or no association (3, 10). Martinez-Garcia and colleagues also found that higher eosinophil thresholds (e.g., <150 or <300 cells/μl) were not associated with pneumonia risk, but very low eosinophil counts (<100 cells/μl) were associated with pneumonia, and this was the most important risk factor in the adjusted Cox regression model, ahead of age and $FEV_1$ (6). This is an observational study, in contrast to previous analyses of eosinophils and pneumonia risk that were based on data from randomized controlled trials (RCTs) (3, 10), and differences in study design or population characteristics may explain the varying results. Also, the way that pneumonia was defined varied, and even when chest radiographs are obtained for all exacerbations and independently adjudicated as to the presence of infiltrates, the differentiation of the two events can be challenging (8).

The Global Initiative for Chronic Obstructive Lung Disease strategy document recommends that ICS not be used in those with <100 eosinophils/μl because that predicts a low probability of treatment benefit (5). The findings of Martinez-Garcia and colleagues suggest that these patients also have the highest pneumonia risk (6). Confirmation of these findings from other cohorts is needed and, if validated, then <100 eosinophils/μl would be a biomarker of both reduced ICS effect and increased pneumonia risk.

ICS use increases pneumonia risk in RCTs (2, 7, 8), although this finding is not consistent across all studies. The risk appears ICS-dose dependent and is less commonly observed in less severe (using $FEV_1$ criteria) populations with fewer exacerbation or hospitalization events (11, 12). Here, ICS use was not an independent risk factor for pneumonia in the Cox regression model in the overall population. However, ICS did appear to increase pneumonia risk in patients with both CBI and <100 eosinophils/μl. Perhaps the inconsistent results from RCTs regarding ICS and pneumonia risk are related to variation between populations in the proportion of patients with CBI and/or <100 eosinophils/μl. These findings demonstrate complex interactions between pneumonia risk factors, further highlighted in the network analysis model. Although clinical characteristics (e.g., age and lower $FEV_1$) have been commonly recognized as risk factors for pneumonia (2), this study suggests we should also look more closely at blood eosinophil counts and the results of repeated sputum cultures.

Bacterial airway colonization in the stable state is associated with lower sputum eosinophil counts in patients with COPD (13). Furthermore, acute sepsis reduces blood eosinophil counts (14). These observations lend support to the concept that lower blood eosinophil counts are associated with bacterial colonization or pneumonia, as reported by Martinez-Garcia and colleagues (6). However, the mechanistic reasons for this inverse relationship (lower eosinophil counts: more bacteria) is unclear. Eosinophils have antibacterial activity but appear to lack activity against common pathogens found in patients with COPD (15). Perhaps there are other aspects of airway inflammation that account for the apparently increased susceptibility to bacterial infection in patients with COPD who have <100 eosinophils/μl.

Before concluding that we have unraveled the network of risk factors for pneumonia in COPD, several limitations of the study should be mentioned, some of which the authors have acknowledged. First, the sample size is relatively small and thus it is possible that other significant associations could have been missed, particularly in the eosinophil and CBI subgroups. Second, the population is highly selected, being almost all male, capable of repeatedly producing acceptable spontaneous sputum



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samples, and with a high prevalence of bronchiectasis–the latter proving to be a major predictor of CBI. These factors may limit the generalizability of the results and call for them to be validated. Lastly, the definition of CBI was not based on a single baseline assessment but on repeated sampling over time, which complicates its clinical utility as a risk prediction tool and may have confounded the observed relationship between CBI and pneumonia.

The results of this study are biologically plausible and logically appealing. The presence of low blood eosinophil counts and/or CBI appear to be risk factors that increase pneumonia risk and, therefore, influence the benefit–risk calculation for the use of ICS in COPD. That said, large-scale, routine, and repeated sputum collection and analysis poses logistic and implementation challenges, particularly in primary care. Unless this practical hurdle is overcome, it seems likely that decisions about ICS use will remain part science, part art. ■

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# Airway Occlusion Pressure Revisited

The use of airway occlusion pressure (P0.1) as a measure of respiratory drive was introduced by Whitelaw and colleagues 45 years ago based on two basic assumptions (1). First, in the absence of flow or volume change during the occlusion, pressure generated by the inspiratory muscles is transmitted directly (1:1 ratio) to the external airway. Second, if the occlusion is brief (i.e., 0.1 s), there is no time for behavioral responses to influence the pressure output of the inspiratory muscles. Hence, the change in airway pressure during a constant brief time reflects the rate of rise of inspiratory muscle pressure at the beginning of spontaneous inspiration, which has been shown to correlate well with the rate of rise of inspiratory muscle activity, at least in normal subjects.



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