

Impact of Utilizing a Composite versus a Symptom-Only Validation Standard in the Development of the Asthma Impairment and Risk Questionnaire

Bradley E Chipps¹, Robert S Zeiger², David A Beuther³, Robert A Wise⁴, William McCann⁵, Joan Reibman⁶, Maureen George⁷, Ileen Gilbert⁸, James M Eudicone⁸, Karin S Coyne⁹, Gale Harding⁹, Kevin R Murphy¹⁰

¹Capital Allergy & Respiratory Disease Center, Sacramento, CA, USA; ²Department of Clinical Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA, USA; ³Department of Medicine, National Jewish Health, Denver, CO, USA; ⁴Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ⁵Allergy Partners, Asheville, NC, USA; ⁶Department of Medicine, New York University School of Medicine, New York, NY, USA; ⁷Columbia University School of Nursing, New York, NY, USA; ⁸BioPharmaceuticals Medical, AstraZeneca, Wilmington, DE, USA; ⁹Evidera, Bethesda, MD, USA; ¹⁰Boys Town National Research Hospital, Boys Town, NE, USA

Correspondence: Bradley E Chipps, Capital Allergy & Respiratory Disease Center, 5609 J Street, Suite C, Sacramento, CA, 95819, USA, Tel +1 916-453-1454, Email bchipps@capitalallergy.com

Introduction

Despite decades of research resulting in targeted biologic treatments and new rescue therapy paradigms combining fast-acting bronchodilators with inhaled corticosteroids, approximately 41% of adolescents and 60% of adults with asthma in the United States have uncontrolled disease, and more than 9.8 million had an asthma attack in 2021.¹ To determine an optimal assessment and management strategy to address asthma morbidity, it is critical to heighten awareness of patients at risk for adverse asthma outcomes, such as exacerbations requiring systemic steroids. The current standard for assessment of asthma control includes utilization of an impairment-based tool, such as the Asthma Control Test (ACTTM), the Asthma Control Questionnaire (ACQ), or the 4 consensus-based Global Initiative for Asthma (GINA) symptom control questions, in combination with an evaluation of GINA-suggested risk factors.²

The Asthma Impairment and Risk Questionnaire (AIRQ[®]) consists of 7 symptom-based impairment and 3 exacerbation-based risk items in a single, equally weighted, yes/no, control tool.³ The AIRQ was validated against a standard that combined symptom impairment (ACT score) and exacerbation risk (number and type of prior-year exacerbations). AIRQ differentiates patients with varying levels of current control,³ lung function,³ and health-related quality of life⁴ and is predictive of future exacerbation risk.⁵ Moreover, AIRQ is less likely than the ACT to overestimate current control and categorize patients with prior- and subsequent-year exacerbations as well-controlled (WC).⁶

The cross-sectional validation standard for AIRQ differed from that used for the ACT,⁷ in which the impairment questions and cut points of control were determined by specialist ratings of control, as outlined in the National Heart, Lung, and Blood Institute guidelines (2002). The objective of the current analysis was to investigate how the AIRQ validation standard of ACT plus prior-year exacerbations supported the validity of the AIRQ as a measure of both current disease control and future exacerbation risk. Thus, these findings will inform developmental strategies for future asthma control measures, including those for children aged 5–11 years.

Methods

This post hoc analysis used data from a 12-month longitudinal study of the AIRQ's ability to predict exacerbations in patients aged ≥ 12 years who were previously diagnosed with asthma and taking therapies appropriate for all disease

severities.⁵ Only those patients whose data contributed to the cross-sectional validation of the AIRQ questions and cut points of control were included.³ Patients were recruited from 12 geographically diverse US specialty care sites between May and August 2019.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Committee on Harmonisation Good Clinical Practices, Good Pharmacoevidence Practices, and US and local laws. Central institutional review board (E&I IRB; Independence, MO, USA) approval of the study protocol was granted on March 26, 2019. Adults and legal guardians of adolescents provided written informed consent; adolescents provided verbal assent.

Sites were required to have access to patient records for the 12 months prior to enrollment to provide documentation of exacerbation history. Exacerbation was defined as a change in asthma clinical status requiring one of the following: a course of systemic corticosteroids (oral steroids for ≥ 3 days); an emergency department (ED), urgent care, or unplanned office visit for an asthma exacerbation (not associated with a hospitalization); or a hospital stay for asthma for >24 hours. For analysis purposes, these 3 exacerbation types were mutually exclusive, with the most intensive healthcare resource utilization category utilized in the AIRQ cross-sectional validation standard.

At enrollment, patients completed the initial 10 potential AIRQ yes/no impairment and risk questions that had been developed by over 140 clinicians through a modified Delphi process and evaluated in patient cognitive interviews.³ Five additional yes/no impairment questions identified through literature review and expert opinion were also included. These latter items reflected new concepts or frequencies of symptom occurrence and were used to assess whether alternative questions or ways of expressing the content would better discriminate differing levels of asthma control. Patients also completed the ACT, which is scored from 5 for worst to 25 for best control based on responses to five Likert scale impairment items.⁷ ACT asthma control is defined as WC for scores of 20–25, not well-controlled (NWC) for scores of 16–19, and very poorly controlled (VPC) for scores of 5–15.³

After the in-person enrollment clinic visit, patients were followed monthly via email web survey to capture asthma exacerbation-related oral corticosteroid (OCS) use, ED or urgent care visits, and hospitalizations in the prior month. For longitudinal analysis purposes, these exacerbation categories were mutually exclusive and combined to provide a total number of exacerbation events over the subsequent 12-month observation period.

The AIRQ cross-sectional validation standard consisted of 3 levels of asthma control: WC, NWC, and VPC. Each category combined the validated ACT control level⁷ (to reflect the impairment domain of control) with a level of prior-year exacerbation occurrence (to represent the risk domain of control). The WC category required an ACT ≥ 20 and no OCS use, ED or unplanned visits, or hospitalizations for asthma. The NWC category consisted of an ACT score of 16–19 or 1 burst of an OCS or 1 ED or unplanned visit, but no hospitalizations in the prior year due to asthma. The VPC category was characterized by an ACT ≤ 15 ; or ≥ 2 OCS bursts, ≥ 2 ED or unplanned visits, ≥ 2 OCS bursts or ED or unplanned visits combined in the prior year for asthma; or ≥ 1 hospitalization for asthma in the prior year for asthma. The comparative standard analyzed in this current analysis used the same ACT control-level categorizations but without consideration of prior-year exacerbations.

Descriptive statistics were used to characterize the sample in terms of sociodemographic and clinical features, baseline distribution of patients within AIRQ control categories, and subsequent 1-year patient-reported exacerbation outcomes. Group comparisons for categorical data were performed using chi-square test, whereas comparisons for continuous data were performed using a general linear model with Scheffe's adjustment for pairwise comparisons. Statistical analysis was conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A P value ≤ 0.05 was considered to be statistically significant.

Multivariable logistic regression analyses were used to determine which of the 15 candidate AIRQ questions provided the greatest validity in discriminating among patients of varying levels of control, as defined by ACT plus prior-year exacerbations and the ACT alone validation standards. Two dichotomous comparisons were made for each validation standard analysis by changing the dependent variable groups as follows: Model 1, WC vs NWC/VPC; Model 2, WC/NWC vs VPC. A comparison was made between the validation standards as to which of the candidate questions performed well in discriminating control as per the AIRQ cross-sectional validation methodology.³ Models were evaluated for best model fit using R^2 , Hosmer and Lemeshow, and Akaike information criterion; receiver

operating characteristic (ROC) curves; and individual item performance. The validated AIRQ and summary of the validation methodology results are shown in the [Supplementary Figure 1](#) and [Supplementary Methods](#).

Results

A total of 442 patients were enrolled, of whom 437 had baseline ACT data; all were included in the analysis. Additionally, 428 patients had ≥ 1 month of web-based, patient-reported exacerbation data (mean [SD] 11.3 [2.2] monthly survey completions) and were included in the current analyses: age 44.0 (± 20) years; 73% female; 84% White, 8% Black, 3% Hispanic or Latino. At enrollment, 206 (47.1%) patients had ACT scores of ≥ 20 , WC; 111 (25.4%) of 16–19, NWC; and 120 (27.5%) of ≤ 15 , VPC. With AIRQ, 141 (31.9%) had scores of 0–1, WC; 172 (38.9%) of 2–4, NWC; and 126 (28.5%) of 5–10, VPC. Overall, prior-year chart-documented exacerbations were experienced by 194 (43.9%) of the population (82 [18.6%] 1 OCS burst or 1 ED or unplanned visit and 112 [25.3%] ≥ 2 OCS bursts, ≥ 2 ED or unplanned visits, ≥ 2 OCS or ED or unplanned visits combined, or ≥ 1 hospitalization). Subsequent-year exacerbations were reported by 204 (47.7%) patients.

[Table 1](#) shows how the 15 AIRQ candidate questions evaluated in the cross-sectional AIRQ validation study³ performed when the validation standard of ACT plus prior-year exacerbations was changed to ACT alone as the dependent variable in the logistic regression models. All 7 impairment items chosen for inclusion in the initial AIRQ validation study showed statistically significant contributions to the ACT WC vs NWC/VPC and/or ACT WC/NWC vs VPC prediction models; however, none of the 3 risk questions (ie, oral steroids or injections, ED or unplanned visits, or overnight hospital stays for asthma in past 12 months) contributed significantly to either model.

Comparative control category patient distributions relative to AIRQ cross-sectional validation standards of ACT plus prior-year exacerbations vs ACT alone are shown in [Figure 1](#). If the ACT alone had been the validation standard, of the 437 patients with baseline ACT data, 22.7% ($n = 99$) would have been placed in a more controlled category and none in a less controlled category. The number of patients categorized as WC and NWC using the ACT alone vs ACT plus prior-year exacerbations standard would have increased by 44% ($n = 63$) and 13% ($n = 13$), respectively, whereas those assessed as VPC would have decreased by 39% ($n = 76$). Of those patients who would have shifted into the WC category from the NWC ($n = 23$) and VPC ($n = 40$) groups, 43% and 50%, respectively, went on to have ≥ 1 subsequent-year exacerbation, resulting in a 21% increase in the proportion of WC patients at baseline who experienced subsequent-year exacerbations. Overall, had ACT alone vs ACT plus prior-year exacerbations been the AIRQ validation standard, 48% of those who would have shifted into the WC category at baseline would have experienced at least 1 subsequent-year exacerbation.

Discussion

The AIRQ validation study used models utilizing a prediction standard that combined impairment (ACT) and risk (number and types of exacerbations) in a manner that had not been validated previously. The importance of utilizing this composite standard, as opposed to the validated ACT alone, is confirmed by the current study's analyses that show no risk questions would have contributed to either ACT model of differentiating asthma control (ie, WC vs NWC/VPC or WC/NWC vs VPC asthma). Most importantly, an AIRQ utilizing only the impairment items that contributed statistically to the ACT prediction models would have resulted in a symptom control tool in which approximately 1 out of 3 patients categorized as WC was at risk of subsequent-year exacerbations and potentially being overlooked by clinicians as needing educational and/or therapeutic interventions.

The validation standard used in the development of the AIRQ may explain differences between the AIRQ and the ACT that have been reported in the categorization of current control and prediction of exacerbations. ACT has been shown to categorize significantly more patients with ≥ 1 and ≥ 2 prior-year exacerbations as having WC asthma than those categorized as WC by the AIRQ. Moreover, of these patients with prior-year exacerbations who were identified as WC by ACT vs AIRQ, over 3 times more went on to have ≥ 1 exacerbation and over 2.5 times more had ≥ 2 subsequent-year exacerbations.⁶ More information about the previously published validation analyses of the AIRQ is shown in [Supplementary Table 1](#).

There are limitations to the observations of this post hoc analysis. The patients studied were followed in specialty care practices in the US and were predominantly White, non-Hispanic, and treated for moderate-to-severe disease; thus,

Table I AIRQ Item Selection Based on a Validation Standard of ACT Plus Prior-Year Exacerbations vs ACT Alone

Question	Validation standard: ACT Plus Prior-year Exacerbations ^a		Validation standard: ACT Alone	
	Dependent variable: WC vs NWC/VPC	Dependent variable: WC/NWC vs VPC	Dependent variable: WC vs NWC/VPC	Dependent variable: WC/NWC vs VPC
1. Are you currently prescribed any of the inhalers below? (GINA 4/5 ICS/LABA fixed-dose combinations)	–	–	–	–
In the past 2 weeks, has coughing, wheezing, shortness of breath, or chest tightness:				
2. Caused you to use your rescue inhaler or nebulizer more than 4 times?	–	–	–	$P < 0.05$
3. Limited the activities you want to do every day?	$P < 0.05$	–	$P < 0.05$	$P < 0.05$
4. Bothered you during the day on more than 4 days?	$P < 0.001$	–	$P < 0.001$	–
5. Woke you up from sleep more than 1 time?	–	$P < 0.05$	$P < 0.001$	$P < 0.001$
In the past 12 months has coughing, wheezing, shortness of breath, or chest tightness:				
6. Caused you to take steroid pills or shots, such as prednisone or Medrol?	$P < 0.001$	$P < 0.001$	–	–
7. Caused you to go to the emergency department or have unplanned visits to a health care provider?	–	$P < 0.001$	–	–
8. Caused you to stay in the hospital overnight?	–	–	–	–
Has coughing, wheezing, chest tightness, or shortness of breath:				
9. Ever caused you to be in an intensive care unit, have a breathing tube put down your throat, or made you think your life was in danger?	–	–	–	–
Spirometry is a breathing test where you are coached to blow all your air out as hard and as fast as you can (“blow, blow, blow”) until there is no more air to blow out:				
10. Has it been more than a year since you had this test?	–	–	–	–
In the past 2 weeks:				
11. Did you have to limit your social activities (such as visiting with friends/relatives or playing with pets/children) because of your asthma?	$P < 0.001$	$P < 0.001$	$P < 0.05$	$P < 0.05$
12. Do you feel that it is difficult to control your asthma?	–	$P < 0.001$	$P < 0.05$	$P < 0.05$
13. Has wheezing, coughing, shortness of breath, or chest tightness caused you to use your rescue inhaler or nebulizer every day?	$P < 0.001$	$P < 0.001$	$P < 0.05$	$P < 0.05$
14. Has wheezing, coughing, shortness of breath, or chest tightness limited your ability to exercise?	$P < 0.05$	–	$P < 0.001$	$P < 0.05$
15. Has wheezing, coughing, shortness of breath, or chest tightness bothered you during the day every day?	–	–	–	$P < 0.05$

Notes: ^aAdapted from Murphy KR, Chipps B, Beuther DA et al. Development of the Asthma Impairment and Risk Questionnaire (AIRQ): a composite control measure. *J Allergy Clin Immunol Pract*, volume 8(7), 2263–2274 e2265, copyright 2020, with permission from Elsevier.³ Bold rows indicate the 7 impairment questions included in the final AIRQ.

Abbreviations: ACT, Asthma Control Test; AIRQ, Asthma Impairment and Risk Questionnaire; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; NWC, not well-controlled; VPC, very poorly controlled; WC, well-controlled.

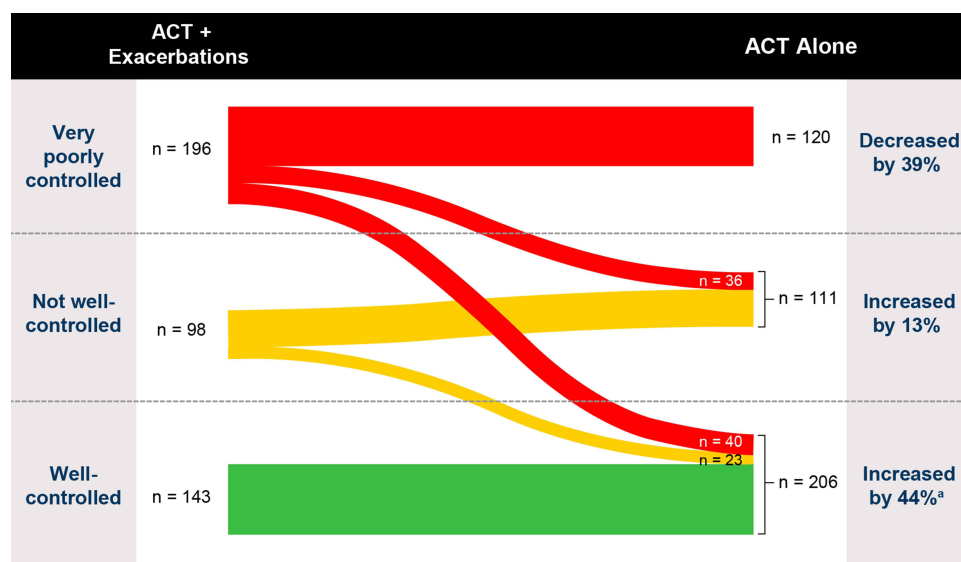


Figure 1 Patient control category distributions relative to AIRQ cross-sectional validation standards. ^a48% of patients who shifted to well-controlled went on to have ≥ 1 subsequent-year exacerbation. The change in asthma control status as noted by validation standard (ACT+ exacerbations vs ACT Alone). The shift in control groups is reflected from left to right in the figure. N = 437 for patients with baseline AIRQ and ACT, whereas n = 428 for patients with 1-year follow-up data.

findings may differ in more diverse populations and for patients with asthma outside of the US. Although the AIRQ validation standard used a validated measure of impairment, the exacerbation history criteria utilized to represent levels of risk were based on clinical judgement of the authors and their interpretation of the literature. Of note, however, the threshold used in the AIRQ cross-sectional validation standard to separate WC from uncontrolled asthma is the same threshold proposed by GINA as a risk factor for future exacerbations.²

As the AIRQ is a tool that assesses both domains of control and predicts exacerbations in patients with asthma 12 years of age and older, studies have been instituted to develop a suitable composite measure for children aged 5 to 11 years. The observations of the current study confirm the importance of employing a cross-sectional validation standard for a pediatric AIRQ that combines impairment with exacerbation history.

Conclusions

The high proportion of US adults and children with asthma who have uncontrolled disease and experience exacerbations mandate development and utilization of composite asthma assessment tools that can better identify patients with current asthma morbidity who are at risk for adverse health outcomes.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

Editorial support was provided by Karen Kurtyka, MPH, of Oxford PharmaGenesis Inc., Newtown, PA, United States, which was in accordance with Good Publication Practice (GPP 2022) guidelines and funded by AstraZeneca.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Funding

This study was supported by AstraZeneca (Wilmington, DE, USA). The Asthma Impairment and Risk Questionnaire (AIRQ) was developed with support from the AstraZeneca PRECISION program.

Disclosure

B.E. Chipps has served as an advisor, consultant, and as a speaker for AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Novartis, Regeneron, and Sanofi. R.S. Zeiger has received grants from Aerocrine, ALK-Abelló, Genentech, GlaxoSmithKline, MedImmune/AstraZeneca, Merck, Quest, Sanofi, Teva, and the National Heart, Lung, and Blood Institute; has completed consultant activity for AstraZeneca, Bayer, Genentech/Novartis, Merck, Regeneron; and holds warrant shares in DBV Technologies. D. A. Beuther has participated in advisory boards for AstraZeneca. R. A. Wise has received consultant fees and honoraria from AbbVie, AstraZeneca, Beyond Air, Boehringer Ingelheim, Bristol Myers Squibb, Contrafect, Galderma, GlaxoSmithKline, Kamada, Merck, Novartis, Pulmonx, Regeneron, Roche, Savara, and Verona. He has received grant support from AstraZeneca, Chiesi, Genentech, and Verona. W. McCann has served as a consultant and speaker for AstraZeneca; has served as a speaker for Regeneron; and has served as a consultant for Aimmune. J. Reibman has served on advisory boards for AstraZeneca, Genentech, and Novartis; has received grants from Novartis; and has received research support from AstraZeneca, Novartis, and Teva. M. George has served as a consultant to AstraZeneca, Genentech, GlaxoSmithKline, Insmed, Regeneron, and Teva; and has served as a speaker for AstraZeneca and Regeneron. I. Gilbert and J. M. Eudicone are employees of AstraZeneca and may hold stock or stock options. K.S. Coyne and G. Harding are employees of Evidera, which was contracted by AstraZeneca for study design and to collect and analyze data for this study. K. R. Murphy has served as a consultant and is a speaker for AstraZeneca, Boehringer Ingelheim, Genentech, GSK, Greer, Merck, Mylan, Novartis, Optinose, Pharming, Regeneron, Sanofi, and Teva. The authors report no other conflicts of interest in this work.

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