The search for the "healthy" blood eosinophil count

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Characteristics other than allergy are associated with higher blood eosinophil counts in the general population and the healthy range in eosinophils might be lower than what we currently perceive as normal http://bit.ly/2WgSKEP

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Although traditionally associated with allergy and parasitic infections, eosinophils are pleiotropic cells. They function as modulators of innate and adaptive immunity and are implicated in the pathogenesis of several local and systemic inflammatory processes, tissue injury and tumour immunity [1]. In the respiratory tract, eosinophils are specifically associated with the development of allergic asthma and are recruited to the lungs by cytokines released by activated Th2 cells as part of the inflammatory response [2]. COPD is classically regarded as a Th1-mediated disease dominated by neutrophil cells; however, a subset of COPD shows evidence of eosinophilic airway inflammation [3]. In observational studies, high blood eosinophil counts are associated with higher risk of asthma and COPD exacerbations [4, 5], and both the Global Initiative for Asthma [6] and the Global Strategy for the Diagnosis, Management and Prevention of COPD [7] recognise the use of blood eosinophil counts to guide therapy in asthma and COPD.

Although mostly measured in blood, eosinophils are mainly tissue-dwelling cells [8]. In peripheral blood, they constitute less than 5% of all leukocytes [9]. The number of eosinophils in the circulation is influenced by bone marrow proliferation and the migration of cells from the blood stream to various extravascular tissues. In absolute counts, blood eosinophils are reported to range from 0.05–0.5×10^9 cells·L^{-1}, and eosinophilia is traditionally defined by a count equal to or above 0.5×10^9 cells·L^{-1} [10]. Eosinophilia indicates underlying disease which can be either due to clonal haematological disorders or reactive, cytokine-mediated conditions [11]; the latter account for most cases. However, eosinophilia is a relatively common finding in routine blood samples, having a frequency of 4% in a study of more than 350 000 individuals from the general population [12]. Recent data from the general population further suggests that the median blood eosinophil count is approximately 0.16×10^9 cells·L^{-1} [5, 12, 13], which is at the lower end of the reference interval. The blood eosinophil count in the general population seems to be non-normally distributed with a right-skewed distribution with the tail of the distribution going towards higher counts [5, 14]. Such an asymmetrical distribution suggests that there are factors within the sample population that drive the mean towards higher counts. This could be the prevalence of subclinical disease or other conditions associated with higher counts. An asymmetrical distribution could also imply differences related to subgroups within the population, *e.g.* sex and age.

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It is well established that levels of blood eosinophils can be higher in atopic individuals [9, 15], but higher blood eosinophil counts are neither closely linked nor solely present in atopic individuals. In an outpatient setting, no direct cause could be detected in more than one-third of individuals with mild blood eosinophilia [9], and in the general population, data on the characteristics correlated with higher eosinophil counts, besides allergy, are limited. Therefore, the article published in this issue of the *European Respiratory Journal* by Hartl *et al.* [16] is of considerable interest. This is a large study of the general population in which the authors aim to identify factors associated with high blood eosinophil counts and to estimate normal values in a healthy subpopulation using the Austrian LEAD cohort. Consistent with previous findings, Hartl *et al.* [16] find a right-skewed distribution of the blood eosinophil count with a mean of 0.128×10^9 cells·L^{-1}; again in the lower end of what is currently perceived as normal. As many as 75% of the individuals studied had an eosinophil count below 0.210×10^9 cells·L^{-1}. Factors associated with a blood count higher than 0.210×10^9 cells·L^{-1} were male sex, younger age, a positive skin prick test, current smoking, obesity, the metabolic syndrome and a diagnosis of either asthma or COPD. Furthermore, the study demonstrates that individuals with the highest blood eosinophil count were those with a positive skin prick test in combination with metabolic syndrome and current smoking. After excluding individuals with variables associated with higher eosinophil counts, the study found a median eosinophil count of 0.120×10^9 cells·L^{-1} in males and 0.100×10^9 cells·L^{-1} in females with 95th percentiles consistently lower than the upper normal range used in the clinic. Interestingly, in the adult healthy populations the values for the 95th percentiles were around 0.300×10^9 cells·L^{-1}, which is close to the cut-off associated with higher risk of exacerbations in studies of individuals with COPD [5, 17]. A cut-off of 0.300×10^9 cells·L^{-1} is also used to identify COPD patients that are most likely to benefit from treatment with inhalation corticosteroids and to identify patients with severe asthma that are eligible for targeted biological therapy [6, 7]. Some of these thresholds have been questioned as they lie well below the upper reference range of 0.5×10^9 cells·L^{-1} currently used in clinical practice. Although results from the study by Hartl *et al.* [16] do not provide evidence for correct cut-offs for guiding therapy in asthma and COPD, or for the appropriate threshold used to define eosinophilic inflammation in chronic airway disease, the study finds that counts above 0.300×10^9 cells·L^{-1} is less common among healthy adults and thus indirectly supports the cut-off used in chronic airway disease.

Still, there are several unanswered questions regarding how to interpret the blood eosinophil count in the general population and in patients with chronic airway disease. To what extent does the blood eosinophil count reflect tissue eosinophilia? Blood eosinophils provide no information on the extravasation of cells and the potential site of inflammation. Although the present study by Hartl *et al.* [16] offers some data on how to interpret the blood eosinophil count in a more nuanced way and suggests that factors such as age, sex, comorbidities and lifestyle should be given more attention, the study also highlights the need for a more profound understanding of the role of eosinophils in health and disease. Certainly, it is difficult to interpret a test result without information on normal values. These normal values should preferably be established in individuals that are well defined and representative of the general population; with a poorly described reference population, the reference range and limits become uncertain and difficult to interpret. Now, the study from Hartl *et al.* [16] suggests that we should revise our understanding of the "healthy" blood eosinophil range, and hopefully the quest for a deeper understanding of the role of eosinophils in chronic airway disease continues.

Conflict of interest: None declared.

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