

Letter to the Editor

The asthma index: A continuous variable to characterize exacerbations of asthma

To the Editor:

Achievement of asthma control and prevention of exacerbations are becoming recognized as specific goals for asthma management¹ and as primary outcome variables in asthma clinical trials.^{2,3} Although instruments have been developed and validated for assessment of asthma control,⁴ criteria for asthma exacerbation have not been standardized and generally do not incorporate both objective and symptomatic elements of exacerbation together in a quantitative manner. We sought to develop a continuous variable reflecting both objective and subjective measures of asthma control for the purpose of defining asthma exacerbation and for documenting the time course of changes associated with asthma triggers, such as colds.

We studied 47 subjects with physician-diagnosed asthma (age range, 18-52 years; median, 23 years; 68% female) and 22 nonasthmatic nonatopic subjects (age range, 18-43 years; median, 21 years; 64% female) who were participating in either an experimental cold (16 with asthma and 15 without asthma) or a naturally occurring cold (31 with asthma and 7 without asthma) study. All procedures were approved by the institutional review board, and informed consent was obtained for each subject. Subjects in the natural cold protocol were enrolled during acute cold symptoms and then re-evaluated more than 4 weeks later during a baseline reference period of no cold symptoms and asthma stability. Subjects in the experimental cold protocol were all inoculated with human rhinovirus-16 after completing at least 1 week of baseline monitoring under stable conditions; subjects with a history of severe virus-induced exacerbation were excluded from this protocol.

Each subject maintained a diary in which peak expiratory flow rates (PEFRs) and symptom scores were recorded each morning and each evening, and the numbers of puffs of albuterol used and nocturnal awakenings caused by asthma symptoms were recorded each morning. Asthma symptom scores were recorded for wheezing, chest tightness, shortness of breath, and cough, each on a 0- to 3-point scale. A sum of all the individual asthma symptom scores, along with the numbers of albuterol puffs and nocturnal awakenings, totaled a subjective sum for each morning and evening entry.

A reference PEFR was obtained as the mean evening PEFR during the stable baseline week, and each recorded PEFR was expressed as a percentage decrease relative to the reference PEFR. A PEFR score was computed as a moving average of PEFRs (percentage decrease) over a 48-hour period, with each PEFR score being the mean of 2 morning and 2 evening percentage decrease in PEFR values (the current entry plus its preceding 3 consecutive entries). A subjective score was computed as the total sum of 2 morning and 2 evening subjective sums from the same 48-hour period as the PEFR score. The PEFR score was determined as the mean and the subjective score was determined as the total sum for the 48-hour period to assign similar weights to objective and subjective measurements. An asthma score was then computed for each time point as the sum of the PEFR score and the subjective score, and the asthma index was obtained by subtracting the mean of the stable baseline week

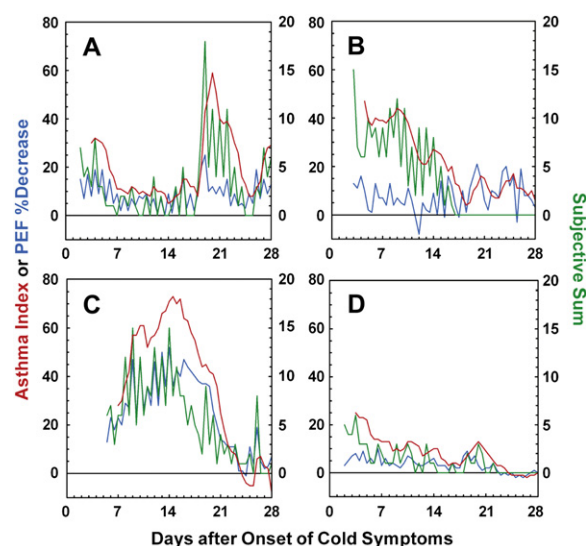


FIG 1. Examples of 4 subjects with asthma during a naturally occurring cold showing individual data points for PEFR percentage decrease (blue) and subjective sum (green; right ordinate axes) and the computed asthma index (red). Subjects **A** and **B** had mild exacerbations, subject **C** had a severe exacerbation, and subject **D** had no exacerbation. Subject **A** had dual peaks in the asthma index.

asthma scores from each individual asthma score. A computation worksheet template that generates these variables from the diary data is available in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org. Thus the asthma index is an indicator of changes in both PEFR and subjective variables relative to the individual's stable baseline and smoothed over a 48-hour period.

Examples of changes in the asthma index during a cold-induced exacerbation are shown in [Fig 1](#), showing the time course of the asthma index, along with the individual measures of PEFR percentage decrease and subjective sum that contributed to the index. Although changes in PEFR and in symptoms/albuterol use are weighted to have about equal influence on the asthma index among many subjects, these 2 indicators of asthma control might change asynchronously with one another for individual subjects ([Fig 1](#)). The asthma index can be partitioned readily into its objective and subjective components for further analysis, as indicated.

To determine how the asthma index correlates with established criteria for asthma exacerbation, we used the exacerbation criteria of Pauwels et al⁵: mild exacerbation was defined as 2 or more consecutive days of a PEFR of 80% of baseline mean morning PEFR or less, nocturnal awakenings caused by asthma symptoms, or an increase of 3 or more puffs/d over baseline albuterol use, and severe exacerbation was defined as 2 or more consecutive days of a PEFR of 70% of baseline morning PEFR or less or the need for systemic corticosteroid treatment. [Fig 2](#) summarizes the peak asthma index occurring in the first 21 days after the onset of cold symptoms versus the exacerbation criteria for subjects with naturally occurring colds and with experimentally induced colds. A peak asthma index of greater than 33 correlated well with meeting the Pauwels criteria for either mild or severe exacerbation (classification tree procedure, 100% positive predictive value and 94% negative predictive value). Compared with the

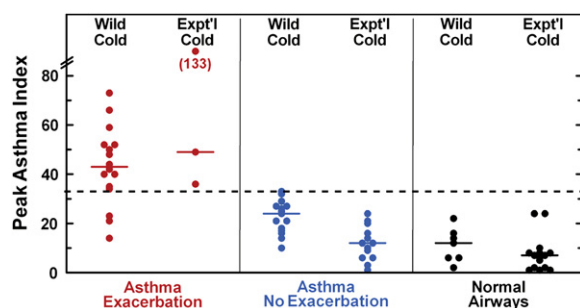


FIG 2. Peak asthma index for subjects with naturally occurring (Wild) colds and experimental rhinovirus-16 (Expt'l) colds comparing asthmatic subjects with (red) and without (blue) exacerbation and nonasthmatic subjects (black). Solid bars are group medians, and the broken line shows the point of best discrimination between the exacerbation groupings.

Pauwels criteria for exacerbation, the asthma index is less sensitive to isolated decreases in PEFR or nocturnal awakenings but more sensitive to increased asthma symptoms that are not accompanied by changes in PEFR, albuterol use, or nocturnal awakenings that individually exceed a threshold for the exacerbation criteria. The asthma index did not discriminate as well between the mild and severe exacerbation classifications of Pauwels et al, in that subjects having high symptom scores and albuterol use had a higher asthma index but did not meet the criteria for severe exacerbation unless they also had the larger decrease in PEFR. The asthma index remained less than 30 in all subjects during periods of no colds and asthma stability, suggesting that a score of 30 or greater might serve as an appropriate threshold for defining an exacerbation.

In addition to providing a criterion for defining qualitatively the occurrence of an exacerbation, the asthma index is a continuous variable that can be used for a comparison of magnitudes of changes among groups and for tracking the time course of changes associated with an event such as viral illness. For example, asthmatic subjects with a natural cold had higher peak asthma index scores overall than those with experimental colds ($P = .0017$, Mann-Whitney test) and a higher incidence of exacerbation (52% vs 19%; $P = .03$, χ^2 test), perhaps because of exclusion of subjects with a history of severe virus-induced exacerbation from the experimental cold protocol and the inclusion criterion of unequivocal cold symptoms for the natural cold protocol. The asthma index also revealed unexpected patterns in the time course of virus-induced changes in asthma control. The initial peak of the asthma index occurred at a median of 5 days after the onset of cold symptoms in both naturally occurring and experimental colds. In asthmatic subjects with a naturally occurring cold, a second peak in asthma index (defined as an

increase of ≥ 15 points from a trough sustained for 3 days after recovery from the initial peak) occurred in 10 of the total 31 subjects and in 6 of the 13 subjects who met the Pauwels criteria for mild exacerbation (Fig 1, A). The 3 subjects classified as having severe exacerbations based on the Pauwels criteria had a single prolonged peak in the asthma index (Fig 1, C). When it occurred, the second peak usually was higher than the first, and it appeared a median of 14 days after the first peak. Dual peaks were not observed in the experimental cold group.

In conclusion, the asthma index is a continuous variable that reflects the magnitude and the timing of changes in asthma control, with objective and subjective elements weighted similarly. In addition to functioning comparably with established criteria for defining qualitatively the occurrence of an asthma exacerbation, the asthma index also provides a continuous variable that can be used for quantitative comparisons among groups and for exploring time-linked associations between asthma control and other viral and biologic variables of interest.

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REFERENCES

- Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl):S94-138.
- Bacharier LB, Phillips BR, Bloomberg GR, Zeiger RS, Paul IM, Krawiec M, et al. Severe intermittent wheezing in preschool children: a distinct phenotype. *J Allergy Clin Immunol* 2007;119:604-10.
- Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007;119:64-72.
- Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma control test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;117:549-56.
- Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337:1405-11.

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Example Computation:

Reference Period:

Subject ID	Date	AM/PM	Study Day	Cold Day	Puffs Albut	Noct Awk	PEF	Chest Tight
Ex1	12/28/06	AM	99	101,0	0	0	457	2
Ex1	12/28/06	PM	99,5	101,5			481	0
Ex1	12/29/06	AM	100	102,0	0	0	481	0
Ex1	12/29/06	PM	100,5	102,5			472	0
Ex1	12/30/06	AM	101	103,0	0	0	488	0
Ex1	12/30/06	PM	101,5	103,5			478	0
Ex1	12/31/06	AM	102	104,0	0	0	468	0
Ex1	12/31/06	PM	102,5	104,5			481	0
Ex1	01/01/07	AM	103	105,0	0	0	490	0
Ex1	01/01/07	PM	103,5	105,5			500	0
Ex1	01/02/07	AM	104	106,0	1	0	496	0
Ex1	01/02/07	PM	104,5	106,5			465	0
Ex1	01/03/07	AM	105	107,0	0	0	461	0
Ex1	01/03/07	PM	105,5	107,5			494	0

Study Period:

Subject ID	Date	AM/PM	Study Day	Cold Day	Puffs Albut	Noct Awk	PEF	Chest Tight
Ex1	20/09/2006	PM	0,5	2,5			507	1
Ex1	21/09/2006	AM	1	3,0	0	1	484	2
Ex1	21/09/2006	PM	1,5	3,5			474	1
Ex1	22/09/2006	AM	2	4,0	0	0	454	1
Ex1	22/09/2006	PM	2,5	4,5			471	1
Ex1	23/09/2006	AM	3	5,0	4	0	482	1
Ex1	23/09/2006	PM	3,5	5,5			502	0
Ex1	24/09/2006	AM	4	6,0	3	0	484	1
Ex1	24/09/2006	PM	4,5	6,5			489	0
Ex1	25/09/2006	AM	5	7,0	1	0	480	0
Ex1	25/09/2006	PM	5,5	7,5			495	0
Ex1	26/09/2006	AM	6	8,0	0	0	489	0
Ex1	26/09/2006	PM	6,5	8,5			494	0
Ex1	27/09/2006	AM	7	9,0	0	0	496	0
Ex1	27/09/2006	PM	7,5	9,5			500	0
Ex1	28/09/2006	AM	8	10,0	0	0	499	0
Ex1	28/09/2006	PM	8,5	10,5			484	0
Ex1	29/09/2006	AM	9	11,0	0	0	493	1
Ex1	29/09/2006	PM	9,5	11,5			487	0
Ex1	30/09/2006	AM	10	12,0	0	0	499	1
Ex1	30/09/2006	PM	10,5	12,5			492	0
Ex1	01/10/2006	AM	11	13,0	0	0	495	1
Ex1	01/10/2006	PM	11,5	13,5			488	0
Ex1	02/10/2006	AM	12	14,0	0	0	499	0
Ex1	02/10/2006	PM	12,5	14,5			471	1
Ex1	03/10/2006	AM	13	15,0	0	0	495	0
Ex1	03/10/2006	PM	13,5	15,5			472	0
Ex1	04/10/2006	AM	14	16,0	0	0	482	0
Ex1	04/10/2006	PM	14,5	16,5			488	0
Ex1	05/10/2006	AM	15	17,0	0	0	474	0
Ex1	05/10/2006	PM	15,5	17,5			481	0

Ex1	06/10/2006	AM	16	18,0	1	0	478	0
Ex1	06/10/2006	PM	16,5	18,5			497	0
Ex1	07/10/2006	AM	17	19,0	1	1	490	1
Ex1	07/10/2006	PM	17,5	19,5			485	0
Ex1	08/10/2006	AM	18	20,0	0	0	450	1
Ex1	08/10/2006	PM	18,5	20,5			401	2
Ex1	09/10/2006	AM	19	21,0	4	1	401	1
Ex1	09/10/2006	PM	19,5	21,5			332	2
Ex1	10/10/2006	AM	20	22,0	5	2	355	3
Ex1	10/10/2006	PM	20,5	22,5			369	3
Ex1	11/10/2006	AM	21	23,0	5	1	405	1
Ex1	11/10/2006	PM	21,5	23,5			368	2
Ex1	12/10/2006	AM	22	24,0	4	1	411	2
Ex1	12/10/2006	PM	22,5	24,5			390	2
Ex1	13/10/2006	AM	23	25,0	3	1	418	2
Ex1	13/10/2006	PM	23,5	25,5			440	1
Ex1	14/10/2006	AM	24	26,0	4	1	443	1
Ex1	14/10/2006	PM	24,5	26,5			417	2
Ex1	15/10/2006	AM	25	27,0	3	0	410	2
Ex1	15/10/2006	PM	25,5	27,5			434	1
Ex1	16/10/2006	AM	26	28,0	3	0	445	2
Ex1	16/10/2006	PM	26,5	28,5			443	2
Ex1	17/10/2006	AM	27	29,0	3	0	446	1
Ex1	17/10/2006	PM	27,5	29,5			447	2
Ex1	18/10/2006	AM	28	30,0	3	0	446	1
Ex1	18/10/2006	PM	28,5	30,5			447	2

Reference PEF= 482
Reference Asthma Score= 1

Wheeze	Cough	SOB	PEF %Dcr	Subj Sum	Subj Score	PEF Score	Asthma Score
0	0	1	5	3			
0	0	0	0	0			
0	0	0	0	0			
0	0	0	2	0	3	2	5
0	0	0	-1	0	0	0	0
0	0	0	1	0	0	1	1
0	0	0	3	0	0	1	1
0	0	0	0	0	0	1	1
0	0	0	-2	0	0	1	1
0	0	0	-4	0	0	-1	-1
0	0	0	-3	1	1	-2	-1
0	0	0	4	0	1	-1	0
0	0	0	4	0	1	0	1
0	0	0	-2	0	1	1	2

Peak Asthma Index in 1st 21 days after initial cold symptoms=

Wheeze	Cough	SOB	PEF %Dcr	Subj Sum	Subj Score	PEF Score	Asthma Score
0	0	0	-5	1			
1	0	0	0	4			
0	0	1	2	2			
1	1	1	6	4	11	1	12
0	1	2	2	4	14	3	17
0	0	2	0	7	17	3	20
1	0	2	-4	3	18	1	19
0	0	2	0	6	20	-1	19
0	0	1	-1	1	17	-1	16
1	0	0	0	2	12	-1	11
0	0	0	-3	0	9	-1	8
0	0	0	-1	0	3	-1	2
0	0	0	-2	0	2	-2	0
0	0	0	-3	0	0	-2	-2
0	0	0	-4	0	0	-3	-3
0	0	0	-4	0	0	-3	-3
0	0	0	0	0	0	-3	-3
0	1	0	-2	2	2	-3	-1
0	0	0	-1	0	2	-2	0
0	0	0	-4	1	3	-2	1
0	0	0	-2	0	3	-2	1
0	0	0	-3	1	2	-3	-1
0	0	0	-1	0	2	-3	-1
0	0	0	-4	0	1	-3	-2
0	0	0	2	1	2	-2	0
0	0	0	-3	0	1	-2	-1
0	0	0	2	0	1	-1	0
0	0	0	0	0	1	0	1
0	0	0	-1	0	0	-1	-1
0	0	0	2	0	0	1	1
0	0	0	0	0	0	0	0

0	0	0	1	1	1	1	2
0	0	0	-3	0	1	0	1
1	1	0	-2	5	6	-1	5
0	0	0	-1	0	6	-1	5
1	0	2	7	4	9	0	9
1	1	2	17	6	15	5	20
0	1	2	17	9	19	10	29
2	2	2	31	8	27	18	45
1	3	2	26	16	39	23	62
2	3	2	23	10	43	24	67
1	1	1	16	10	44	24	68
0	1	1	24	4	40	22	62
0	2	2	15	11	35	20	55
0	2	2	19	6	31	19	50
0	1	1	13	8	29	18	47
0	1	1	9	3	28	14	42
0	1	1	8	8	25	12	37
0	1	1	13	4	23	11	34
1	1	1	15	8	23	11	34
0	0	1	10	2	22	12	34
0	1	1	8	7	21	12	33
0	1	2	8	5	22	10	32
0	0	1	7	5	19	8	27
0	0	1	7	3	20	8	28
0	0	1	7	5	18	7	25
0	0	1	7	3	16	7	23

```

COMPUTE 1
NV      481
NV      472
NV      478
NV      481
NV      500
NV      465
NV      494

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44

Asthma Index

	NV	
	NV	
	NV	
11		11
16		16
19		19
18		18
18		18
15		15
10		10
7		7
1		1
-1		-1
-3		-3
-4		-4
-4		-4
-4		-4
-2		-2
-1		-1
0		0
0		0
-2		-2
-2		-2
-3		-3
-1		-1
-2		-2
-1		-1
0		0
-2		-2
0		0
-1		-1

1		1
0		0
4		4
4		4
8		8
19		19
28		28
44		44
61	NV	
66	NV	
67	NV	
61	NV	
54		
49		
46		
41		
36		
33		
33		
33		
32		
31		
26		
27		
24		
22		