



1 **Blood eosinophils for prediction of exacerbation in preschool children with recurrent wheezing**

2 Online Data Repository

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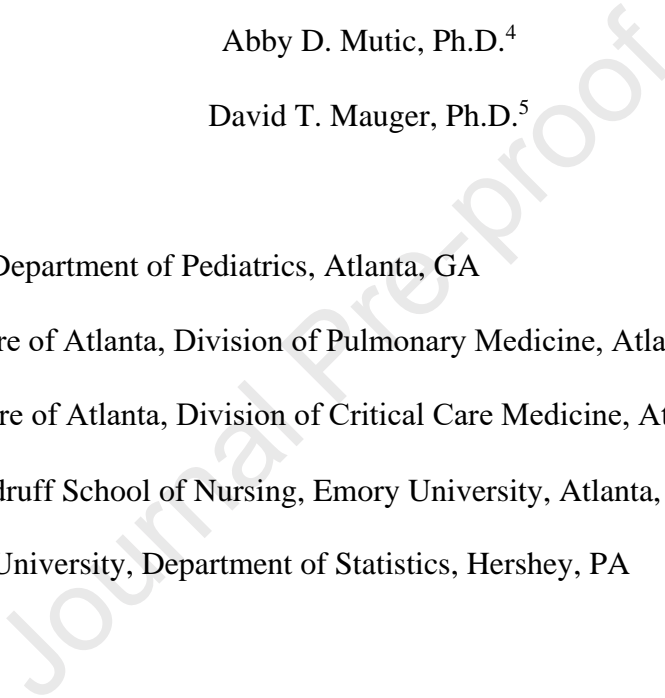
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16 **Table E1.** Features of the included studies.

Study feature	AIMS	MIST	APRIL
Years conducted	2004	2008-2010	2011-2015
Participants enrolled	238	278	607
Age of participants	12-59 months	12-53 months	12-71 months
Additional requirements in the past year	≥2 clinically significant wheezing exacerbations ¹	≥1 clinically significant wheezing exacerbation ¹ with a positive modified Asthma Predictive Index ²	≥2 clinically significant wheezing exacerbations ¹
Study design	Parallel arm	Parallel arm	Parallel arm
Run-in period	2 weeks	2 weeks	2-4 weeks
Run-in medication	No medication	Placebo	No medication
Treatment arm duration	52 weeks	52 weeks	52-78 weeks
Treatment arm interventions	Intermittent ICS, intermittent LTRA, versus placebo during respiratory illnesses	Daily ICS versus intermittent ICS during respiratory illnesses	Azithromycin versus placebo during respiratory illnesses

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18 ICS=inhaled corticosteroid, LTRA=leukotriene receptor antagonist

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20 ¹ Defined as a wheezing episode necessitating an urgent care visit, hospitalization, or systemic corticosteroids

21 ² Defined as frequent wheezing (at least 4 episodes in the previous year) and either 1 major risk factor (parental history of asthma, personal history of atopic dermatitis, or aeroallergen sensitization) or 2 of 3 minor risk factors (peripheral blood eosinophilia ≥4%, wheezing without colds, or allergic sensitization to foods)

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24 **Table E2.** Associations between combined blood eosinophil and sensitization predictors and
 25 exacerbation occurrence (primary outcome) with further adjustment for an exacerbation treated
 26 with oral corticosteroids in the previous year.

Model	Adjusted odds ratio ¹ (95% CI)	Change in odds ratio
Blood eosinophils ≥ 150 cells/microliter, plus:	1.33 (0.98, 1.80)	--
Any food or aeroallergen sensitization	1.54 (1.18, 2.02)	13.6%
Any aeroallergen sensitization	1.56 (1.19, 2.05)	14.7%
Any food sensitization	1.60 (1.21, 2.11)	16.9%
Multiple aeroallergen sensitization	1.81 (1.34, 2.44)	26.5%
Multiple food sensitization	1.81 (1.29, 2.54)	26.5%
Food and aeroallergen sensitization	1.71 (1.27, 2.32)	22.2%
Blood eosinophils ≥ 200 cells/microliter, plus:	1.50 (1.14, 1.97)	--
Any food or aeroallergen sensitization	1.54 (1.18, 2.02)	2.6%
Any aeroallergen sensitization	1.57 (1.19, 2.07)	4.5%
Any food sensitization	1.66 (1.25, 2.21)	9.6%
Multiple aeroallergen sensitization	1.80 (1.33, 2.45)	16.7%
Multiple food sensitization	1.81 (1.28, 2.56)	17.1%
Food and aeroallergen sensitization	1.78 (1.31, 2.43)	15.7%
Blood eosinophils ≥ 250 cells/microliter, plus:	1.39 (1.07, 1.81)	--
Any food or aeroallergen sensitization	1.55 (1.17, 2.04)	10.3%
Any aeroallergen sensitization	1.59 (1.19, 2.12)	12.6%
Any food sensitization	1.86 (1.38, 2.52)	25.3%
Multiple aeroallergen sensitization	1.78 (1.29, 2.46)	21.9%
Multiple food sensitization	1.99 (1.38, 2.86)	30.2%
Food and aeroallergen sensitization	2.02 (1.47, 2.79)	31.2%
Blood eosinophils ≥ 300 cells/microliter, plus:	1.48 (1.13, 1.93)	--
Any food or aeroallergen sensitization	1.56 (1.17, 2.08)	5.1%
Any aeroallergen sensitization	1.62 (1.21, 2.17)	8.6%
Any food sensitization	1.93 (1.41, 2.64)	23.3%
Multiple aeroallergen sensitization	1.81 (1.30, 2.51)	18.2%
Multiple food sensitization	2.21 (1.51, 3.22)	33.0%
Food and aeroallergen sensitization	2.09 (1.50, 2.91)	29.2%
Blood eosinophils ≥ 350 cells/microliter, plus:	1.45 (1.11, 1.90)	--
Any food or aeroallergen sensitization	1.71 (1.27, 2.29)	15.2%
Any aeroallergen sensitization	1.76 (1.30, 2.39)	17.6%
Any food sensitization	1.98 (1.43, 2.73)	26.8%

Multiple aeroallergen sensitization	1.98 (1.40, 2.78)	26.8%
Multiple food sensitization	2.14 (1.44, 3.18)	32.2%
Food and aeroallergen sensitization	2.12 (1.51, 2.98)	31.6%

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28 CI = confidence interval

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30 ¹ Adjusted for daily inhaled corticosteroid treatment, intermittent inhaled corticosteroid
31 treatment, sex, age group (<3 years versus ≥3 years), tobacco smoke exposure, and an
32 exacerbation treated with oral corticosteroids in the previous year

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35 **Table E3.** Receiver operating curve analyses depicting the sensitivity and specificity of blood
 36 eosinophil cut points plus sensitization variables for the prediction of exacerbation occurrence.

Model	Sensitivity	Specificity
Blood eosinophils ≥ 150 cells/microliter, plus:		
Any food or aeroallergen sensitization	0.837	0.193
Any aeroallergen sensitization	0.849	0.144
Any food sensitization	0.890	0.182
Multiple aeroallergen sensitization	0.896	0.095
Multiple food sensitization	0.920	0.167
Food and aeroallergen sensitization	0.925	0.081
Blood eosinophils ≥ 200 cells/microliter, plus:		
Any food or aeroallergen sensitization	0.755	0.296
Any aeroallergen sensitization	0.779	0.239
Any food sensitization	0.825	0.273
Multiple aeroallergen sensitization	0.836	0.160
Multiple food sensitization	0.874	0.211
Food and aeroallergen sensitization	0.883	0.155
Blood eosinophils ≥ 250 cells/microliter, plus:		
Any food or aeroallergen sensitization	0.652	0.408
Any aeroallergen sensitization	0.683	0.344
Any food sensitization	0.747	0.403
Multiple aeroallergen sensitization	0.731	0.260
Multiple food sensitization	0.805	0.325
Food and aeroallergen sensitization	0.833	0.264
Blood eosinophils ≥ 300 cells/microliter, plus:		
Any food or aeroallergen sensitization	0.579	0.484
Any aeroallergen sensitization	0.633	0.404
Any food sensitization	0.675	0.485
Multiple aeroallergen sensitization	0.687	0.325
Multiple food sensitization	0.770	0.421
Food and aeroallergen sensitization	0.792	0.324
Blood eosinophils ≥ 350 cells/microliter, plus:		
Any food or aeroallergen sensitization	0.532	0.568
Any aeroallergen sensitization	0.578	0.502
Any food sensitization	0.630	0.545
Multiple aeroallergen sensitization	0.634	0.426
Multiple food sensitization	0.690	0.482
Food and aeroallergen sensitization	0.733	0.405

38 **Table E4.** Caregiver reported asthma control scores (mean \pm SEM) and associations (kendall's tau-b) with changes in offline exhaled
 39 nitric oxide concentration after treatment initiation with intermittent or maintenance inhaled corticosteroid in the MIST trial.

Predictor variable	Intermittent inhaled corticosteroid		Maintenance inhaled corticosteroid	
	Asthma control score ¹	Correlation with change in exhaled nitric oxide ²	Asthma control score ¹	Correlation with change in exhaled nitric oxide ²
Blood eosinophils ≥ 150 cells/microliter	0.28 \pm 0.05	-0.117	0.17 \pm 0.33	-0.388*
Plus any aeroallergen sensitization	0.21 \pm 0.04	-0.121	0.17 \pm 0.05	-0.457*
Blood eosinophils ≥ 200 cells/microliter	0.28 \pm 0.05	-0.201	0.18 \pm 0.04	-0.354*
Plus any aeroallergen sensitization	0.22 \pm 0.05	-0.150	0.19 \pm 0.05	-0.419*
Blood eosinophils ≥ 250 cells/microliter	0.22 \pm 0.04	-0.302	0.18 \pm 0.04	-0.407*
Plus any aeroallergen sensitization	0.18 \pm 0.04	-0.232	0.16 \pm 0.05	-0.450*
Blood eosinophils ≥ 300 cells/microliter	0.22 \pm 0.19	-0.272	0.19 \pm 0.05	-0.352*
Plus any aeroallergen sensitization	0.19 \pm 0.04	-0.189	0.17 \pm 0.05	-0.484*
Blood eosinophils ≥ 350 cells/microliter	0.24 \pm 0.05	-0.234	0.21 \pm 0.04	-0.419
Plus any aeroallergen sensitization	0.19 \pm 0.04	-0.189	0.17 \pm 0.05	-0.545*

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41 *p < 0.05 for correlation coefficient

42 ¹ Obtained after treatment initiation, no baseline available. Lower scores reflect better asthma control.

43 ² Change in exhaled nitric oxide between baseline and after treatment initiation

44 **Figure Legends**

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46 **Figure E1.** word count = 31

47 (A) Distribution of blood eosinophil counts in all study participants (horizontal line at median)
48 and (B) association between blood eosinophil counts and blood eosinophil percentages.
49 CI=confidence interval (shown as dashed line).

50

51 **Figure E2.** word count = 34

52 (A) Distribution of blood eosinophil counts by ethnicity (horizontal line at median), (B) race, (C)
53 inhaled corticosteroid (ICS) treatment prior to study enrollment and (D) leukotriene receptor
54 antagonist (LTRA) treatment prior to study enrollment.

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56 **Figure E3.** word count = 40

57 (A) Associations between blood eosinophil counts and total serum IgE concentrations, (B) the
58 percentage of positive aeroallergens (of 8 aeroallergens), and (C) the percentage of total positive
59 allergens (of 11 total aeroallergens and foods). CI=confidence interval (shown as dashed line).

60

61 **Figure E4.** word count = 46

62 Receiver operating curves depicting the sensitivity and specificity of blood eosinophil counts for
63 prediction of exacerbation occurrence in (A) all participants, (C) participants with sensitization
64 to any food or aeroallergen, (C) participants with sensitization to food, and (D) participants with
65 sensitization to any aeroallergen. CI=confidence interval

66

67 **Figure E5.** word count = 37

68 (A) Annualized exacerbation rate (mean \pm standard error of the mean) and (B) percentage of
69 children hospitalized for an exacerbation, by blood eosinophil (eos) grouping and food
70 sensitization variables. *p < 0.05 vs. cut point not met.

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