

Letter to the Editor

The influence of asthma control on the severity of virus-induced asthma exacerbations

To the Editor:

Our understanding of asthma control has evolved in recent years to include both the idea of current control (gauged mostly from symptoms) and a link with future risk, notably exacerbations.¹ Despite currently available therapies, many patients remain uncontrolled and asthma exacerbations, which are most frequently triggered by rhinovirus infections, remain a major unmet need.² The development of human experimental models of rhinovirus-induced asthma exacerbations has led to important advances in our understanding of exacerbation pathogenesis³; however, to date, studies have been limited through the inclusion of patients with well-controlled asthma only.³ It is therefore unknown how the level of control at the time of infection influences the severity of the exacerbation; however, studies of naturally occurring exacerbations support a relationship between control and exacerbation frequency.^{4,5}

We therefore analyzed the relationship between the degree of baseline control in patients with asthma infected with rhinovirus-16 (RV16) and clinical measures of exacerbation severity following inoculation. A comparison of clinical outcomes between subjects with and without asthma including the same subjects as reported herein has been published elsewhere.⁶

Twenty-eight adult volunteers with asthma were recruited (Table I). The study was approved by a local research ethics committee (09/H0712/59), and all volunteers provided written informed consent to participate. The degree of asthma control at baseline was assessed using the Juniper Asthma Control Questionnaire (ACQ-7), with 3 control groups defined by ACQ cutoff scores of 0.75 or less for well-controlled ($n = 12$), 0.76 to 1.49 for partially controlled ($n = 8$), and 1.5 or more for uncontrolled asthma ($n = 8$), respectively.⁷ For full inclusion/exclusion criteria, see this article's [Methods](#) section in the Online Repository at www.jacionline.org.

Subjects were seen at baseline and on days 2, 3, 4, 5, 7, 10, and 42 postinoculation with RV16. Daily diary cards of upper and lower respiratory tract symptoms and FEV₁ measurements were commenced 2 weeks before baseline sampling and continued for 6 weeks.⁶ The lower respiratory tract score was calculated from scores graded 0 to 3 for cough on waking; wheeze on waking; daytime cough; daytime wheeze; daytime chest tightness; daytime shortness of breath; nocturnal cough, wheeze, or shortness of breath.⁶ Bronchial mucosal lining fluid was sampled for measurement of a range of cytokines and chemokines including IL-4, IL-5, IL-6, IL-13, IL-33, CXCL10/IP-10, and CXCL11/ITAC using the technique of bronchosorption.⁶ This involves passing a specially designed probe with a synthetic absorptive tip down the operating port of a bronchoscope. Further

TABLE I. Baseline demographic and clinical characteristics of study volunteers

Characteristic	Well-controlled ACQ score ≤ 0.75 ($n = 12$)	Partially controlled ACQ score 0.76-1.49 ($n = 8$)	Uncontrolled ACQ score ≥ 1.50 ($n = 8$)	P value	
				Across all groups	Between groups
Age (y)	33 $\pm$ 12	38 $\pm$ 10	36 $\pm$ 10	.542	—
Sex (%)				.087	—
Female	75	50	25		
Male	25	50	75		
White ethnicity (% of subjects)	10 (83)	5 (63)	7 (88)	.426	—
Baseline FEV ₁ % of predicted value	95 $\pm$ 10	78 $\pm$ 7	82 $\pm$ 10	.001	Well vs part: .001 Well vs un: .02 Part vs un: 1.0
Asthma severity (as defined by GINA)				.013	Well vs part: .31 Well vs un: .01 Part vs un: .23
Mild asthma (% of subjects)	8 (66.7)	3 (37.5)	0 (0)		
Moderate asthma (% of subjects)	4 (33.3)	5 (62.5)	8 (100)		
Baseline histamine PC ₂₀ (mg/mL)	1.55 $\pm$ 1.95	0.29 $\pm$ 0.61	1.78 $\pm$ 2.78	.277	—
Baseline asthma control (ACQ score)	0.56 $\pm$ 0.27	1.18 $\pm$ 0.15	1.86 $\pm$ 0.32	<.001	Well vs part: <.001 Well vs un: <.001 Part vs un: <.001
Use of inhaled corticosteroids (% of subjects)	4 (33)	4 (50)	7 (88)	.063	—
Dose of inhaled corticosteroids (beclometasone/equivalent) (μ g)					
Median	450	350	400	.71	—
Interquartile range	250-875	200-875	200-500		
IgE (IU/mL)					
Median	95	356	152	.183	—
Interquartile range	65-212	122-1105	52-710		
BAL eosinophilia (%)					
Median	0.3	1.3	0.3	.225	—
Interquartile range	0-1.0	0.3-3.0	0-1.8		

BAL, Bronchoalveolar lavage; GINA, Global Initiative for Asthma; part, partially controlled; un, uncontrolled.

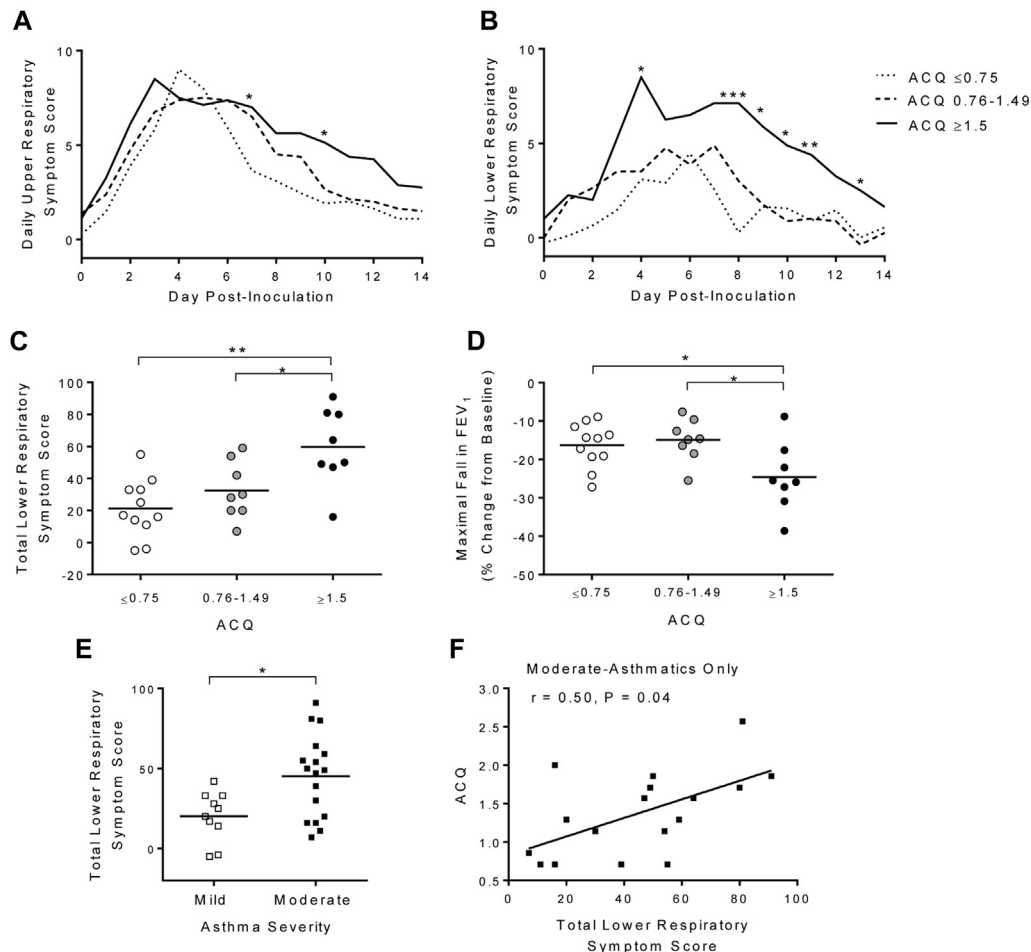


FIG 1. The response to rhinovirus infection in asthma according to baseline control status. Daily upper (A) and lower (B) respiratory tract symptoms are shown over the 14 days postinoculation with rhinovirus. The daily lower respiratory tract scores have been corrected for baseline symptoms and any effect of bronchospasm. The total lower respiratory tract symptom score is the summation of the daily scores over 14 days (C) and the maximal fall in FEV₁ (as a percentage change from baseline) (D) are shown for all subjects according to the ACQ score group. The total lower respiratory tract symptom score is also shown according to asthma severity (E), with the relationship between ACQ score and total lower respiratory tract symptoms shown for those with moderately severe asthma only (F). Results shown as lines are mean values (Fig 1, A-E). Statistically significant differences shown in A and B refer to differences across all groups (1-way ANOVA). Clinical data are missing for 1 patient with well-controlled asthma ($n = 11$). * $P < .05$; ** $P < .01$; *** $P < .001$.

details regarding study design, methodology, and statistical analyses are provided in this article's Online Repository at www.jacionline.org and have been previously published.⁶

Following RV16 infection, we observed an increase in upper and lower respiratory tract symptoms across all asthma control categories. However, those with uncontrolled asthma (ACQ score, ≥ 1.5) experienced significantly greater virus-induced respiratory symptoms than did those with superior baseline control. Specifically, although upper respiratory tract symptoms reached a similar magnitude across the groups, those with uncontrolled asthma experienced a more prolonged cold than did others with asthma (Fig 1, A).

Analysis of lower respiratory tract symptom scores also revealed substantial differences between control categories: Those with uncontrolled asthma experienced a greater maximal level of lower respiratory tract symptoms on day 4 ($P < .05$) and a slower recovery with significant differences in symptoms observed on days 8 to 11 and 13 between control

groups (all $P < .05$) (Fig 1, B). Analysis of the total lower respiratory tract symptom score (summation of daily scores during the 14 days postinoculation, a more complete measure of exacerbation severity) demonstrated that those with uncontrolled asthma had a significantly greater mean score (59.8 ± 8.6) than did those with asthma with better baseline control (ACQ score, ≤ 0.75 ; total score, 21.3 ± 5.5 [$P = .001$]; ACQ score, 0.76-1.49; total score, 32.5 ± 6.3 [$P = .02$]) (Fig 1, C). Importantly, virus-induced increases in lower respiratory tract symptom scores were corrected for preinfection levels and were therefore over and above any baseline symptom for each subject (see this article's [Methods](#) section in the Online Repository).

The relationship between baseline control and virus-induced symptom severity was mirrored by changes in lung function: Analysis of daily FEV₁ measurements highlighted that those with uncontrolled asthma had significantly greater virus-induced falls in FEV₁ from baseline: $24.6\% \pm 3.1\%$ compared with

16.3% $\pm$ 1.7% for subjects with an ACQ score of 0.76 to 1.49 ($P = .025$), and 14.9% $\pm$ 2.0% for the well-controlled group ($P = .021$) (Fig 1, D). Taken together, those with uncontrolled asthma experienced a more severe and prolonged exacerbation than did those with asthma with better baseline control.

Categorizing those with asthma by asthma severity (defined by the Global Initiative for Asthma⁸) rather than asthma control revealed significantly greater virus-induced lower respiratory tract symptoms in those with moderately severe asthma ($n = 17$) than in those with mild asthma ($n = 11$) ($P = .01$; Fig 1, E). However, analysis of those with moderately severe asthma alone demonstrated that the observed relationship between control and exacerbation severity persisted within this single severity category ($r = 0.5$; $P = .04$) (Fig 1, F). A significant relationship was also evident when the correlation was limited to those with asthma on inhaled corticosteroid therapy ($r = 0.58$; $P = .02$). Interestingly, no relationship in asthma was seen between lower respiratory tract symptoms and baseline FEV₁ ($r = -0.14$; $P = .49$). Unfortunately, because of the small number of subjects in each control category, it has not been possible to address the potential for confounding factors further and future larger studies are required to investigate this. In addition, it should be noted that most of those with well-controlled asthma (8 of 12) had mild asthma.

Measurement of a range of T_H1 (CXCL10/IP-10 and CXCL11/ITAC), T_H2 (IL-4, IL-5, IL-13, IL-33), and proinflammatory (IL-6) cytokines/chemokines in bronchial mucosal lining fluid was performed at baseline and on day 4 postinoculation and analyzed according to asthma control group (see Table E1 in this article's Online Repository at www.jacionline.org). Overall, there were no significant differences across control groups for these mediators; however, we were interested to note that the most marked virus-induced increases in the T_H1/antiviral chemokines CXCL10/IP-10 and CXCL11/ITAC were seen in those with well-controlled asthma (Table E1). In addition, virus load (VL) was measured in nasal lavage samples at 6 time points between day 2 and day 10 postinoculation as well as in bronchoalveolar lavage on day 4. At each of these time points, median VL was numerically greater in those with uncontrolled asthma than in either of the other groups; however, these differences did not reach significance (Table E2 in this article's Online Repository at www.jacionline.org).

To our knowledge, this study is the first to analyze the influence of asthma control on the outcome of a rhinovirus infection in asthma. We observed more severe exacerbations in those with uncontrolled asthma irrespective of asthma severity or treatment status. These results support findings by Bateman et al,⁵ demonstrating the influence of control on the risk of future exacerbations, as well as findings of the Gaining Optimal Asthma control study in which unscheduled health care utilization for exacerbations related to the level of control achieved rather than the treatment received.⁴

We acknowledge that the small sample size (8-12 per group) makes it difficult to draw significant mechanistic conclusions from our study. However, the higher levels of T_H2 cytokines and VL and the finding of less marked T_H1/antiviral induction in subjects with asthma compared with healthy controls observed reproducibly in our earlier reports^{3,6,9} cannot explain why uncontrolled asthma is associated with greater rhinovirus

infection-induced asthma symptoms, because trends in these responses did not reach statistical significance in the numbers studied (Tables E1 and E2). We plan to address this critical gap in knowledge in future studies using high throughput discovery approaches and greater numbers of poorly controlled subjects. Interestingly, a recent trial of inhaled IFN- β in asthma¹⁰ identified significant improvements in the outcome of naturally occurring respiratory virus infections in those with more severe and poorly controlled asthma only.

The data presented here extend our existing understanding of the link between the 2 domains of asthma control—current control and future risk—and further highlight the importance of maintaining adequate control in reducing the likelihood of severe asthma exacerbations.

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METHODS

Inclusion and exclusion criteria have been previously published.^{E1}

Inclusion criteria for subjects with asthma:

- Age 18 to 55 years
- Patient-reported doctor diagnosis of asthma
- PC₂₀ histamine less than 8 µg/mL
- Mild to moderate disease based on Global Initiative for Asthma criteria^{E2}
- Worsening asthma symptoms with infection since last change in asthma therapy
- Atopic on skin testing (≥1 positive skin prick test result on a panel of 10 aeroallergens)

Exclusion criteria for subjects with asthma:

- History of severe asthma
- Smoking history over past 6 months or more than 5 pack-year history
- Current symptoms of allergic rhinitis
- Current or previous history of significant other respiratory disease
- Any clinically relevant abnormality on screening or detected significant systemic disease
- Asthma exacerbation or viral illness within the previous 6 weeks
- Treatment with oral steroids in the previous 3 months
- Current use of any nasal medication, oral or systemic antihistamine, antileukotrienes, anticholinergic, or anti-IgE therapy
- Serum antibodies to RV-16
- Pregnant or breast-feeding women
- Contact with infants or elderly at home or at work

Symptom scores and spirometry recording

Symptoms were assessed by daily diary cards as previously published.^{E1} from 2 weeks before baseline sampling until 4 weeks postinoculation. The daily cold score was measured using the Jackson^{E3} scale and summated from individual scores (sneezing, headache, malaise, chilliness, nasal discharge, nasal obstruction, sore throat, cough, fever) graded 0 (absent) to 3 (severe). The daily lower respiratory tract score was calculated from symptom scores (cough on waking; wheeze on waking; daytime cough; daytime wheeze; daytime chest tightness; daytime shortness of breath; nocturnal cough, wheeze, or shortness of breath), also graded 0 to 3. The same diary cards recorded home spirometry on waking each morning, recording the best of 3 recordings of FEV₁ (Piko-1; nSpire).

Analysis of lower respiratory tract symptom scores and lung function

As previously reported,^{E1} lower respiratory tract symptom scores were analyzed in 2-week blocks as the baseline and acute infection stages. Both contained a bronchoscopy on the fourth day of each 2-week block. Daily symptom scores during infection, corrected for baseline symptoms and the effects of bronchoscopy, were calculated by subtracting scores obtained during the baseline 2-week block from the corresponding days of the acute infection 2-week block. Total lower respiratory tract scores were calculated by summing the corrected daily scores for the 2-week infection period. The % change in morning FEV₁ from baseline during infection was calculated for each subject as the % fall from the mean of the

7-day period before inoculation. Maximal fall from baseline (%) for each subject represented the greatest fall from baseline over the 2-week period following inoculation.

Virus inoculation

RV-16 (100 TCID₅₀) was diluted in 250 µL of 0.9% saline and inoculated into both nostrils using an atomizer (no. 286; De Vilbiss Co, Heston, United Kingdom) as described.^{E1}

Nasal lavage

Nasal lavage with sterile 0.9% sodium chloride was performed as previously published^{E1} using a 10-mL syringe attached to a hollow nasal adapter ("olive") used to obstruct the nostril and prevent leakage of lavage fluid. A total of 5 mL of sterile normal saline was instilled into the left nostril and the fluid withdrawn into the 10-mL syringe and flushed back into the nasal cavity 20 times over a 1-minute period. Fluid was collected, aliquoted, and stored at −80°C.

Virologic confirmation of RV16 infection

All subjects were seronegative for RV16 at screening. Rhinovirus infection was confirmed by positive nasal lavage quantitative PCR for rhinovirus or seroconversion, defined as a titer of serum-neutralizing antibodies to RV16 of at least 1:4 at 6 weeks postinoculation. Serology was performed at screening, day 0, and day 42 postinfection. Full methods and serology results have been previously published.^{E1}

Statistical analysis

All data analyses were conducted using SPSS v20.0 (IBM Corp, New York, NY). Data are presented as mean (±SEM) values for normally distributed data or as median (interquartile range) values for nonparametric data. Differences between groups were analyzed by using unpaired *t* tests or Mann-Whitney tests. When differences were assessed between 3 asthma control groups, ANOVA and Kruskal-Wallis tests were performed for parametric and nonparametric comparisons, respectively. Within-group comparisons were analyzed with paired *t* tests or Wilcoxon's signed rank test. Correlations between data sets were examined using Pearson's correlation for normally distributed data and Spearman's rank correlation coefficient for nonparametric data. Differences were considered significant for all statistical tests at *P* values of less than .05. All reported *P* values are 2-sided.

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TABLE E1. Cytokine and chemokine measurements in bronchial mucosal lining fluid

Cytokine	ACQ score ≤ 0.75 n = 12 (baseline) n = 11 (day 4)	ACQ score 0.76-1.49 n = 7 (baseline) n = 6 (day 4)	ACQ score ≥ 1.5 n = 6 (baseline) n = 8 (day 4)	P value across all groups
IL-4 (pg/mL)				
Baseline	0.0 (0.0-1.3)	0.6 (0.0-1.0)	0.0 (0.0-0.2)	NS
Day 4	0.8 (0.0-2.1)	0.3 (0.0-0.8)	0.0 (0.0-0.9)	NS
IL-5 (pg/mL)				
Baseline	0.0 (0.0-1.4)	0.7 (0.6-1.2)	0.3 (0.0-1.2)	NS
Day 4	0.7 (0.0-1.5)	1.0 (0.6-2.2)	1.6 (0.0-4.1)	NS
IL-6 (pg/mL)				
Baseline	24.3 (12.9-56.1)	28.3 (15.6-141.0)	36.3 (17.5-135.8)	NS
Day 4	37.8 (12.8-122.7)	49.8 (26.3-67.8)	94.5 (40.3-1047.8)	NS
IL-13 (pg/mL)				
Baseline	0.0 (0.0-1.4)	0.8 (0.6-1.0)	0.0 (0.0-0.9)	NS
Day 4	0.6 (0.0-1.1)	0.8 (0.5-1.2)	0.8 (0.0-2.8)	NS
IL-33 (ng/mL)				
Baseline	1.81 (0.54-4.70)	3.49 (1.53-5.48)	2.05 (1.23-4.70)	NS
Day 4	0.92 (0.59-3.92)	2.83 (1.14-4.46)	2.96 (0.95-5.59)	NS
CXCL10/IP-10 (ng/mL)				
Baseline	1.02 (0.45-1.76)	0.86 (0.36-1.52)	1.01 (0.65-1.17)	NS
Day 4	2.64 (1.73-5.27)*	1.44 (0.85-4.45)†	1.96 (0.97-5.25)†	NS
CXCL11/ITAC (pg/mL)				
Baseline	18.6 (12.7-42.5)	16.0 (11.4-34.0)	23.9 (14.1-33.0)	NS
Day 4	179.8 (64.9-527.7)*	78.3 (18.3-972.6)†	64.1 (24.5-612.6)†	NS

Values shown are at baseline and on day 4 postinoculation (medians and interquartile range). Bronchial sampling was not possible for 3 subjects at baseline and 5 subjects on day 4.

NS, Not statistically significant.

* $P < .01$ represents statistical significance for day 4 vs baseline.

† $P < .05$ represents statistical significance for day 4 vs baseline.

TABLE E2. Virus load

Baseline ACQ score	Peak nasal	Day 2 nasal	Day 3 nasal	Day 4 nasal	Day 5 nasal	Day 7 nasal	Day 10 nasal	Day 4 BAL
≤0.75 n = 12	3.3×10^6 (6.8×10^5 - 6.1×10^6)	5.4×10^4 (4887- 5.9×10^5)	1.7×10^6 (3.5×10^5 - 4.3×10^6)	5.4×10^4 (1.6×10^5 - 1.5×10^6)	3.7 (0 - 6.6×10^5)	2447 (0 - 1.2×10^5)	3809 (0 - 2.7×10^5)	2572 (0 - 5.2×10^5)
0.76-1.49 n = 8	8.1×10^6 (2.6×10^5 - 8.0×10^7)	6213 (0 - 1.3×10^6)	7.2×10^4 (6466- 1.6×10^7)	3.0×10^4 (8811- 4.5×10^7)	1.7×10^4 (1026- 3.6×10^5)	2.1×10^4 (3366- 5.3×10^5)	6971 (0 - 1.1×10^5)	3458 (471 - 3.3×10^4)
≥1.5 n = 8	9.4×10^6 (5.2×10^5 - 3.7×10^7)	8.9×10^5 (82- 4.3×10^6)	9.3×10^6 (6.1×10^4 - 3.7×10^7)	8.1×10^5 (1308- 3.4×10^6)	7.2×10^4 (2343- 2.6×10^5)	4.4×10^4 (5066- 3.0×10^5)	5.1×10^4 (1.3×10^4 - 2.1×10^5)	9427 (322 - 8.2×10^5)

Values represent medians and interquartile range (copies/mL). Peak value represents the maximal value for each subject. No group differences reached statistical significance.

BAL, Bronchoalveolar lavage; NL, nasal lavage.