Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Clinical characteristics of asthmatic patients with influenza-like illness and risk of severe exacerbations in Mexico

Paulina Paulin-Prado, MD; Katherine Nishimura, PhD, MPH; Laura Freimanis-Hance, MD, PhD; Sally Hunsberger, PhD; John Beigel, MD; Arturo Galindo Fraga, MD; Ana A. Ortiz Hernandez, MD; Beatriz Llamosas-Gallardo, MD; Sarbelio Moreno-Espinosa, MD; Martin Magaña-Aquino, MD; Guillermo M. Ruiz Palacios, MD; Alejandra Ramirez-Venegas, MD; on behalf of the Mexico Emerging Infectious Diseases Clinical Research Network

**Institute Nacional de Enfermedades Respiratorias, Mexico City, Mexico**

1. National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

2. Leidos Biomedical, Bethesda, Maryland

3. Westat, Rockville, Maryland

4. Hospital Infantil de México "Dr. Federico Gómez," Mexico City, Mexico

5. Hospital Central "Dr. Ignacio Morones Prieto," San Luis Potosí, México

**Article info**

**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 ILI and asthma 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.

© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

**Introduction**

Acute respiratory infections are estimated to cause 3.9 million deaths annually; many of these infections present as influenza-like illnesses (ILI), 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, and the community.

**Reprints:** Alejandra Ramirez-Venegas, MD, Instituto Nacional de Enfermedades Respiratorias, Calzada de Tlalpan 4502, Col. Sección XVI, Del. Tlalpan, C.P. 14080, Mexico City, Mexico; E-mail: aleravas@hotmail.com.

**Disclaimer:** The content of this publication does not necessarily reflect the views or policies of the US Department of Health and Human Services, Leidos Biomedical, or Westat, and mention of trade names, commercial products, or organizations does not imply endorsement by the US government.

**Disclosure:** The authors have nothing to disclose.
Asthma exacerbations are responsible for half the cost of the disease and for 5000 deaths in the United States every year. Several reviews suggest that viral infections are present in up to 50% of adult exacerbations and more than 60% of pediatric exacerbations. It is estimated that the prevalence of asthma in Mexico is approximately 5%1; 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.3 Despite virus-induced exacerbation being frequently cited, few studies have found this viral involvement in asthma exacerbation.3-8 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 asked 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 enrollment. Sample processing has been described previously.12 Viral pathogens were identified using the 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 χ2 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 (32.9% vs 55.8%), eye symptoms (32.5% 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 lymphopenia (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

| Characteristic                        | Patients with severe asthma exacerbation (n = 365) | Patients without asthma exacerbation (n = 77) | P value for patients with severe vs without asthma exacerbation |
|---------------------------------------|--------------------------------------------------|---------------------------------------------|---------------------------------------------------------------|
| 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                | 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 (9.1)                                     |                                                              |
| 3-4                                   | 2 (0.6)                                          | 1 (1.3)                                     |                                                              |
| Type of virus                         |                                                  |                                             |                                                              |
| Rhinovirus                            | 109 (29.9)                                       | 22 (28.6)                                   | .82                                                          |
| Respiratory syncytial virus           | 17 (4.7)                                         | 5 (6.5)                                     | .50                                                          |
| Influenza A                           | 46 (12.6)                                        | 12 (15.6)                                   | .48                                                          |
| Influenza B                           | 9 (2.5)                                          | 2 (2.6)                                     | .99                                                          |
| Coronavirus                           | 33 (9.0)                                         | 11 (14.3)                                   | .16                                                          |
| Parainfluenza virus                   | 22 (6.0)                                         | 3 (3.9)                                     | .59                                                          |
| Other                                 | 31 (8.5)                                         | 3 (3.9)                                     | .24                                                          |

Abbreviation: ILI, influenza-like illness.

*Data are presented as number (percentage) of patients unless otherwise indicated.

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

| Finding                          | Patients with severe asthma exacerbation (n = 365) | Patients without asthma exacerbation (n = 77) | P value for patients with severe vs without asthma exacerbation |
|----------------------------------|--------------------------------------------------|---------------------------------------------|---------------------------------------------------------------|
| 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                      | 120 (32.9)                                       | 41 (53.3)                                   | <.001                                                        |
| Nasal symptoms                   | 277 (75.9)                                       | 64 (83.1)                                   | .17                                                          |
| Gastrointestinal symptoms        | 51 (14.0)                                        | 26 (33.8)                                   | <.001                                                        |
| Hyperemic pharynx                | 64 (17.5)                                        | 38 (49.4)                                   | <.001                                                        |
| Laboratory findings              |                                                  |                                             |                                                              |
| Leukocytosis                      | 237 (64.9)                                       | 18 (23.4)                                   | <.001                                                        |
| Neutrophilia                      | 293 (80.3)                                       | 44 (57.1)                                   | .002                                                         |
| Lymphocytopenia                   | 296 (81.1)                                       | 36 (46.8)                                   | <.001                                                        |
| CPK                              | 44 (12.1)                                        | 5 (6.5)                                     | .15                                                          |
| LDH                              | 219 (60.0)                                       | 51 (66.2)                                   | .39                                                          |
| C-reactive protein               | 180 (48.3)                                       | 41 (53.3)                                   | .95                                                          |

Abbreviations: CPK, creatine phosphokinase; ILI, influenza-like illness; LDH, lactate dehydrogenase.

*Data are presented as number (percentage) of patients unless otherwise indicated.

*The **P** value for categorical variables (Fisher exact test) was used if any cell had n < 5. Missing categories were omitted from the **P** tests.

*Symptoms included bloodshot or watery eyes.

*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 females; and C-reactive protein, greater than 0.8 g/dL.
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, 0.25-0.67), 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.

### Table 3

| Predictor                                    | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|----------------------------------------------|------------------------|----------------------|
| Overweight or obese                          | 1.90 (1.15-3.15)       | 1.57 (0.92-2.67)     |
| Cough with phlegm                            | 2.47 (1.48-4.12)       | 2.38 (1.39-4.07)     |
| Muscle pain                                  | 0.38 (0.23-0.63)       | 0.39 (0.23-0.67)     |
| Eye symptoms                                 | 0.43 (0.26-0.71)       | 0.42 (0.25-0.70)     |
| Gastrointestinal symptoms                    | 0.32 (0.18-0.56)       | 0.36 (0.20-0.65)     |
| Hyperemic pharynx                            | 0.22 (0.13-0.37)       | 0.25 (0.14-0.43)     |
| Leukocytosis                                 | 6.09 (3.43-10.82)      | 7.15 (3.85-13.30)    |
| Neutrophilia                                 | 2.58 (1.39-4.79)       | 2.74 (1.42-5.29)     |
| Lymphocytopenia                              | 4.11 (2.32-7.27)       | 4.47 (2.43-8.23)     |
| Leukocytosis                                 | 6.09 (3.43-10.82)      | 7.15 (3.85-13.30)    |
| Neutrophilia                                 | 2.58 (1.39-4.79)       | 2.74 (1.42-5.29)     |
| Lymphocytopenia                              | 4.11 (2.32-7.27)       | 4.47 (2.43-8.23)     |

Abbreviations: CI, confidence interval; OR, odds ratio.

*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.

### 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. Nonetheless, we did not find any virus associated with exacerbations, and the distribution of viral infections among those with severe 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. 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, and associated with asthma exacerbations among children 2 to 17 years old. It has also been suggested that members of the Rhinovirus family might be more virulent and/or have a greater propensity to cause exacerbation. 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 and environmental allergens together with viral infections are likely responsible for the risk factors for hospital admission.

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.
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. 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. 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. 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. 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. 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. 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 and refuting an association. 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. Our failure to find an association could be confounded from having access to a standardized cohort that 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.

Acknowledgments

Principal investigators, coprincipal investigators, and study staff include the following: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán: M. Lourdes Guerrero, Diana Aguilar Cruz, Brícia Roa, Itzel Cruz, Marco Villanueva Reza, Santiago Pérez Patrígdon, María del Pilar Ramos Cervantes, Luis Alberto García Andrade, Violeta Ibarra, Fernando Ledesma, Julieta Martínez–López, Delia G. Isidoro Fernández, Juana Flores; Hospital General y de Alta Especialidad Dr. Manuel Gea González: Irma Jiménez Escobar, Ana Laura Corona, Adriana Magaly Farfán Zúñiga, Patricia Rodríguez Zulueta, Lorena Hernández Delgado, Javier Martínez García; Instituto Nacional de Pediatría: Juliana Estévez, Diana Andrade; Instituto Nacional de Enfermedades Respiratorias: Angélica Nolasco, Nora Edith Bautista, José Velásquez; Hospital Infantil de México Federico Gómez: Brizard López Martínez, Mónica González, Luis Mendoza, Ana Estela Gamiño; San Luis Potosí: Hospital Central Dr. Ignacio Morones Prieto/Universidad Autónoma de San Luis Potosí: Luis Fernando Pérez, Javier Araujo Meléndez, Alejandro Gómez Gómez, Juana del Carmen Báez Cruz, Norma Perea, Elvira Fuentes, Ana Sandoval Fuentes; Universidad Autónoma de San Luis Potosí: Daniel Ernesto Noyola Cherpil, Christian Alberto García Sepúlveda, Daniel Hernández Ramírez, Network Coordinating Center: Juan-Francisco Galán-Herrera, Hugo Arroyo-Figueroa, Nadine Mascareñas, Jessica Ponce Malagón, Sarahy Segura; National Institute of Allergies and Infectious Disease: Cliff Lane, Mary Smol skis, Dean Follmann, Sally Hunsberger, Wenjuan Gu; Leidos Biomedical Research Inc: Theresa Engel; Westat Inc: Isabel Trejos Salguero, Yolanda Bertucci.

References

[1] World Health Organization. World Health Report 2002. Geneva, Switzerland: World Health Organization; 2002.
[2] Kurao D, Saraya T, Ishii H, Takizawa H. Virus-induced exacerbations in asthma and COPD. Front Microbiol. 2013;4:293.
[3] Proud D, Wai Chow CW. Role of viral infections in asthma and chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2006;35:513–518.
[4] Teichtahl H, Buckmaster N, Pertnikovs E. The incidence of respiratory tract infection in adults requiring hospitalization for asthma. Chest. 1997;112: 591–596.
[5] Tan WC, Xiang X, Qiu D, Ng TP, Lam SF, Hegele RG. Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease. Am J Med. 2003;115:272–277.
[6] Murray CS, Simpson A, Custovic A. Allergens, viruses, and asthma exacerbations. Am Thorac Soc. 2004;1:99–104.
[7] Del-Río-Navarro B, Del-Río-Chivardi JM, Berber A, Sienra-Monge JJ, Rosas-Vargas MA, Baeza-Bacab M. Asthma prevalence in children living in north Mexico City and a comparison with other Latin American cities and world regions. Allergy Asthma Proc. 2006;27:334–340.

[8] Leigh R, Proud D. Virus-induced modulation of lower airway diseases: pathogenesis and pharmacologic approaches to treatment. Pharmaco Ther. 2015;148:185–198.

[9] Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. BMJ. 1995;310:1225–1229.

[10] Nicholson KG, Kent J, Ireleand DC. Respiratory viruses and exacerbations of asthma in adults. BMJ. 1993;307:982–986.

[11] Johnston SL, Pattemore PK, Sanderson G, et al. Relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. Am J Respir Crit Care Med. 1996;154:654–660.

[12] Galindo-Fraga A, Ortiz-Hernández AA, Ramírez-Venegas A, et al. Clinical characteristics and outcomes of influenza and other influenza-like illnesses in Mexico City. Int J Infect Dis. 2013;17:e510–e517.

[13] Reddel HK, Taylor DR, Batenman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180:1096–1103.

[14] Tan WC. Viruses in asthma exacerbations. Curr Opin Pulm Med. 2005;11:21–26.

[15] van Elden LJ, Sachs AP, van Loon AM, et al. Enhanced severity of virus associated lower respiratory tract disease in asthma patients may not be associated with delayed viral clearance and increased viral load in upper respiratory tract. Clin Virol. 2008;41:116–121.

[16] Corne JM, Marshall C, Smith S, et al. Frequency, severity and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. Lancet. 2002;359:831–834.

[17] Murray KS, Polerti G, Kebadze T. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. Thorax. 2006;61:376–382.

[18] Miller EK, Lu X, Erdman DD, et al.; New Vaccine Surveillance Network. Rhinovirus-associated hospitalizations in young children. J Infect Dis. 2007;195:773–781.

[19] Khetsuriani N, Kazerouni NN, Erdman DD, et al. Prevalence of viral respiratory tract infections in children with asthma. J Allergy Clin Immunol. 2007;119:314–321.

[20] Miller EK, Khuri-Bulos N, Williams IV, et al. Human rhinovirus C associated with wheezing in hospitalised children in the Middle East. J Clin Virol. 2009;46:85–89.

[21] Lau SK, Yip CC, Lin AW, et al. Clinical and molecular epidemiology of human rhinovirus C in children and adults in Hong Kong reveals a possible distinct human rhinovirus C subgroup. J Infect Dis. 2005;200:1096–1103.

[22] Jackson DJ, Trujillo-Torralbo MB, del-Rosario J, et al. The influence of asthma control on the severity of virus-induced asthma exacerbations. J Allergy Clin Immunol. 2015;136:497–500.e3.

[23] Watase H, Hagiwara Y, Chiba T, Camargo CA Jr, Hasegawa K. Multicentre observational study of adults with asthma exacerbations: who are the frequent users of the emergency department in Japan? BMJ Open. 2015;5:1–7.

[24] Wells RE, Garb J, Fitzgerald J, Kleppel R, Rothberg MB. Factors associated with emergency department visits in asthma exacerbation. South Med J. 2015;108:276–280.

[25] Hasegawa K, Bittner JC, Nonas SA, et al. Children and adults with frequent hospitalizations for asthma exacerbation, 2012-2013: a multicenter observational study. J Allergy Clin Immunol Pract. 2015;3:751–758.e1.

[26] Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. BMJ. 2002;324:1–5.

[27] Biggerstaff M, Jung MA, Reed C, Fry AM, Balluz L, Finelli L. Influenza-like illness, the time to seek healthcare, and influenza antiviral receipt during the 2010–2011 influenza season-United States. J Infect Dis. 2014;210:535–544.

[28] Wang L, Chang LS, Lee IK, et al. Clinical diagnosis of pandemic A(H1N1) 2009 influenza in children with negative rapid influenza diagnostic test by lymphotoxin and lower C-reactive protein levels. Influenza Other Respir Viruses. 2014;8:91–98.

[29] Pizzichini MM, Pizzichini E, Efthimiadis A, et al. Asthma and natural colds: inflammatory indices in induced sputum: a feasibility study. Am J Respir Crit Care Med. 1998;158:1178–1184.

[30] Wark PAR, Gibson PG. Asthma exacerbations 3: pathogenesis. Thorax. 2006;61:909–915.

[31] Hasegawa K, Tsugawa Y, Lopez BL, Smithline HA, Sullivan AF, Camargo CA. Body mass index and risk of hospitalization among adults presenting with asthma exacerbation to the emergency department. Ann Am Thorac Soc. 2014;11:1439–1444.

[32] Schatz M, Zeiger RS, Yang SJ, et al. Prospective study on the relationship of obesity to asthma impairment and risk. J Allergy Clin Immunol Pract. 2015;3:560–565.e1.

[33] Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med. 2006;100:648–657.

[34] Mosen DM, Schatz M, Magid DJ, Camargo CA Jr. The relationship between obesity and asthma severity and control in adults. J Allergy Clin Immunol. 2008;122:507–511.e6.

[35] Farah CS, Kermode JA, Downie SR, et al. Obesity is a determinant of asthma control independent of inflammation and lung mechanics. Chest. 2011;140:659–666.

[36] Pisi R, Aiello M, Tzani P, et al. Overweight is associated with airflow obstruction and poor disease control but not with exhaled nitric oxide change in an asthmatic population. Respiration. 2012;84:416–422.

[37] Clerisme-Beaty EM, Karam S, Rand C, et al. Does higher body mass index contribute to worse asthma control in an urban population? J Allergy Clin Immunol. 2009;124:207–212.

[38] Sastre J, Olaguíbel JM, López Viña A, et al. Increased body mass index does not influence of asthma exacerbation to the emergency department. Ann Allergy Asthma Immunol. 2013;110:660–666.

[39] Adeniyi FB, Young T. Weight loss interventions for chronic asthma. Cochrane Database Syst Rev. 2012;7:CD009339.