

Letter to the Editor

High blood eosinophil counts predict sputum eosinophilia in patients with severe asthma

To the Editor:

In asthmatic patients sputum eosinophilia predicts steroid response¹ and identifies an inflammatory phenotype that responds to anti- T_H2 biologic agents, such as mepolizumab.² However, sputum induction is not without risk in patients with severe asthma nor is it always successful, and processing requires expertise and is time consuming. A recent study from the Severe Asthma Research Program analyzed same-day blood and sputum eosinophil counts, concluding that the former cannot be reliably used to predict the latter.³ Cutoffs to define sputum eosinophilia of 2% or greater and blood eosinophilia of 0.3×10^9 cells/L or greater were chosen. The upper limit of the normal range for sputum eosinophil counts in the healthy (nonasthmatic) population is 1.9% or less,⁴ and therefore 2% seems appropriate, especially where most patients are already treated with eosinophil-suppressing corticosteroids. For blood eosinophil counts, however, a higher cutoff of normality of greater than 0.45×10^9 cells/L is more commonly used, both in our hospital and in the literature, although this is by no means universal.⁵ Visual inspection of the graphic data provided in the article by Hastie et al³ suggests that this higher cutoff might have a higher

positive predictive value for sputum eosinophilia and potentially could be used to classify the airway inflammatory phenotype in a subgroup of patients with severe asthma and hence remove the requirement for sputum induction and processing in some patients.

We run a tertiary severe asthma service and routinely analyze sputum cell counts to help characterize the airway status of newly referred patients and to facilitate management decisions in returning patients. Blood is often collected on the same visit, and therefore we investigated whether in our cohort blood eosinophilia could predict sputum eosinophilia and whether a higher cutoff could increase the clinical utility of the test.

We collected data from our clinical database of patients attending the Manchester Severe Asthma Service between 2006 and 2013. All patients were receiving at least 1000 $\mu\text{g/d}$ inhaled beclomethasone or equivalent with or without 5 mg of oral prednisone and with or without intramuscular triamcinolone.

Sputum was collected either as a spontaneous sample or induced by using hypertonic saline and processed, as previously described.⁶ A venous blood sample was collected and analyzed during the same episode. For practical reasons, blood samples were sometimes collected up to 2 days on either side of the sputum visit.

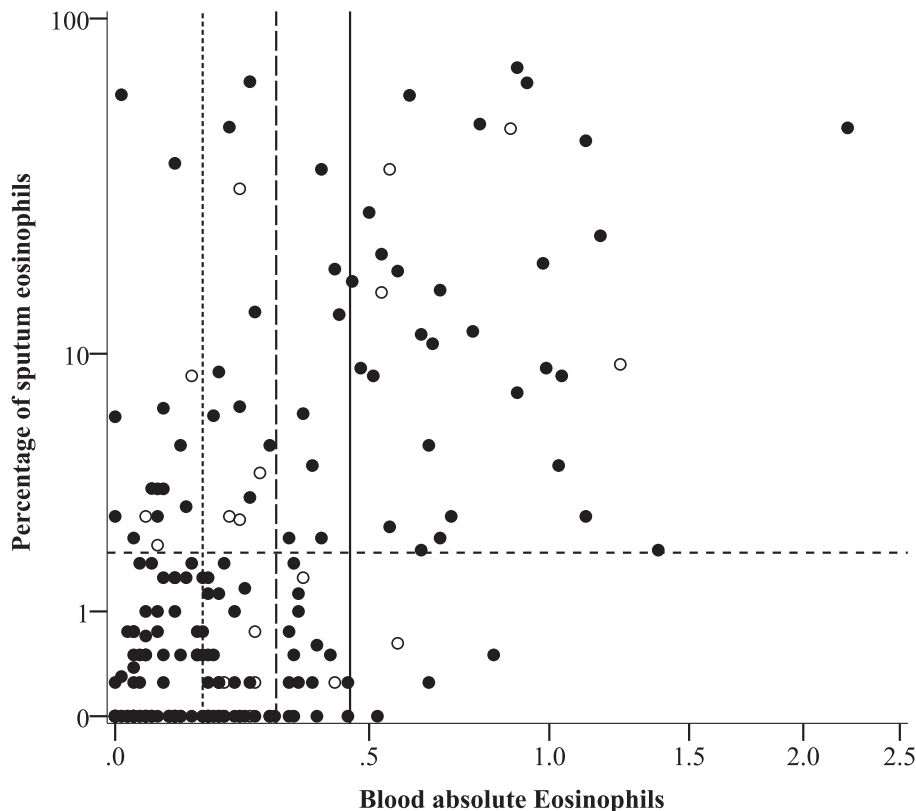


FIG 1. Scatter plot of blood eosinophils ($\times 10^9$ cells/L) against sputum eosinophils (as a percentage), with cutoffs shown for sputum eosinophilia of 2% or greater (dashed line) and blood eosinophil counts of 0.15×10^9 cells/L or greater (dotted line), 0.3×10^9 cells/L or greater (dashed line), and greater than 0.45×10^9 cells/L (solid line). Open circles represent samples from patients receiving moderate-dose steroids, and solid circles represent samples from those receiving high-dose steroids (≥ 10 mg/d prednisolone, 80 mg of intramuscular triamcinolone within the previous month, or ≥ 2000 $\mu\text{g/d}$ beclomethasone or equivalent).

TABLE I. Performance characteristics (percentages) for prediction of at least 2% sputum eosinophilia in patients with moderate and severe asthma by using blood eosinophil count cutoffs of 0.15, 0.3, and 0.45×10^9 cells/L

	Blood eosinophil cutoff ($\times 10^9$ cells/L)		
	≥ 0.15	≥ 0.30	> 0.45
Sensitivity	77.6	59.7	49.3
Specificity	53.3	84.4	97.0
Positive predictive value	45.2	65.6	89.2
Negative predictive value	82.8	80.9	79.4

Data presented are descriptive, with performance characteristics also reported for the ability of blood eosinophil counts of 0.15×10^9 cells/L or greater, 0.3×10^9 cells/L or greater, and greater than 0.45×10^9 cells/L to predict sputum eosinophilia of 2% or more. Data were analyzed with SPSS software (version 20; SPSS, Chicago, Ill).

Complete data sets were available from 163 patients providing samples on 202 sample days. Blood samples were collected on the same day as the sputum sample on all but 15 occasions.

Demographic details (at the index visits where patients provided multiple samples) were mean age of 46.6 years (SD, 12.2 years), 56% female sex, 63% receiving systemic corticosteroids, 9% receiving second-line systemic immunosuppressants, and mean inhaled beclomethasone dipropionate dose equivalent of 2293 μ g/d (SD, 1158 μ g/d).

Blood and sputum eosinophil counts correlated (Spearman correlation = 0.493, $P < .001$). Values for each of the 202 blood-sputum pairs are plotted in Fig 1, and a receiver operating characteristic curve with coordinates is presented in Fig E1 and Table E1 in this article's [Online Repository](#) at www.jacionline.org.

Changing the threshold from 0.3 to 0.45×10^9 cells/L improved the positive predictive value for sputum eosinophilia from 65.6% to 89.2% and the specificity from 84.4% to 97%. There was a marginal loss of sensitivity/negative predictive value (Table I). A blood eosinophil cutoff of 0.15×10^9 cells/L had a positive predictive value of less than 50%.

In our cohort of patients with severe asthma, the majority receiving very high doses of inhaled or systemic corticosteroids, a blood eosinophil count of greater than 0.45×10^9 cells/L can correctly predict sputum eosinophilia in 9 of 10 cases. We have included only patients with severe asthma in our study, and therefore we believe our results are important because these are the patients who will be considered for novel T_H2 -targeting biologic agents.

The search for biomarkers of airway inflammation has been made more urgent by the advance of novel therapies that act specifically by targeting this inflammation. To this end, recent studies that aimed to investigate the potential benefit of mepolizumab in patients with eosinophilic asthma identified patients by using blood eosinophil cutoffs as low as 0.15×10^9 cells/L.^{7,8} As demonstrated both here and in the article from the Severe Asthma Research Program group,⁴ this cutoff would include many patients who in fact do not have contemporaneous sputum eosinophilia (more than half in this study) and therefore potentially would not be in the group of patients who could benefit from treatment. The consequence of this in a trial of a biologic agent is that the magnitude of benefit could be underestimated or even missed,

as happened previously when mepolizumab was trialed in unselected patients.⁹ The other potential consequence of using blood eosinophil counts as a surrogate for sputum is the very high risk of false-negative results; from our data, approximately 1 in 5 patients without blood eosinophilia had airway eosinophilia and hence could be missed by using this selection method. Choosing a simple and universally available biomarker (blood eosinophil counts) is attractive, but in this case does not lead to a personalized medicine approach.

In conclusion, we have shown that using a cutoff of 0.45×10^9 cells/L for blood eosinophilia can usefully predict airway eosinophilia in patients with severe asthma receiving high levels of treatment. However, we agree with Hastie et al³ that lower cutoffs are not useful. We would propose that study design for novel antieosinophil therapies could use this higher cutoff to investigate the effect of these therapies but that patients should also be included with airway but not blood eosinophilia, as previously described.⁸ In the meantime, more work needs to be done to develop useful minimally invasive and accurate surrogate markers for airway inflammation, including composite biomarkers comprising, for example, exhaled nitric oxide and serum periostin levels together with blood eosinophil counts.

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Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2014.09.034>

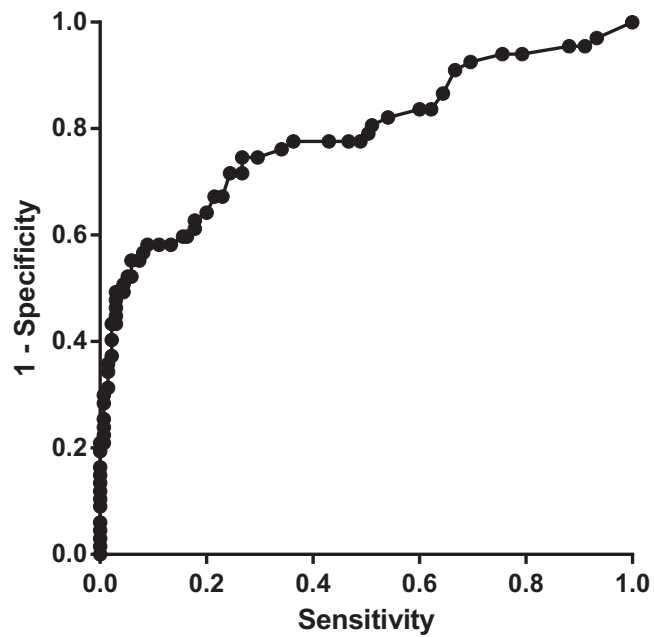


FIG E1. Receiver operating characteristic curve for use of blood eosinophil counts to predict sputum eosinophil values of at least 2%. The area under the receiver operating characteristic curve was 0.79 (95% CI, 0.72-0.86; $P < .001$).

TABLE E1. Coordinates of the receiver operating characteristics curve in Fig E1 showing sensitivity and 1 – specificity for blood eosinophil counts to predict sputum eosinophils of at least 2% (eg, blood eosinophil counts of at least 0.46×10^9 cells/L has a sensitivity of 49.3% and a specificity of 97.0% for sputum eosinophilia)

Blood eosinophil cutoff ($\times 10^9$ cells/L)	Sensitivity	1 – Specificity
0.00	1.000	1.000
0.01	0.970	0.933
0.02	0.955	0.911
0.03	0.955	0.881
0.04	0.940	0.793
0.05	0.940	0.756
0.06	0.925	0.696
0.07	0.910	0.667
0.08	0.866	0.644
0.09	0.836	0.622
0.10	0.836	0.600
0.11	0.821	0.541
0.12	0.806	0.511
0.13	0.791	0.504
0.14	0.776	0.489
0.15	0.776	0.467
0.16	0.776	0.430
0.17	0.776	0.363
0.18	0.761	0.341
0.19	0.746	0.296
0.20	0.746	0.267
0.21	0.716	0.267
0.22	0.716	0.244
0.23	0.672	0.230
0.24	0.672	0.215
0.25	0.642	0.200
0.26	0.627	0.178
0.27	0.612	0.178
0.29	0.597	0.163
0.31	0.597	0.156
0.33	0.582	0.133
0.34	0.582	0.111
0.35	0.582	0.089
0.36	0.567	0.081
0.38	0.552	0.074
0.39	0.552	0.059
0.40	0.522	0.059
0.42	0.522	0.052
0.43	0.507	0.044
0.44	0.493	0.044
0.46	0.493	0.030
0.47	0.478	0.030
0.49	0.463	0.030
0.51	0.448	0.030
0.52	0.433	0.030
0.53	0.433	0.022
0.54	0.403	0.022
0.56	0.373	0.022
0.59	0.358	0.015
0.62	0.343	0.015
0.64	0.313	0.015
0.66	0.299	0.007
0.67	0.284	0.007
0.70	0.254	0.007
0.74	0.239	0.007
0.78	0.224	0.007

(Continued)

TABLE E1. (Continued)

Blood eosinophil cutoff ($\times 10^9$ cells/L)	Sensitivity	1 – Specificity
0.81	0.209	0.007
0.86	0.209	0.000
0.89	0.194	0.000
0.92	0.164	0.000
0.96	0.149	0.000
0.99	0.134	0.000
1.01	0.119	0.000
1.04	0.104	0.000
1.08	0.090	0.000
1.15	0.060	0.000
1.21	0.045	0.000
1.31	0.030	0.000
1.80	0.015	0.000
3.22	0.000	0.000