populations, these results should be interpreted in light of their limitations. First, the study population is limited to U.S. ICUs, and the coding algorithms may not generalize internationally. Second, the study was performed in an era of *ICD-9* reporting and could not evaluate the performance of *ICD-10* codes. However, all claims-based ICU studies are still using *ICD-9* codes. Although we would not expect the *ICD-10* crosswalk to yield different results, future studies are needed to address this issue.

On the basis of these findings, we recommend that researchers can use *ICD-9* procedure codes for mechanical ventilation alone to identify populations of mechanically ventilated patients in administrative data, with the understanding that the population captured will not represent the entire population of mechanically ventilated patients. These data suggest that researchers can be confident that identified patients will have truly been ventilated and will help characterize the patients who may have been missed by *ICD-9* procedure codes. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Meeta Prasad Kerlin, M.D., M.S.C.E.
Gary E. Weissman, M.D.
Katherine A. Wonneberger, M.D.
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Saida Kent, B.A.
University of Kentucky College of Medicine
Lexington, Kentucky

Vanessa Madden, B.S.
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Vincent X. Liu, M.D., M.S.
Kaiser Permanente Division of Research
Oakland, California

Scott D. Halpern, M.D., Ph.D.
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

ORCID IDs: 0000-0002-3239-1443 (M.P.K.); 0000-0001-9588-3819 (G.E.W.).

References

1. Kahn JM, Carson SS, Angus DC, Linde-Zwirble WT, Iwashyna TJ. Development and validation of an algorithm for identifying prolonged mechanical ventilation in administrative data. *Health Serv Outcomes Res Methodol* 2009;9:117–132.
2. Nanchal R, Kumar G, Majumdar T, Taneja A, Patel J, Dagar G, Jacobs ER, Whittle J. Utilization of mechanical ventilation for asthma exacerbations: analysis of a national database. *Respir Care* 2014; 59:644–653.
3. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med* 2010;38:1947–1953.
4. Quan H, Parsons GA, Ghali WA. Validity of procedure codes in International Classification of Diseases, 9th revision, clinical modification administrative data. *Med Care* 2004;42:801–809.
5. Mehta AB, Syeda SN, Wiener RS, Walkey AJ. Epidemiological trends in invasive mechanical ventilation in the United States: a population-based study. *J Crit Care* 2015;30:1217–1221.
6. Liu V, Herbert D, Foss-Durant A, Marelich GP, Patel A, Whippy A, Turk BJ, Ragins AI, Kipnis P, Escobar GJ. Evaluation following staggered implementation of the "Rethinking Critical Care" ICU care bundle in a multicenter community setting. *Crit Care Med* 2016;44: 460–467.
7. Liu V, Turk BJ, Ragins AI, Kipnis P, Escobar GJ. An electronic Simplified Acute Physiology Score-based risk adjustment score for critical illness in an integrated healthcare system. *Crit Care Med* 2013; 41:41–48.

Omalizumab Is Associated with Reduced Acute Severity of Rhinovirus-triggered Asthma Exacerbation

To the Editor:

Omalizumab is an anti-IgE monoclonal antibody that reduces both baseline disease activity and the risk of allergen-triggered acute exacerbations among patients with allergic asthma. The effect of omalizumab on asthma exacerbation caused by rhinovirus, the dominant trigger for acute exacerbation among children, is less well understood (1, 2). Furthermore, whether IgE-targeted therapy moderates the actual severity of acute asthma exacerbation has not been addressed.

In this observational prospective cohort study, 265 subjects aged 6 to 17 years with physician-diagnosed asthma were enrolled at the time of acute asthma exacerbation and followed until they had returned to symptomatic baseline. The Boston Children's Hospital institutional review board approved this study, and consent was obtained before participation. Study methods are published elsewhere (3). Here we present data on the subset of patients (n = 161) who were single positive only for rhinovirus (out of a panel of 12 common respiratory viruses) at the time of presentation to the emergency department with acute asthma exacerbation. Study cohort characteristics are shown in Table 1. Time to every-2-hours albuterol refers to the hours over which β-agonist therapy was weaned. A standard clinical assessment and management plan, which matched treatments to clinical symptom scores, dictated the albuterol weaning schedule. The Modified Pulmonary Index Score is a validated indicator of acute asthma exacerbation severity (4).

Comparisons were made between subjects treated with omalizumab (n = 28) and those managed primarily with inhaled

Supported by National Institutes of Health grants T32 HD040128 (D.B.K.), K12 HD047349 (D.B.K.), U01 AI110397 (W.P.), U01 AI126614 (W.P.), R01 AI073964 (W.P.), K24 AI106822 (W.P.), and U10 HL098102 (W.P.); the American Medical Association Seed Grant (D.B.K.); and the American Asthma Foundation (J.N.H.). This work was conducted with support from Harvard Catalyst, The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102), and financial contributions from Harvard University and its affiliated academic healthcare centers.

Author Contributions: D.B.K., W.P., and J.N.H.: study conceptualization, design, and implementation; data acquisition, statistical analysis, and interpretation; and manuscript preparation and critical revision. M.C.M., N.S., B.J.S., and C.D.S.: data acquisition and manuscript revision. K.A.N.: study conceptualization, design, and implementation; data acquisition; and manuscript revision. All authors agree to the final version of the manuscript and to be held accountable for all aspects of the work.

Table 1. Study Population Characteristics

	Total	Omalizumab−	Omalizumab+	*P* Value*
Enrolled, n (% total)	161 (100)	133 (83)	28 (17)	n/a
Age, mean (SD), yr	10.5 (3.2)	9.8 (3.2)	13.8 (1.66)	<0.001
Male, n (%)	100 (62)	72 (62)	82 (64)	0.486
Ethnicity, n (%)				
Black/African	80 (50)	71 (53)	10 (36)	0.100
Hispanic	21 (16)	16 (26.7)	6 (21)	0.577
White/European	42 (26)	34 (26)	8 (29)	0.813
Other	11 (7)	7 (5)	4 (14)	0.101
BMI, mean (SD)	21.2 (4.9)	21.1 (5.0)	21.7 (4.4)	0.547
Hospital disposition, n (%)				
Discharged	43 (27)	25 (19)	13 (46)	0.036
Hospital admission	115 (71)	100 (75)	15 (54)	0.036
ICU admission	68 (42)	62 (47)	6 (21)	0.020
Baseline lung function, mean (SD)				
FEV_1, % predicted	99.6 (16.0)	100.1 (17.3)	97.5 (15.8)	0.431
FEV_1/FVC	86.4 (6.3)	87.0 (6.7)	85.2 (6.1)	0.317
Composite severity, mean (SD)†	7.4 (2.9)	7.2 (3.0)	8.4 (2.1)	0.035
Adherence scale, mean (SD)‡	3.9 (0.9)	4.0 (0.9)	3.6 (0.6)	0.033
Lapsed prescription, n (%)§	79 (49.0)	67 (50.4)	12 (42.9)	0.470
Controller regimen, n (%)				
Low daily dose ICS	49 (30.4)	45 (33.8)	3 (10.7)	0.021
Medium daily dose ICS	27 (16.8)	18 (13.5)	9 (32.0)	0.025
High daily dose ICS	65 (40.4)	50 (37.5)	16 (57.2)	0.061
Oral corticosteroids	8 (5.0)	4 (3.0)	4 (14.3)	0.032
LABA	56 (34.8)	42 (32.6)	14 (50.0)	0.081
LTRA	101 (62.7)	83 (62.4)	18 (64.2)	1.000
Symptom duration, mean (SD), h	39.6 (33.1)	40.3 (33.2)	36.0 (33.1)	0.535
ImmunoCAP positives, mean (SD)‖	4.1 (1.9)	3.8 (1.9)	4.6 (2.5)	0.124
Allergen sensitization, n (%)				
Mouse	123 (76.4)	104 (78.2)	19 (67.8)	0.326
Dust mite	112 (69.5)	94 (70.7)	18 (64.3)	0.505
Total IgE, mean (SD), U/ml	672 (938)	693 (1,028)	572 (197)	0.539
Eosinophils, mean (SD), 10^3 cells/μl	0.49 (0.56)	0.49 (0.60)	0.50 (0.52)	0.913
ETS exposure (ever), n (%)	86 (53.4)	67 (50.4)	19 (67.9)	0.100
Allergen exposure, %				
Mouse¶	58	58	58	1.000
Dust mite**	54	54	50	0.790
Annual income > $25,000, n (%)	103 (64.0)	83 (62.4)	20 (71.4)	0.397
Season of exacerbation, n (%)				
Spring	59 (36.7)	51 (38.3)	8 (28.6)	0.392
Summer	41 (25.5)	37 (27.8)	4 (14.3)	0.159
Fall	43 (26.7)	31 (23.3)	12 (42.8)	0.058
Winter	18 (11.2)	14 (10.5)	4 (14.3)	0.521

Definition of abbreviations: BMI = body mass index; ETS = environmental tobacco smoke; ICS = inhaled corticosteroids; ICU = intensive care unit; LABA = long-acting β-agonist; LTRA = leukotriene receptor antagonist; n/a = not applicable.
*Student's *t* test or Pearson chi-square test for continuous and categorical variables, respectively.
†Composite Asthma Severity Index (6).
‡Medication Adherence Report Scale for Asthma (11).
§More than 60 d without filling controller prescription.
‖Greater than 0.35 kU/L.
¶One hundred eighteen dust samples collected, exposure defined as ⩾0.5 μg Mus m1/g of dust.
**Ninety-seven dust samples collected, exposure defined as ⩾2.0 μg Der f1/g of dust.

corticosteroids (ICS; n = 133). Individuals in the omalizumab group had all received treatment within the 4 weeks before study enrollment. Accounting for body weight and total IgE levels, each subject was current with their anti-IgE therapy according to a revised omalizumab dosing table (5). Multivariate linear and logistic regression analyses were used to investigate associations between predictor variables and continuous and binary outcome variables, respectively. Covariates for multivariable models were chosen based on a purposeful selection algorithm, with a significance threshold of 0.25 and a change in coefficient threshold of 20%. The following covariates were included in the multivariable models: age, sex, race, baseline FEV_1 percent predicted, composite asthma severity index (6), lapsed prescriptions (>60 d since filling controller medication), high-dose daily ICS, symptom duration before presentation, total number of immunoCAP positives (out of a panel of nine antigens), annual income, and season. A two-sided P value < 0.05 was considered significant.

Examining multiple outcome measures, we found that the acute severity of rhinovirus-triggered asthma exacerbation among omalizumab-treated patients was significantly lower than patients treated primarily with ICS therapy (Table 2), even though the omalizumab group had worse baseline disease activity (Table 1). These outcome measures included assessment of initial clinical severity (Modified Pulmonary Index Score, exacerbation peak expiratory flow), risk of hospital admission, intensity of therapeutic interventions (risk of using supplemental oxygen, noninvasive positive pressure ventilation, and intensive care unit admission), and duration of treatment (time to albuterol every 2 h and hospital length of stay). The association between omalizumab and reduced acute severity remains significant even after adjusting for the following confounders: age, sex, race, baseline lung function, baseline disease activity (6), medication adherence, controller regimen, symptoms duration, total number of immunoCAP positives (a measure of allergen-specific IgE), annual income, and season (Table 2). Omalizumab therapy was associated with a 62% reduction in the time to every-2-hours albuterol (omalizumab positive, 15 h; omalizumab negative, 30.8 h; $P < 0.001$) and also with a 42% reduction in hospital length of stay (omalizumab positive, 34.5 h; omalizumab negative, 58.5 h, $P < 0.001$). Finally, to verify that omalizumab treatment effectively interfered with binding of IgE to the cognate Fc receptor, we measured free IgE using well-established methods (7) and found that treated patients often had near undetectable free IgE levels (omalizumab positive, mean 66 ± 76.4 units/ml; omalizumab negative, 383 ± 335 units/ml; $P < 0.001$).

Rhinovirus is the dominant trigger for acute exacerbation among children with asthma and is associated with the actual severity of acute exacerbation (3). Here we report a strong association between omalizumab treatment and reduced severity of acute asthma exacerbation triggered by rhinovirus, one that is robust to the outcome measure used and encompasses several different facets of acute severity. Although previous studies have found that omalizumab reduces the risk of seasonal asthma exacerbation, to our knowledge this is the first study to offer evidence that IgE-targeted therapy might directly modify the phenotype of asthma exacerbation caused by an infectious trigger. A role for omalizumab in mitigating the severity of rhinovirus-triggered asthma exacerbation is biologically plausible, as rhinovirus has been shown to interact with allergic status to regulate asthma phenotypes (3).

Several lines of evidence suggest that the factors that contribute to the risk of asthma exacerbation may be distinct from those that regulate the actual severity of acute exacerbation in children (e.g., References 4, 8, and 9). Even in adults, the factors related to baseline disease activity demonstrate poor overall sensitivity and specificity for predicting future severe exacerbations (10). Indeed, the factors that contribute to interindividual variation in acute severity of asthma exacerbation are poorly understood and represent a considerable knowledge gap. The distinction between factors that contribute to the risk of asthma exacerbation and those that influence asthma exacerbation severity are important to understand because health care costs, morbidity, and mortality each have a strong relationship to the severity of asthma exacerbation (12).

This study has several limitations. First, this is an observational study in which patients were not randomized to receive omalizumab, so our results may be confounded by unmeasured covariates. However, it is notable that patients treated with omalizumab had significantly worse baseline disease activity than patients treated primarily with ICS (Table 1). Second, this study was not adequately powered to determine whether omalizumab mitigates the severity of acute asthma exacerbation triggered by other viruses. However, there is robust clinical and biological evidence demonstrating an interaction between rhinovirus and allergic sensitization (Reference 3 and references therein), which raises the possibility that omalizumab may specifically alter the clinical course of rhinovirus infection in pediatric patients with asthma. Last, the associations that we identified in this cohort of children presenting to the emergency department may not be generally applicable to other populations of children with asthma.

Our results suggest that therapies targeting IgE-initiated signaling events, which have been shown to modify baseline disease activity and reduce the frequency of exacerbation (2), may also be effective in reducing the actual severity of rhinovirus-triggered acute asthma exacerbation. Given the lack of antiviral therapies against rhinovirus, IgE-targeted therapies may offer a promising avenue to explore for prevention and treatment

Table 2. Omalizumab Is Associated with Reduced Acute Exacerbation Severity

	Univariate Analysis			Multivariate Analysis		
Outcomes	**Coef or OR***	**95% CI**	***P* Value**	**Coef or OR**	**95% CI**	***P* Value**
Continuous						
Exacerbation MPIS	−3.32	−4.82 to −1.82	<0.001	−2.83	−4.01 to −1.66	<0.001
Exacerbation PEF%	16.49	8.56 to 24.42	<0.001	13.72	6.99 to 20.45	<0.001
Time to albuterol every 2 h	−15.85	−24.28 to −7.43	<0.001	−16.59	−24.05 to −9.13	<0.001
Hospital length of stay	−24.01	−37.32 to −10.70	0.001	−24.57	−36.17 to −12.98	<0.001
Dichotomous						
Hospital admission	0.38	0.16 to 0.88	0.024	0.30	0.11 to 0.83	0.021
ICU admission	0.31	0.12 to 0.82	0.018	0.24	0.08 to 0.75	0.014
Supplemental O_2	0.26	0.09 to 0.74	0.011	0.24	0.07 to 0.79	0.019
Noninvasive PPV	0.17	0.04 to 0.74	0.035	0.21	0.04 to 1.01	0.052

Definition of abbreviations: CI = confidence interval; Coef = coefficient; ICU = intensive care unit; MPIS = Modified Pulmonary Index Score; OR = odds ratio; PEF = peak expiratory flow; PPV = positive pressure ventilation.
*Coefficient for continous variables and OR for dichotomous variables.

of rhinovirus-triggered severe acute asthma exacerbation in children. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

David B. Kantor, M.D., Ph.D.
Boston Children's Hospital
Boston, Massachusetts
and
Harvard Medical School
Boston, Massachusetts

Molly C. McDonald, B.A.
Nicole Stenquist, B.A.
Blake J. Schultz, M.D.
Craig D. Smallwood, R.R.T.
Boston Children's Hospital
Boston, Massachusetts

Kyle A. Nelson, M.D., M.P.H.
Wanda Phipatanakul, M.D., M.S.*
Boston Children's Hospital
Boston, Massachusetts
and
Harvard Medical School
Boston, Massachusetts

Joel N. Hirschhorn, M.D., Ph.D.*
Boston Children's Hospital
Boston, Massachusetts
Harvard Medical School
Boston, Massachusetts
and
Broad Institute of Harvard and Massachusetts Institute of Technology
Cambridge, Massachusetts

*Co–senior authors.

References

1. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, Wildfire JJ, Gergen PJ, Cohen RT, Pongracic JA, *et al*. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136: 1476–1485.
2. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, *et al*. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364:1005–1015.
3. Kantor DB, Stenquist N, McDonald MC, Schultz BJ, Hauptman M, Smallwood CD, Nelson KA, Perzanowski MS, Matsui EC, Phipatanakul W, *et al*. Rhinovirus and serum IgE are associated with acute asthma exacerbation severity in children. *J Allergy Clin Immunol* [online ahead of print] 15 Jun 2016; DOI: 10.1016/j.jaci.2016.04.044.
4. Carroll CL, Schramm CM, Zucker AR. Severe exacerbations in children with mild asthma: characterizing a pediatric phenotype. *J Asthma* 2008;45:513–517.
5. Lowe PJ, Georgiou P, Canvin J. Revision of omalizumab dosing table for dosing every 4 instead of 2 weeks for specific ranges of bodyweight and baseline IgE. *Regul Toxicol Pharmacol* 2015;71:68–77.
6. Wildfire JJ, Gergen PJ, Sorkness CA, Mitchell HE, Calatroni A, Kattan M, Szefler SJ, Teach SJ, Bloomberg GR, Wood RA, *et al*. Development and validation of the Composite Asthma Severity Index: an outcome measure for use in children and adolescents. *J Allergy Clin Immunol* 2012;129:694–701.
7. Hamilton RG, Marcotte GV, Saini SS. Immunological methods for quantifying free and total serum IgE levels in allergy patients receiving omalizumab (Xolair) therapy. *J Immunol Methods* 2005; 303:81–91.
8. Elizur A, Bacharier LB, Strunk RC. Pediatric asthma admissions: chronic severity and acute exacerbations. *J Asthma* 2007;44: 285–289.
9. Wu AC, Tantisira K, Li L, Schuemann B, Weiss ST, Fuhlbrigge AL; Childhood Asthma Management Program Research Group. Predictors of symptoms are different from predictors of severe exacerbations from asthma in children. *Chest* 2011;140:100–107.
10. McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med* 2003;168:740–759.
11. Cohen JL, Mann DM, Wisnivesky JP, Home R, Leventhal H, Musumeci-Szabó TJ, Halm EA. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy Asthma Immunol* 2009;103:325–331.
12. Lane S, Molina J, Plusa T. An international observational prospective study to determine the cost of asthma exacerbations (COAX). *Respir Med* 2006;100:434–450.

Can Dead Space Ventilation Really Be Measured without Pa_{CO_2}?

To the Editor:

We read with great interest the study by Kee and colleagues reporting the association of increased dead space ventilation with decreased diffusing capacity of the lung for carbon monoxide and exercise capacity in patients with advanced systolic heart failure (1). We fully agree with the authors that increased dead space ventilation is a major feature in patients with cardiorespiratory disorders that contributes to exertional dyspnea (2). Because dead space ventilation provides such important insight into pathophysiological alterations in these patients, there is a need to discuss how it was estimated in the study by Kee and colleagues (1).

The gold standard for dead space measurements is the physiological dead space, which is the sum of anatomical dead space and alveolar dead space and is calculated from Pa_{CO_2} and end-tidal CO_2 pressure ($P_{ET_{CO_2}}$) with the Bohr-Enghoff equation. In the study by Kee and colleagues, Pa_{CO_2} was not measured (1). Instead, it was estimated from $P_{ET_{CO_2}}$ using the equation described by Jones and colleagues in healthy subjects (3). The Jones equation relies on the assumption that the difference between Pa_{CO_2} and $P_{ET_{CO_2}}$ is of the order of 5 mm Hg and that this difference is similar in all subjects (i.e., that physiological dead space is similar in all subjects). It is predictable that such an assumption cannot be made in subjects with lung or heart disease, in whom physiological dead space is elevated in comparison with healthy subjects due to ventilation/perfusion heterogeneity in the lung. It is noteworthy that this limitation of the Jones equation was recognized at the time of publication by its authors themselves (3).

Clinical data confirm that noninvasive approaches on the basis of measurements of exhaled air fail to accurately predict Pa_{CO_2} and thus physiological V_D/V_T in the clinic. As cited by Kee and colleagues (1), Lewis and colleagues showed unequivocally that dead space ventilation estimated using the Jones equation underestimated physiological dead space ventilation when it was truly elevated in patients with lung