



Short communication

Prevalence of eosinophilia in hospitalized patients with asthma exacerbation



Kohei Hasegawa ^{a,*}, Samantha J. Stoll ^{a,b}, Jason Ahn ^{a,b}, Jane C. Bittner ^a,
Carlos A. Camargo Jr. ^a

^a Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

^b Department of Emergency Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:

Received 12 May 2015

Received in revised form

2 July 2015

Accepted 15 July 2015

Available online 17 July 2015

Keywords:

Acute asthma

Hospitalization

Prevalence

Eosinophilia

Asthma phenotypes

Biologic therapies

ABSTRACT

Background: Recent studies have identified the “eosinophilic phenotype” of asthma that is characterized by persistent eosinophilic inflammation and frequent exacerbations. However, the prevalence of eosinophilia in patients hospitalized for asthma exacerbation is not known.

Methods: We performed a pilot study in two sites participating in a multicenter chart review project of children and adults hospitalized for asthma exacerbation during 2012–2013. The pilot study investigated the prevalence of blood eosinophilia in this patient population. Eosinophilia was defined as a count of ≥ 300 cells/microliter at some time during the hospitalization.

Results: Among 80 patients hospitalized for asthma exacerbation, 47 (59%) underwent CBC with differential and had data on blood eosinophil count. These 47 comprised the analytic cohort. The median patient age was 32 years (IQR, 24–44 years), and 51% were female. Overall, 40% (95% CI, 26%–56%) of patients had eosinophilia. Although statistical power was limited, there were no statistically significant differences in patient characteristics or hospital course between patients with eosinophilia and those without (all $P > 0.05$).

Conclusion: Our pilot study showed that 40% of patients hospitalized for asthma exacerbation had eosinophilia. The clinical meaning of this biomarker in the emergency department/inpatient setting requires further study in much larger samples with long-term follow-up; such studies appear feasible.

© 2015 Elsevier Ltd. All rights reserved.

Asthma remains an important public health problem in the United States. Asthma prevalence is at historically high levels, affecting 26 million in 2011 [1]. Despite the availability of many treatments, approximately 10% of patients have severe disease that is associated with substantial morbidity and economic effects [2]. The clinical syndrome of severe chronic asthma is increasingly recognized as comprised of various phenotypes [3]. For example, individuals who develop asthma during early childhood differ in many ways from those who develop it during middle-age. Several studies have identified the “eosinophilic phenotype” that is characterized by persistent eosinophilic inflammation and frequent exacerbations [4–7]. Moreover, recent clinical trials with

monoclonal antibodies against interleukin-5 and interleukin-4 receptor have demonstrated decreases in the rate of asthma exacerbations and the dose of systemic corticosteroids required in patients with blood eosinophilia [8–11]. These data collectively support blood eosinophilia as a way to identify patients with severe eosinophilic asthma who might benefit from a targeted therapy [12]. Despite the clinical and research importance, to the best of our knowledge, no studies have examined the prevalence of eosinophilia in patients hospitalized for asthma exacerbation. In this context, we sought to determine the prevalence of patients with eosinophilia, and to describe their clinical characteristics by using the data of a well-characterized cohort of patients hospitalized with asthma exacerbation.

To address the knowledge gap, we added a pilot study to our multicenter chart review project – the 37th Multicenter Airway Research Collaboration (MARC-37) Study. The study design, setting, participants, and measured variables have been reported previously [13,14]. Briefly, we used a primary discharge diagnosis of

Abbreviations: CI, confidence interval; IQR, interquartile range; MARC, Multicenter Airway Research Collaboration.

* Corresponding author. Department of Emergency Medicine, Massachusetts General Hospital, 326 Cambridge Street, Suite 410, Boston, MA 02114, USA.

E-mail address: khasegawa1@partners.org (K. Hasegawa).

<http://dx.doi.org/10.1016/j.rmed.2015.07.011>

0954-6111/© 2015 Elsevier Ltd. All rights reserved.

Table 1

Characteristics of patients hospitalized with asthma exacerbation According to blood eosinophilia status.

	Eosinophilia (≥ 300 cells/mcl)	No eosinophilia	P value
Patient characteristics	n = 19	n = 28	
Demographics			
Age (year), median (IQR)	37 (25–44)	32 (24–43)	0.20
Female sex	10 (52)	14 (50)	0.86
Race/ethnicity			0.17
Non-hispanic white	5 (26)	2 (7)	
Non-hispanic black	6 (32)	11 (39)	
Hispanic ethnicity	7 (37)	8 (29)	
Others/missing	1 (5)	7 (25)	
Health insurance			0.43
Private	5 (26)	5 (18)	
Public	13 (68)	23 (82)	
No insurance	1 (5)	0 (0)	
Estimated median household income (\$), median (IQR)	47,073 (40,713–73,542)	41,150 (38,575–52,878)	0.11
Having primary care physician	15 (79)	26 (93)	0.30
Chronic asthma factors			
Current smoker	5 (26)	7 (25)	0.92
Hospitalization for asthma in past 12 months	9 (47)	20 (71)	0.10
Chronic asthma management			
Current asthma medications			
Chronic use of oral corticosteroids	1 (5)	1 (4)	0.78
Current use of ICS	12 (63)	24 (86)	0.09
Current use of ICS-LABA	6 (32)	16 (57)	0.12
Current use of leukotriene modifiers	8 (42)	9 (32)	0.49
Seen by asthma specialist in past 12 months	3 (16)	5 (18)	0.92
Presentation and ED/clinic course			
Vital signs			
Initial respiratory rate (breaths/min), median (IQR)	26 (20–32)	24 (20–34)	0.56
Initial oxygen saturation (%), median (IQR)	94 (90–98)	95 (90–98)	0.88
Initial PEF (L/min) ^a , median (IQR)	250 (150–300)	180 (105–273)	0.46
Blood neutrophil count (cells/microliter)	10,257 (8469–11,243)	9107 (5952–11,945)	0.93
Concomitant medical disorders ^b	6 (32)	9 (32)	0.83
Inpatient course			
Initial admission location			0.99
ED observation unit	6 (32)	8 (29)	
Hospital ward	9 (47)	14 (50)	
ICU	4 (21)	6 (21)	
Acute asthma treatment			
Non-invasive positive pressure ventilation	1 (5)	3 (11)	0.64
Intubation	3 (16)	1 (4)	0.29
Hospital length-of-stay (d), median (IQR)	2 (0–4)	3 (1–4)	0.26
Disposition			0.99
Sent home	19 (100)	27 (96)	
Died in the hospital	0 (0)	1 (4)	

IQR, interquartile range; ED, emergency department; ICS, inhaled corticosteroids; LABA, long-acting β -agonist; PEF, peak expiratory flow; ICU, intensive care unit.

Data were presented as % unless otherwise indicated.

^a Analyzed for 13 patients with initial PEF available.^b Defined by pneumonia, congestive heart failure, pneumothorax, arrhythmia, and others.

asthma (ICD-9-CM code, 493) to identify all hospitalizations made by children and adults with history of physician-diagnosed asthma in 2012–2013. After completing training (lecture, practice charts, and certification), onsite chart abstractors reviewed 40 randomly-selected charts. Using a standardized form, investigators abstracted data, including patients' demographics, past asthma history and medications, presentation, and asthma management in the hospital. In two of the participating hospitals (Brigham and Women's Hospital and Massachusetts General Hospital), we performed an ancillary (pilot) study to collect information on blood eosinophil count during the in-hospital course (i.e., emergency department/clinic and inpatient setting). All patients were managed at the discretion of the treating physician. The institutional review board of participating hospitals approved the study.

The primary outcome was the prevalence of eosinophilia. Based on the eligibility criterion used in prior trials [8–11], eosinophilia was defined as an eosinophil count ≥ 300 cells/microliter in peripheral blood at some time during the hospitalization. We compared patient demographic characteristics, asthma history, and clinical course between patients with eosinophilia and those

without, by using χ^2 , Fisher exact, or Wilcoxon-Mann-Whitney tests as appropriate. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC). All tests were two-tailed, and $P < 0.05$ was regarded as statistically significant.

Among 80 patients hospitalized for asthma exacerbation, 47 (59%) had data on blood eosinophil count and were included in this analysis. The analytic ($n = 47$) and non-analytic ($n = 33$) cohort differed by age (median, 32 vs 11 years, respectively; $P < 0.001$). Age-adjusted comparison of other factors suggested the groups were mostly similar ($P > 0.05$; Supplemental Table 1); but the analytic cohort was more likely to have markers of severe chronic asthma (e.g., hospitalization for asthma in the previous year) and markers of severe acute asthma (e.g., a longer hospital length-of-stay).

Of the 47 patients in the analytic cohort, the median age was 32 years (IQR, 24–44 years), and 51% were female. Additionally, 4% of patients had been on maintenance treatment of oral corticosteroids prior to their hospitalization. Overall, 40% (95% CI, 26%–56%) of patients had blood eosinophilia. Although statistical power was limited, there were no statistically significant differences in patient

characteristics, or hospital course between patients with eosinophilia and those without (all $P > 0.05$; Table 1). The use of an alternative blood eosinophil cut-off level (≥ 150 cells/microliter) demonstrated that 64% of patients ($n = 30$) had an elevated eosinophil count (i.e., 36% had a blood eosinophil level of < 150 cells/microliter).

This pilot study of patients hospitalized for asthma exacerbation demonstrated that 40% of patients had blood eosinophilia. To the best of our knowledge, this is the first study to investigate the prevalence of blood eosinophilia in hospitalized patients. This study population contributes to a substantial public health burden – 372,000 asthma-related hospitalizations with an estimated direct cost of more than \$2 billion annually [15]; therefore, our findings are relevant to hundreds of thousands of high-risk and costly patients with asthma. Additionally, these patients are at higher risk of future exacerbations [16], and hence are the ones for which targeted interventions are most urgently warranted.

Because of the population and setting of this study, our findings might not be fully generalizable to those in the community or ambulatory settings. The 40% estimate is helpful, however, because the previous community-based studies of chronic severe asthma that identified the eosinophilic phenotype did not report the prevalence of blood eosinophilia [4–7]. Our findings should facilitate further investigation of patients with severe eosinophilic asthma who might benefit from targeted therapies.

Our study has several potential limitations. First, approximately 40% of patients did not have data on blood eosinophil count, and exclusion of these patients may have introduced bias. The higher proportion of patients with more-severe chronic and acute asthma in the analytic cohort suggests that our study population was sicker than overall patients hospitalized for asthma exacerbation. However, it is precisely this population for which better identifications and prevention strategies are warranted. Second, the data relied on chart review, and therefore, measurement error is possible. However, we used a previously-applied data collection system with uniform definitions and rigorous training, which achieved a high inter-rater agreement in our previous study [17]. Finally, we found no statistically significant differences in patient characteristics between groups. We believe, however, that this is likely due to the small sample size.

In sum, our pilot study showed that a surprisingly high percentage (40%) of patients hospitalized for asthma exacerbation had blood eosinophilia (defined as ≥ 300 cells/microliter). The clinical meaning of this biomarker in the emergency department/inpatient setting requires further investigation in much larger samples with a long-term follow-up; such studies appear feasible. Better identification of acutely ill patients at increased risk of future asthma exacerbations will facilitate research into new prevention strategies for this high-risk and costly patient population.

Funding

The study was supported, in part, by Novartis Pharmaceuticals Corporation to Massachusetts General Hospital (PI: Camargo). The sponsor had no role in the conduct of the study, or collection,

management, analysis or interpretation of the data, nor preparation, review, or approval of the manuscript.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2015.07.011>.

References

- [1] Trends in Asthma Morbidity and Mortality, American Lung Association, 2012 [Cited 2015 July 1] Available from: <http://www.lung.org/finding-cures/our-research/epidemiology-and-statistics-rpts.html>.
- [2] E.D. Bateman, H.A. Boushey, J. Bousquet, W.W. Busse, T.J. Clark, R.A. Pauwels, et al., Can guideline-defined asthma control be achieved? The gaining optimal asthma control study, *Am. J. Respir. Crit. Care Med.* 170 (2004) 836–844.
- [3] S.E. Wenzel, Asthma phenotypes: the evolution from clinical to molecular approaches, *Nat. Med.* 18 (2012) 716–725.
- [4] W. Wu, E. Bleeker, W. Moore, W.W. Busse, M. Castro, K.F. Chung, et al., Un-supervised phenotyping of severe asthma research program participants using expanded lung data, *J. Allergy Clin. Immunol.* 133 (2014) 1280–1288.
- [5] C. Miranda, A. Busacker, S. Balzar, J. Trudeau, S.E. Wenzel, Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation, *J. Allergy Clin. Immunol.* 113 (2004) 101–108.
- [6] M. Amelink, J.C. de Groot, S.B. de Nijs, R. Lutter, A.H. Zwinderman, P.J. Sterk, et al., Severe adult-onset asthma: a distinct phenotype, *J. Allergy Clin. Immunol.* 132 (2013) 336–341.
- [7] P. Haldar, I.D. Pavord, D.E. Shaw, M.A. Berry, M. Thomas, C.E. Brightling, et al., Cluster analysis and clinical asthma phenotypes, *Am. J. Respir. Crit. Care Med.* 178 (2008) 218–224.
- [8] H.G. Ortega, M.C. Liu, I.D. Pavord, G.G. Brusselle, J.M. FitzGerald, A. Chetta, et al., Mepolizumab treatment in patients with severe eosinophilic asthma, *N. Engl. J. Med.* 371 (2014) 1198–1207.
- [9] E.H. Bel, S.E. Wenzel, P.J. Thompson, C.M. Prazma, O.N. Keene, S.W. Yancey, et al., Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma, *N. Engl. J. Med.* 371 (2014) 1189–1197.
- [10] I.D. Pavord, S. Korn, P. Howarth, E.R. Bleeker, R. Buhl, O.N. Keene, et al., Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial, *Lancet* 380 (2012) 651–659.
- [11] S. Wenzel, L. Ford, D. Pearlman, S. Spector, L. Sher, F. Skobieranda, et al., Dupilumab in persistent asthma with elevated eosinophil levels, *N. Engl. J. Med.* 368 (2013) 2455–2466.
- [12] P. Nair, What is an “eosinophilic phenotype” of asthma? *J. Allergy Clin. Immunol.* 132 (2013) 81–83.
- [13] K. Hasegawa, J.C. Bittner, S.A. Nonas, S.J. Stoll, T. Watase, S. Gabriel, et al., Children and adults with frequent hospitalizations for asthma exacerbation, 2012–2013: a multicenter observational study, *J. Allergy Clin. Immunol. In. Pract.* (2015) [epub ahead of print].
- [14] K. Hasegawa, J. Ahn, M.A. Brown, V.G. Press, S. Gabriel, V. Herrera, et al., Underutilization of guideline-recommended chronic asthma management in children hospitalized to the intensive care unit: a multicenter observational study, *Ann. Allergy Asthma Immunol.* 115 (2015) 10–16.
- [15] HCUPnet. U.S. Department of Health and Human Services. Agency For Healthcare Research and Quality. [Cited 2015 July 31]. Available from: <http://hcupnet.ahrq.gov/>.
- [16] M. Schatz, L.M. Meckley, M. Kim, B.T. Stockwell, M. Castro, Asthma exacerbation rates in adults are unchanged over a 5-year period despite high-intensity therapy, *J. Allergy Clin. Immunol. Pract.* 2 (2014), 570–574 e1.
- [17] K. Hasegawa, T. Chiba, Y. Hagiwara, H. Watase, Y. Tsugawa, D.F. Brown, et al., Quality of care for acute asthma in emergency departments in Japan: a multicenter observational study, *J. Allergy Clin. Immunol. Pract.* 1 (2013) 509–515.

Supplemental Material

Prevalence of Eosinophilia in Hospitalized Patients with Asthma Exacerbation

Kohei Hasegawa, MD, MPH; Samantha J. Stoll, MD, MPH; Jason Ahn, MD, MPA; Jane C. Bittner, MPH; and Carlos A. Camargo, Jr., MD, DrPH

Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA; and Department of Emergency Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Supplemental Table 1. Age-standardized Patient Characteristics in the Analytic and non-Analytic Cohort

Patient characteristics	Analytic cohort n=47	Non-analytic cohort n=33	P value
Demographics			
Female sex	46	47	0.99
Race/ethnicity			0.99
Non-Hispanic white	16	17	
Non-Hispanic black	36	20	
Hispanic ethnicity	31	39	
Others	8	6	
Health insurance			0.29
Private	20	29	
Public	73	66	
No insurance	0	4	
Estimated median household income (\$), mean (SD)	51,031 (14,839)	56,956 (13,351)	0.31
Having primary care physician	90	80	0.22
Chronic asthma factors			
Current smoker	22	25	0.79
Hospitalization for asthma in past 12 months	67	36	0.01
Chronic asthma management			
Current asthma medications			
Chronic use of oral corticosteroids	3	7	0.57
Current use of ICS	80	67	0.19
Current use of ICS-LABA	42	17	0.03
Current use of leukotriene modifiers	37	19	0.13
Seen by asthma specialist in past 12 months	28	47	0.06
Presentation and ED/clinic course			
Vital signs			
Initial respiratory rate (breaths/min), mean (SD)	29 (7)	26 (6)	0.11
Initial oxygen saturation (%), mean (SD)	93 (5)	95 (3)	0.17
Initial PEF (L/min), mean (SD)	197 (87)	231 (48)	0.45
Concomitant medical disorders	34	9	0.02
Inpatient course			
Initial admission location			0.18
ED observation unit	27	49	
Hospital ward	43	37	
ICU	30	14	
Acute asthma treatment			
Non-invasive positive pressure ventilation	7	0	0.26
Intubation	13	0	0.04

Hospital length-of-stay (d), mean (SD)	3 (3)	1 (1)	0.01
Disposition			0.99
Sent home	97	100	
Died in the hospital	3	0	

ED, emergency department; ICS, inhaled corticosteroids; LABA, long-acting β -agonist; SD, standard deviation; PEF, peak expiratory flow; ICU, intensive care unit
Data were presented as % unless otherwise indicated.