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Clinical characteristics of asthmatic patients with influenza-like illness and risk of severe exacerbations in Mexico

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ABSTRACT

Background: Patients with chronic inflammatory lung diseases, such as asthma, are at higher risk for influenza-like illness (ILI) complications. Viral infections are known to trigger asthma exacerbations, but a thorough description of the clinical characteristics of ILI-associated asthma exacerbations and the role of viruses as a risk factor for severe exacerbation (SE) in ILI has not been published yet.
Objective: To investigate risk factors for SE in patients with ILI and asthma.
Methods: Patients with ILI symptoms were recruited from 6 hospitals of Mexico (LaRed sites) during 2010 to 2014. Those with a previous asthma diagnosis and ILI symptoms and who were 5 years or older were included. Patients were assigned as cases or controls based on symptoms reported. SE was defined when participants presented with wheezing or dyspnea and required hospitalization.
Results: A total of 486 patients with ILI and a diagnosis of asthma were included. There were no differences in the proportion, number, or type of viral illness among those with and without SE. Those with SE were less likely to report ILI symptoms. Muscle pain and nasal drip were predictors for patients not progressing to SE. A delay in seeking medical care was associated with SE (odds ratio, 2.93; 95% CI, 1.46-5.88).
Conclusion: The presence of a particular virus did not predict SE. ILI symptoms in asthma patients are not associated with severe exacerbation. Patients with asthma should be encouraged to seek early medical care when ILI symptoms are first noticed to prevent serious complications.

Introduction

Acute respiratory infections are estimated to cause 3.9 million deaths annually; many of these infections present as influenza-like illnesses (ILIs),[1] which can be caused by many different respiratory viruses. In patients with asthma, respiratory viral infections lead to exacerbations, potentially placing the patient's life at risk and creating an economic burden to the patient, the health care system,

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and society.[2] Asthma exacerbations are responsible for half the cost of the disease and for 5000 deaths in the United States every year.[3] Several reviews suggest that viral infections are present in up to 50% of adult exacerbations and more than 60% of pediatric exacerbations.[4–6] It is estimated that the prevalence of asthma in Mexico is approximately 5%[7]; however, there are no estimates of the economic impact of an asthma exacerbation. Despite strong evidence linking viral infections to asthma exacerbations, the mechanisms by which viral infections trigger exacerbations are not fully understood.[8] Despite virus-induced exacerbation being frequently cited, few studies have found this viral involvement in asthma exacerbation.[9–11] The association between viral infections and asthma exacerbations leads to questions regarding why some patients develop severe exacerbations and others do not. It is known that in hospitalized patients with ILIs, a comorbidity associated with severity is asthma. We hypothesized that certain viral infections, patterns of ILI symptoms, and laboratory values may identify patients who develop severe asthma exacerbations that require subsequent hospitalization.

Methods

ILI002 Study

From April 2010 through March 2014, the Mexico Emerging Infectious Diseases Clinical Research Network (LaRed) began recruitment of a prospective cohort of patients with evaluating hospitalized and outpatient ILI. Participants were enrolled in 6 hospitals, 5 in Mexico City and 1 in the central city of San Luis Potosí. Recruitment occurred year round, and participants were enrolled in the study if they had at least 1 respiratory symptom and at least 1 of the following general symptoms: fever or feverishness, malaise, headache, myalgia, and/or chest pain. Once enrolled, participants had a baseline study visit to collect information on demographics, medical history, laboratory tests, and clinical care needed (outpatient, hospitalization, intensive care admission). Follow-up visits were performed on days 14 and 28 during which information on hospitalization, if any, was collected. This study was approved by the institutional review board of each participating institution; all study procedures were performed after obtaining written patient informed consent and corresponding written assent if appropriate.

Analysis Population

This subgroup analysis was restricted to those who self-reported a diagnosis of asthma on enrollment among adults and children 5 years and older. Patients were assigned case and control status based on symptoms reported at enrollment. Cases were patients with asthma exacerbation—reporting wheezing or dyspnea, and controls were those not reporting these symptoms. We further characterized asthma exacerbations into severe, requiring hospitalization, and mild, not requiring hospitalization. Because asthma is difficult to ascertain in infants and toddlers, children younger than 5 years were excluded from analysis.

Symptoms were self-reported using a standardized questionnaire at enrollment. Patients were ask about the presence of fever, dry cough, cough with phlegm, malaise, fatigue, headache, muscle pain, eye symptoms (bloodshot, watery), nasal symptoms (sneezing, drip, congestion), and gastrointestinal symptoms (nausea, diarrhea). Physical examination was conducted to determine the presence of hyperemic pharynx. If requested during clinical care, chest radiography was performed. Hospitalization outcomes were extracted from medical records.

A nasopharyngeal swab or nasal aspirate was collected at the time of recruitment. Sample processing has been described previously.[12] Viral pathogens were identified using the RespiFinder19 and RespiFinder22 kits (previously RespiFinder Plus, PathoFinder BV, Maastricht, The Netherlands), which uses a multiplex polymerase chain reaction to identify respiratory pathogens.

At enrollment, samples were collected for complete blood cell count with differential and biochemistry. Tests were performed locally using each site's standard laboratory procedures. If test were performed as part of the patient's standard of care, results were obtained from the medical record.

Statistical Analysis

To evaluate predictors of asthma exacerbations among those with ILI symptoms, we compared patients with asthma with and without severe exacerbation. Patients with mild asthma exacerbations were excluded from the analysis because misclassification of exacerbation status was a concern. The American Thoracic Society concedes that mild exacerbations may be indistinguishable from a temporary loss of asthma control.[13]

Differences in characteristics between cases and controls were evaluated using χ^2 tests or Fisher exact tests as appropriate for categorical variables and t tests or analysis of variance with a general linear model for unbalanced categories for continuous variables. Predictors that were statistically significant in univariate analyses were selected for additional analyses with logistic regression to determine their independent association with the outcome. All models controlled for age, sex, body mass index, and current cigarette smoke exposure (current smokers or exposed to secondhand smoke).

Stepwise model selection was used to identify the most parsimonious model. Covariates with univariate $P < .20$ were eligible for entry, and variables with $P < .10$ in the adjusted model were included in the final model. Analyses were conducted using the SAS statistical software (SAS Institute Inc, Cary, North Carolina) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 5,662 participants in the ILI 002 study, 486 met the eligibility criteria for this analysis (77 controls, 44 with mild exacerbations, and 365 with severe exacerbations). Characteristics of study participants are given in Table 1. Those with severe exacerbations were older and more likely to be overweight or obese and to delay seeking medical care. Among all participants with asthma, 64.0% were found to have 1 or more viral infections (Table 1). The most common viral infections were rhinovirus (29.4%), influenza A (13.2%), and coronavirus (10.1%). There was no difference in the type or number of viral infections when comparing those with severe infection and those without exacerbation.

Univariate analyses of ILI symptoms are included in Table 2. Overall, patients with severe exacerbations reported fewer ILI symptoms compared with those with no exacerbation. Cases were more likely to report cough with phlegm (76.7% vs 57.1%) and less likely to report muscle pain (32.6% vs 55.8%), eye symptoms (32.9% vs 53.3%), gastrointestinal symptoms (14.0% vs 33.8%), and sore throat (17.5% vs 49.4%). Overall, cases had more radiologic findings than controls, with the most common finding being abnormal air collection and rib or diaphragm flattening (31.5% vs 1.3%); because of the large number of missing data, results should be interpreted with caution, and no further analysis was conducted.

Those with severe exacerbations were more likely to have leukocytosis (64.9% vs 23.4%), neutrophilia (80.3% vs 57.1%), and lymphocytopenia (81.1% vs 46.8%) compared with those without exacerbations (Table 2). No differences were observed in creatine phosphokinase, lactate dehydrogenase, and C-reactive protein levels.

On the basis of univariate associations, 10 variables were identified to be assessed individually with multivariate logistic regressions (Table 3). In unadjusted analysis, being overweight or

Table 1
Characteristics and identified virus of patients with ILI and preexisting asthma enrolled In the ILI 002 study from 2010 to 2013, stratified by asthma exacerbation status[a]

Characteristic	Patients with severe asthma exacerbation[b] (n = 365)	Patients without asthma exacerbation (n = 77)	*P* value for patients with severe vs without asthma exacerbation[c]
Age, mean (SD), y	37.0 (16.1)	29.6 (18.1)	<.001
Age group, y			
5-18	28 (7.7)	19 (24.7)	<.001
≥18	337 (92.3)	58 (75.3)	
Female sex	250 (68.5)	46 (59.7)	.14
Time from symptom onset until seeking care, d			
0-1	166 (45.5)	58 (75.3)	<.001
2-3	98 (26.9)	12 (15.6)	
≥4	100 (27.4)	7 (9.1)	
Current smoke exposure[d]	66 (18.1)	10 (13.0)	.28
Overweight or obese	236 (64.7)	37 (48.1)	.01
Isolated viruses	232 (63.6)	51 (66.2)	.66
No. of isolated viruses			
0	133 (36.4)	26 (33.8)	.64
1	195 (53.4)	43 (55.8)	
2	35 (9.6)	7 (0.1)	
3-4	2 (0.6)	1 (1.3)	
Type of virus			
Rhinovirus	109 (29.9)	22 (28.6)	.82
Respiratory syncytial virus[e]	17 (4.7)	5 (6.5)	.50
Influenza A[f]	46 (12.6)	12 (15.6)	.48
Influenza B	9 (2.5)	2 (2.6)	.99
Coronavirus[g]	33 (9.0)	11 (14.3)	.16
Parainfluenza virus[h]	22 (6.0)	3 (3.9)	.59
Other[i]	31 (8.5)	3 (3.9)	.24

Abbreviation: ILI, influenza-like illness.
[a]Data are presented as number (percentage) of patients unless otherwise indicated.
[b]Those reporting lower respiratory tract symptoms (wheezing or dyspnea) only were classified as having a mild asthma exacerbation. Those reporting lower respiratory tract symptoms and requiring hospitalization were classified as having a severe asthma exacerbation.
[c]The χ^2 statistic *P* values for categorical variables (Fisher exact test *P* value if any cell had n < 5) and *t* test *P* values for continuous variables. Missing categories were omitted from the χ^2 tests.
[d]Never and former smokers were classified as having no current smoke exposure; passive and current smokers were classified as having current smoke exposure.
[e]Respiratory syncytial virus group includes both respiratory syncytial viruses A and B.
[f]Influenza A group includes H3N1 and H1N1v.
[g]Coronavirus group includes 229E, NL63, OC43, and HKU1.
[h]Parainfluenza virus group includes parainfluenza viruses 1 through 4.
[i]Other group includes adenovirus, metapneumovirus, and bocavirus.

Table 2
Signs, symptoms, and laboratory findings in patients with ILI and preexisting asthma, stratified by asthma exacerbation status[a]

Finding	Patients with severe asthma exacerbation (n = 365)	Patients with without asthma exacerbation (n = 77)	*P* value for patients with severe vs without asthma exacerbation[b]
Symptoms			
No. of symptoms, mean (SD)	5.7 (2.6)	7.2 (3.0)	<.001
Fever	186 (51.0)	46 (59.7)	.16
Dry cough	103 (28.2)	30 (39.0)	.07
Cough with phlegm	280 (76.7)	44 (57.1)	<.001
Malaise or fatigue	285 (78.1)	65 (84.4)	.21
Headache	236 (64.7)	55 (71.4)	.25
Muscle pain	119 (32.6)	43 (55.8)	<.001
Eye symptoms[c]	120 (32.9)	41 (53.3)	<.001
Nasal symptoms[d]	277 (75.9)	64 (83.1)	.17
Gastrointestinal symptoms[e]	51 (14.0)	26 (33.8)	<.001
Hyperemic pharynx	64 (17.5)	38 (49.4)	<.001
Laboratory findings			
Leukocytosis[f]	237 (64.9)	18 (23.4)	<.001
Neutrophilia[f]	293 (80.3)	44 (57.1)	.002
Lymphocytopenia[f]	296 (81.1)	36 (46.8)	<.001
CPK[f]	44 (12.1)	5 (6.5)	.15
LDH[f]	219 (60.0)	51 (66.2)	.39
C-reactive protein[f]	180 (49.3)	41 (53.3)	.95

Abbreviations: CPK, creatine phosphokinase; ILI, influenza-like illness; LDH, lactate dehydrogenase.
[a]Data are presented as number (percentage) unless otherwise indicated.
[b]The χ^2 statistic *P* values for categorical variables (Fisher exact test *P* value if any cell had n < 5). Missing categories were omitted from the χ^2 tests.
[c]Eye symptoms included bloodshot or watery eyes.
[d]Nasal symptoms included sneezing, nasal drip, or nasal congestion.
[e]Gastrointestinal symptoms included nausea or diarrhea.
[f]Laboratory references are as follows: leukocytes, greater than 10×10^3 cells/mm^3; neutrophil, greater than 62%; lymphocytes, less than 20%; CPK, greater than 308 IU/L for males and greater than 192 IU/L for women; LDH, greater than 192 IU/L; and C-reactive protein, greater than 0.8 g/dL.

Table 3
Unadjusted and adjusted ORs for the association of symptoms and laboratory findings with severe asthma exacerbations

Predictor	No. of patients	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Overweight or obese	434	1.90 (1.15-3.15)	1.57 (0.92-2.67)
Cough with phlegm	434	2.47 (1.48-4.12)	2.38 (1.39-4.07)
Muscle pain	434	0.38 (0.23-0.63)	0.39 (0.23-0.67)
Eye symptoms	434	0.43 (0.26-0.71)	0.42 (0.25-0.70)
Gastrointestinal symptoms	434	0.32 (0.18-0.56)	0.36 (0.20-0.65)
Hyperemic pharynx	434	0.22 (0.13-0.37)	0.25 (0.14-0.43)
Leukocytosis	425	6.09 (3.43-10.82)	7.15 (3.85-13.30)
Neutrophilia	398	2.58 (1.39-4.79)	2.74 (1.42-5.29)
Lymphocytopenia	409	4.11 (2.32-7.27)	4.47 (2.43-8.23)
Time from onset to seeking medical attention, d			
0-1 vs 2-3	433	2.85 (1.46-5.58)	2.93 (1.46-5.88)
0-1 vs ≥4		4.99 (2.19-11.36)	5.32 (2.18-12.98)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Logistic regression model 1 was adjusted for age, sex, and current smoke exposure. All remaining models were adjusted for age, sex, current smoke exposure, and overweight or obese status.

obese increased the risk of severe exacerbations. However, after adjusting for age, sex, and current smoke exposure, the association was no longer significant (odds ratio [OR], 1.57; 95% CI, 0.92-2.67). After adjusting for age, sex, current smoke exposure, and overweight or obese status, cough with phlegm (OR, 2.38; 95% CI, 1.39-4.07), leukocytosis (OR, 7.15; 95% CI, 3.85-13.30), neutrophilia (OR, 2.74; 95% CI, 1.42-5.29), and lymphocytopenia (OR, 4.47; 95% CI, 2.43-8.23) were associated with increased odds of severe exacerbation. Patients reporting muscle pain (OR, 0.39; 95% CI, 0.23-0.67), eye symptoms (OR, 0.42; 95% CI, 0.25-0.70), gastrointestinal symptoms (OR, 0.36; 95% CI, 0.20-0.65), and a sore throat (OR, 0.25; 95% CI, 0.14-0.43) were less likely to experience a severe exacerbation. Finally, compared with those who sought medical attention within 0 to 1 days of symptom onset, patients who delayed 2 to 3 days (OR, 2.93; 95% CI, 1.46-5.88) and 4 or more days (OR, 5.32; 95% CI, 2.18-12.98) were at increased risk for a severe exacerbation.

After stepwise modeling of the 14 symptoms and 5 demographic variables (Fig 1), 5 key were identified: Cough with phlegm and delay in seeking medical care were associated with higher odds for severe asthma exacerbation, whereas muscle pain and nasal drip were associated with reduced odds.

Discussion

As far as we know, this is the first study evaluating asthma exacerbations associated with ILI in Mexico. In our population, 64% of individuals had an etiologic agent identified, among them rhinovirus, influenza, and coronavirus, which have been reported in the literature as associated with asthma and asthma exacerbations.[2,14] Nonetheless, we did not find any virus associated with exacerbations, and the distribution of viral infections among those with severe asthma exacerbations was the same as the entire asthmatic population overall.

Although it is generally accepted that viral infections can be associated with asthma exacerbations, there is controversy about how frequently exacerbations are triggered by viral infections. Some studies report an association, particularly among children, whereas others have not found that viruses are associated with asthma exacerbation.[15–17] Multiple studies have implicated rhinovirus as an important trigger, especially among children. Rhinovirus infections were found to be associated with hospital readmissions attributed to asthma among children younger than 13 years, a frequent cause of hospital admission due to asthma among children younger than 5 years,[18] and associated with asthma exacerbations among children 2 to 17 years old.[11,19] It has also been suggested that members of the Rhinovirus family might be more virulent and/or have a greater propensity to cause exacerbation.[20,21] Given the aforementioned studies, we suspect that we were unable to detect an association because our patient population is mainly adults; therefore, our results are most relevant to adults with asthma, and perhaps we did not find a stronger association because all participants had ILI. Our findings suggest that viral infections alone are not the only contributors to adult asthma exacerbations, and efforts should instead be made to assess other factors known to be involved in severe exacerbations. Asthma control[13,22–25] and environmental allergens[26] together with viral infections are likely responsible for the risk factors for hospital admission.[11]

We found that delaying medical care after onset of symptoms was associated with severe exacerbation. Receiving care might have prevented some asthmatic patients from having an exacerbation. Our results suggest that asthmatic patients should be assessed by a medical practitioner as soon as they develop ILI symptoms because delaying care might increase the risk of a severe exacerbation. Our findings mirror those from a recent study published by the Centers for Disease Control and Prevention evaluation

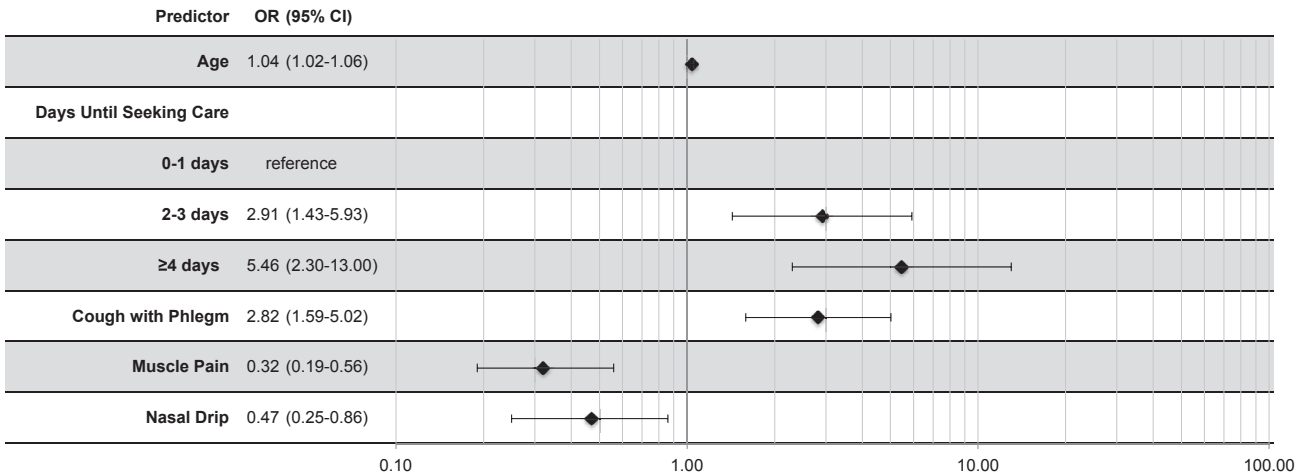

Figure 1. Base model included the following covariates: age, sex, current smoke exposure, overweight or obese, delay since onset of symptoms until seeking treatment in days, and 14 symptom variables (fever, dry cough, cough with phlegm, fatigue, headache, muscle pain, bloodshot eyes, watery eyes, sneezing, nasal drip, nasal congestion, nausea, diarrhea, and malaise). Backwards stepwise regression was used to identify covariates eligible for inclusion in the model ($P < .20$) and allowed covariates with an adjusted $P < .10$ to be included in the final model. CI, confidence interval; OR, odds ratio.

of the 2009 influenza pandemic, where they found that although most adults with underlying medical conditions were more likely to report ILI, they were not more likely to seek urgent medical attention compared with those who did not have an underlying medical condition.[27] Together, these findings suggest a need to better understand health care–seeking behaviors and barriers among these patients.

We were unable to assess symptoms unique to severe exacerbations during viral infections because all participants in this study had ILI. That is, we had no control group of patients who did not have an exacerbation without ILI.

In our study population, the presence of leukocytosis, neutrophilia, and lymphocytopenia was associated with severe exacerbations. Lymphocytopenia is more closely associated with viral infections.[28] The presence of increased leukocytes and neutrophils may be associated with the heterogeneous inflammatory response, possibly attributable to preexisting inflammation due to asthma that might be worsened by exposure to the virus. Production of chemokines by bronchial epithelium in response to a viral infection leads to the entry of neutrophils to the respiratory airways, as confirmed on experimental and naturally induced common cold among asthmatic patients.[29] Neutrophilia in the airways is associated with increased levels of elastase interleukin-6 and interleukin-8 and lactate dehydrogenase, a marker of epithelial injury, but also with bacterial exacerbations. Therefore, it is not always clear which mechanism drives the neutrophil elevation. Although these laboratory parameters are consistent with the high prevalence of viral infections among our patient population, these responses can also be seen in bacterial infections.[29,30] Our results suggest that in patients with asthma and ILI, these laboratory tests might be useful to predict severe exacerbations, although we were not able to determine whether these increases occurred before the exacerbation and whether the patient has a viral or bacterial infection.

Obesity has also been reported as a risk factor for severe asthma exacerbations.[31,32] In a multicentric study in the United States, across 48 emergency departments and 23 states, adults who were obese had a higher risk of hospitalizations than those with normal weight.[32] In our population, nearly 40% of participants were overweight or obese. However, after adjusting for age, current tobacco use, and sex, we did not find an association with exacerbations. Asthma exacerbations are closely tied to asthma control, and the evidence linking obesity to asthma controls is mixed, with studies supporting[32–36] and refuting an association.[37–39] A Cochrane review of weight loss interventions to improve asthma control concluded that there may be weak associations, but noted that research in this area is lacking.[40] Our failure to find an association could be confounded by our inability to assess asthma control before entry into the study. In addition, given that our univariate association was significant, and we did not find a significant adjusted association, our sample size may have been insufficient to detect a weak association.

Our study had limitations that might affect the interpretation of our findings. Because this is a secondary data analysis of an ILI study, participants were selected if they met the criteria for ILI. Therefore, our findings are not generalizable to other types of asthma exacerbations, such as allergen, pollutant, cold, or exercise-induced exacerbations. Asthma was self-reported with no information being collected on accuracy of diagnosis, prescribed medications, or adequacy of asthma symptom control. Information regarding environmental exposures was not collected beyond cigarette use and exposure or on pulmonary function. This information might have been valuable to accurately classify participants, particularly those with mild exacerbations. We also only have information on asthma symptoms on the day of recruitment, and do not have data on symptoms before or after enrollment into the study. For this reason, there may be some misclassification of exacerbation status. However, we have no reason to believe that the misclassification bias is informative and thus only reduces the precision but not the accuracy of our estimates. Finally, patients were recruited from specialty hospitals and are therefore not representative of the overall population.

Despite the limitations, this is the first analysis that highlights ILI symptoms as predictors of severe asthma exacerbations. We benefitted from having access to a standardized cohort that recruited more than 5000 participants for 4 consecutive years, with data collection throughout the year, minimizing the potential for seasonal bias. Asthma patients included adults and children recruited from multiple communities in Mexico. Finally, our study confirmed previous studies conducted on virus-induced asthma exacerbations.

Despite identifying a high proportion of viral infections in participants with ILI and asthma, the presence of respiratory viral infections was not predictive of exacerbations contrary to our hypothesis. ILI symptoms in patients with asthma may not be useful to predict potential severe asthma exacerbation. However, those with asthma should be encouraged to seek early medical care when ILI symptoms occur to prevent serious asthma complications.

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