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Original Article

Serum IgG Concentrations in Adult Patients Experiencing Virus-Induced Severe Asthma Exacerbations

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What is already known about this topic? Many patients suffering from asthma experience virus-induced asthma exacerbations, but the pathophysiology is not fully understood and no biomarkers have been found to predict severity.

What does this article add to our knowledge? Patients hospitalized for asthma exacerbations associated with a positive virus sample have lower serum IgG level than do their negative counterparts. Longer hospital stays and a longer duration of oral steroids were linked to lower serum IgG concentrations.

How does this study impact current management guidelines? Serum IgG quantification during asthma exacerbations may be lower in patients with positive virus samples but more data are needed.

BACKGROUND: Patients experiencing severe asthma exacerbations have a poorer quality of life and an increase in morbidity and mortality. Viruses are frequently involved in asthma exacerbations.
OBJECTIVE: To determine the value of measuring serum IgG concentrations in asthma exacerbations and assess their link with viral infections in patients hospitalized for asthma.
METHODS: Patients hospitalized for asthma exacerbation were included in an observational study from January 1, 2015, to December 31, 2015. Serum IgG concentrations on admission were compared between patients with a positive upper airway viral sample and those with a negative viral sample.
RESULTS: Among the 82 patients included, those with positive viral nasopharyngeal samples (n = 40) presented with lower serum IgG concentrations during exacerbation than those with a negative viral sample (n = 42) (10.1 ± 2.3 g/L vs 11.5 ± 3.6 g/L; $P < .05$). The median concentration of serum IgG was lower in patients hospitalized for more than 3 days compared with those hospitalized for less than 3 days (10.0 g/L [8.2-12.4] vs 11.4 g/L [10.1-12.8]; $P < .05$) and in patients who received oral corticosteroid therapy for more than 5 days compared with those treated with oral steroids for less than 5 days (10.1 g/L [8.3-12.2] vs 11.6 g/L [10.0-13.8]; $P < .05$).
CONCLUSIONS: Serum IgG level was significantly lower when asthma exacerbations were associated with positive viral samples. The patients with lower serum IgG concentrations required longer hospitalizations and longer courses of steroids. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1507-13)

Key words: *Asthma; IgG; Virus; Exacerbation*

INTRODUCTION

Asthma is a chronic respiratory disease associated with airway inflammation.[1] This disease affects approximately 334 million people worldwide and its prevalence is increasing.[2] According to the latest World Health Organization estimates released in December 2016, there were 383,000 asthma-related deaths in 2015.[3] Most of these deaths occur in low- and middle-income countries.[3]

Exacerbations play an important role in asthma morbidity and mortality.[4] An exacerbation is defined as acute or subacute episodes of progressive worsening respiratory symptoms.[5] A severe exacerbation corresponds to an emergency consultation or hospitalization.[6] Asthma is an increasingly common cause of emergency department consultations.[7] Twenty percent of patients with asthma have experienced exacerbations requiring treatment within the emergency department or hospitalization and these patients account for more than 80% of the total direct costs of asthma.[8] Mortality among patients hospitalized for asthma exacerbations accounts for one-third of all asthma-related deaths.[9]

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Abbreviations used
COPD- Chronic obstructive pulmonary disease

Infections with pulmonary tropism are very frequently involved in triggering asthma exacerbations (40%-80% of cases)[10] and are more often associated with failure of conventional treatments in patients with asthma.[11] Rhinovirus, human metapneumovirus, enterovirus, coronavirus, and respiratory syncytial virus are the most common viruses found in asthma exacerbations.[12] Rhinovirus is particularly related to asthma exacerbations and is found in 60% of children experiencing asthma exacerbations.[12] In adults, rhinovirus also seems to be frequently involved in asthma exacerbations.[13]

Regarding virus-induced asthma exacerbations, the antiviral response is complex and involves immune cells leading to the release of inflammatory mediators.[14,15] Immunoglobulins play a key role in the antiviral response, but knowledge remains limited about their involvement in virus-induced asthma exacerbations. Interestingly, it has recently been shown that patients with primary hypogammaglobulinemia are more likely to suffer from viral infections, including rhinovirus, compared with healthy subjects, in spite of intravenous immunoglobulin replacement.[16] The prevalence of asthma appears to be higher in patients with various immune deficiencies including hypogammaglobulinemia, with an estimated prevalence of 15% in the studies.[17] The mechanism causing the increased prevalence of viral infections in patients with hypogammaglobulinemia is unknown. Secretory IgA deficiency in the bronchial mucosa has been suggested.[16] To our knowledge, the link between viral infections and serum immunoglobulin in patients with asthma is poorly understood.

The purpose of this project was to compare the serum IgG concentrations between patients with an upper airway specimen that tested positive for a virus and those with a negative viral specimen at the time of hospitalization for asthma exacerbations.

METHODS

Population

An observational study was conducted from January 1, 2015, to December 31, 2015. Patients with asthma were recruited from the Department of Respiratory Medicine of the University Hospital of Tours, located in the center of France, as well as from the Department of Respiratory Medicine of the University Centre of Reunion, a French island located in the Indian Ocean. The socioeconomic statuses of the patients are very close because both locations are managed in the same way by the French government. Inclusion criteria were patients aged 18 years or older and hospitalized for an asthma exacerbation. An exacerbation was defined as the increase in respiratory symptoms for more than 24 hours or the use of oral corticosteroid therapy. Asthma diagnoses were established on a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and coughing associated with variable expiratory airflow limitation before hospitalization according to the Global Initiative for Asthma.[1] Exclusion criteria were smoking more than 10 packs of cigarettes a year, chronic obstructive pulmonary disease (COPD), and pregnancy. The study was approved by the Institutional Review Board of the *Société de pneumologie de langue Française*. Each patient gave an informed written consent to take part in the study.

Clinical and biological data during asthma exacerbation

Demographic data such as age, sex, body mass index, smoking status quantified in packs per year (P/A), inhaled treatment prescribed before exacerbation, as well as the use and duration of oral steroids during the exacerbation were collected. The total serum IgE concentration (immunoassay technique, ImmunoCAP IgE total, Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden), blood eosinophilia (Beckman Coulter LH 780 Controlled Analyzer), and C-reactive protein (Beckman Coulter LH 780 Controlled Analyzer, Holliston, Mass) were also collected. The severity of exacerbations was characterized by the length of the hospital stay including the time spent in the emergency room and if the patient needed to be treated in the intensive care unit. Controlled asthma was defined as an asthma control test score greater than or equal to 20 points in the month preceding the consultation.

Upper airway viral sampling

Viral carriage was assessed in the nasopharyngeal fluid obtained by nasopharyngeal aspiration performed as soon as possible by qualified nurses accustomed to the technique. The viral identification was performed by multiplex real-time PCR (Tours: Anyplex II RV16, V1.1 detection, Eurobio, France, and Thermal Cycler, C1000, BioRad, US Meeting; Reunion: FTD Respiratory pathogens 21, Fast track diagnostics, Luxembourg and Rotor-Gene Q instrument, Qiagen, France). At least 16 viruses (respiratory syncytial virus A and B, rhinovirus, metapneumovirus, myxovirus influenzae A, H1N1, B, parainfluenzae from 1 to 4, coronavirus 229E, NL63 and OC43, adenovirus, enterovirus) were analyzed in each center. In Reunion, the panel of viruses also included coronavirus HKU1, bocavirus, and parechovirus.

IgG serum concentration

Serum IgG concentrations and IgG subclasses were measured by the nephelometric technique on BN Prospect (Siemens Healthcare Diagnostics, Marburg, Germany) at the time of admission to the hospital section.

Follow-up visit

Patients received a follow-up visit 3 months after exacerbation. Functional respiratory tests were performed via flow-volume curves using a plethysmograph (SensorMedics Vmax Encore, Carefusion, San Diego, Calif). The values of both forced vital capacity and FEV_1 were expressed as a percentage of predicted values according to age, sex, weight, and height. Airway obstruction was defined by a post-bronchodilator FEV_1/forced vital capacity ratio of less than 70%. Measurements were taken according to ATS/ERS 2006 recommendations using the predicted values published by the ERS.[18,19] Prick tests to aeroallergens (house dust mites [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* at both sites and Blomia tropicalis in Reunion]), mold (*Alternaria alternata*), animal dander (cat and dog), cockroaches (*Blattella germanica*), tree pollens (olive tree, birch), and herbaceous plants (ragweed, ambrosia, wormwood, and grasses) were also carried out.

Statistical analyses

Quantitative data with a normal distribution were expressed as mean and SD, and quantitative data with no normal distribution were expressed as median deviation (interquartile range). Qualitative data were expressed as frequencies (%). A Student *t* test (parametric) was used to compare continuous variables with normal distribution. The Mann-Whitney test was used for quantitative data and had no

TABLE I. Characteristics of patients hospitalized because of asthma exacerbations

Characteristic	Value (N = 82)
Age (y)	49.5 (28.8-63.3)
Sex: female	63 (76.8)
Active or former smokers	21 (25.6)
BMI (kg/m^2)	26.3 (22.1-31.2)
Allergen sensitization	35 (42.7)
Use of an inhaled corticosteroid before hospitalization	50 (61.0)
Inhaled corticosteroid dose (beclomethasone equivalent doses) (μg/d)	1600 (800-2000)
≥2 Exacerbations 12 mo before exacerbation	15 (18.3)
Oral corticotherapy duration for exacerbation (d)	7.0 (5.0-8.5)
Length of hospitalization	4.0 (2.0-5.0)
Intensive care unit stay at the time of exacerbation	12 (14.6)
Positive viral sampling	40 (48.8)
FEV_1 after hospitalization (mL) (% predicted values)	76 (63-88)
FEV_1/FVC after hospitalization (%)	74 ± 15
Blood eosinophil (g/L)	0.20 (0.03-0.68)
Total IgE (kIU/L)	339 (148-786)

BMI, Body mass index; *FVC*, forced vital capacity.
Quantitative data with normal distribution are expressed as mean ± SD, and quantitative data without normal distribution are expressed in median (interquartile range). The qualitative data are expressed as frequencies (%).

normal distribution. Statistical significance was defined as a P value of less than .05. Receiver operator characteristic curves were used to assess serum IgG concentrations as a potential marker of a positive virus specimen. The best IgG cutoff was determined using the Youden index. Sensitivity and specificity of IgG cutoff for a positive virus sample were also defined. A Spearman test was used to assess the correlation between serum IgG concentrations and other continuous variables. The linearity of these relations was then tested using linear regression. The statistical analysis was carried out using the Graph Pad Prism 5 software (license reference: GPW6-222441-RILS-2C3D1).

RESULTS

Characteristics of patients and virus distribution

Eighty-two patients were included in this study. The patients' characteristics are summarized in Table I. The median age was 49.5 (28.8-63.3) years. Patients were predominantly female (76.8%) and overweight, with a median body mass index of 26.3 (22.1-31.2) kg/m^2. Inhaled corticosteroid treatment was used in 61% of patients before asthma exacerbation, and 14.6% of all patients required intensive care at the time of exacerbation. The median duration of oral corticosteroid therapy and the median length of stay for the exacerbation were 7.0 days and 4.0 days, respectively.

Nasopharyngeal aspirations were positive for viruses in 48.8% of patients. The most common viruses were rhinovirus (38%), myxovirus influenza (18%), metapneumovirus (12%), and enterovirus (10%) (Figure 1).

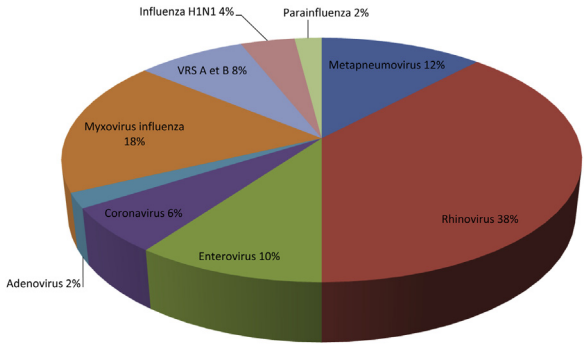

FIGURE 1. Details of viruses found in nasopharyngeal aspirations of patients hospitalized for asthma exacerbation.

Characteristics of patients according to the viral status of nasopharyngeal aspiration

Patients with a positive or negative viral sample showed no statistically significant difference in terms of demographic and biological data (Table II). Patients with positive nasopharyngeal aspiration for viruses were slightly younger than patients with negative nasopharyngeal aspiration for viruses (43.5 vs 50.5 years, respectively) with no statistical significance ($P > .05$). Patients with positive viral specimens also seemed to be hospitalized in intensive care units more often compared with patients harboring negative viral specimens (20% vs. 9.5%, respectively); however, the difference was not significant.

Immunoglobulin blood concentration

Patients with a positive viral sample had significantly lower serum IgG concentrations than patients hosting a negative viral specimen (10.1 ± 2.3 g/L vs 11.5 ± 3.6 g/L; $P < .05$) (Table III). No difference was found for serum IgA and IgM concentrations in both groups. IgG subclasses were similar between groups. An inverse correlation was observed between age and serum IgG concentrations ($P = .016$). No other correlation was shown for the other demographic characteristics.

Serum IgG concentrations and diagnosis of a positive virus sample

Receiver operating characteristic curve analyzing the serum IgG concentrations as a marker for predicting a specimen positive for a virus is presented in Figure 2. According to Youden index, the best cutoff value of serum IgG to predict a positive virus sample is 12.30 g/L, and the optimal sensitivity and specificity were 80.0% and 40.5%, respectively.

IgG concentration and characteristics of asthma exacerbation

The median serum concentration of IgG was significantly lower in patients hospitalized for more than 3 days than in those whose hospital stay was less than or equal to 3 days (10.0 g/L [8.2-12.4] vs 11.4 g/L [10.1-12.8]; $P < .05$) (Figure 3, *B*). Patients receiving oral corticosteroids for more than 5 days had lower median serum IgG concentrations than patients who were given corticosteroid therapy for 5 days or less (10.1 g/L [8.3-12.2] vs 11.6 g/L [10-13.8], respectively; $P < .05$) (Figure 3, *C*). The median serum concentration of IgG was not significantly different if patients were hospitalized in intensive care units or not (Figure 3, *A*). An inverse correlation was observed between the length of stay and the serum

TABLE II. Characteristics of patients hospitalized for asthma exacerbations with positive or negative upper airway viral samples

Characteristic	Virus + (n = 40)	Virus − (n = 42)	*P*
Age (y)	43.5 (24.3-60.3)	50.5 (36.0-68.3)	0.14
Sex: female	33 (82.5)	30 (71.4)	0.30
Active or former smokers	11 (27.5)	10 (23.8)	0.80
BMI (kg/m^2)	29.0 (22.0-33.2)	25.0 (22.3-30.4)	0.42
Allergen sensitization	18 (45.0)	17 (40.5)	0.82
Use of an inhaled corticosteroid before hospitalization	24 (60.0)	26 (61.9)	1.00
Inhaled corticosteroid dose (beclomethasone equivalent doses) (μg/d)	1600 (800-2000)	1600 (800-1600)	0.91
≥2 Exacerbations 12 mo before exacerbation	5 (12.5)	10 (23.8)	0.39
Oral corticotherapy duration for exacerbation (d)	7.0 (5.0-9.5)	6.0 (5.0-8.5)	0.15
Length of hospitalization	4.0 (2.0-5.0)	3.5 (2.0-5.0)	0.31
Intensive care unit stay at the time of exacerbation	8 (20.0)	4 (9.5)	0.22
FEV_1 after hospitalization (% predicted values)	80.5 (61.0-90.5)	75.5 (63.5-86.00)	0.50
FEV_1/FVC after hospitalization (%)	75 ± 12	66 ± 12	0.052
Blood eosinophil (g/L)	0.2 (0.0-0.4)	0.2 (0.0-0.8)	0.39
Total IgE (kIU/L)	349 (185-1003)	310 (127-516)	0.29

BMI, Body mass index; *FVC*, forced vital capacity.
Values are expressed as median (interquartile range) or mean ± SD for quantitative data and raw values (%) for categorical data. A Student *t* test (parametric) is used to compare continuous variables to a normal distribution. The Mann-Whitney test is used for quantitative data that do not have a normal distribution.

TABLE III. Comparison of serum IgG, IgA, IgM, and IgG subclass levels between patients with positive viral samples (Virus +) and negative (Virus −)

Serum levels (g/L)	Virus + (n = 40)	Virus − (n = 42)	*P*
IgG	10.1 ± 2.3	11.5 ± 3.6	<.05
	10.10 (8.15-11.68)	11.25 (9.09-13.43)	
IgA	2.30 (1.77-3.06)	2.34 (1.98-2.86)	.70
IgM	0.88 (0.55-1.15)	0.75 (0.56-1.36)	.91
IgG_1	4.9 (3.5-5.8)	5.5 (4.5-7.0)	.059
IgG_2	3.7 ± 1.0	4.1 ± 1.4	.12
IgG_3	0.58 (0.30-0.80)	0.57 (0.43-0.86)	.38
IgG_4	0.27 (0.15-0.43)	0.27 (0.15-0.60)	.85

Values are expressed as median (interquartile range) or mean ± SD for quantitative data and raw values (%) for categorical data. Both median (interquartile range) and mean ± SD are given for IgG. A Student test (parametric) is used to compare continuous variables to a normal distribution. The Mann-Whitney test is used for quantitative data that do not have a normal distribution.

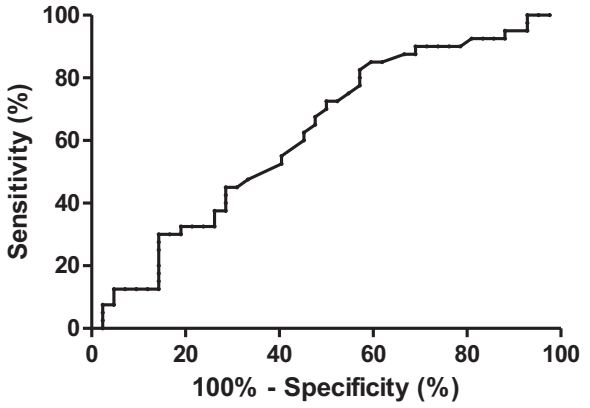

FIGURE 2. Receiver operating characteristic curve analysis of serum IgG concentrations for the prediction of a positive virus sample. At the cutoff value of 12.30 g/L, sensitivity and specificity are 80.0% and 40.5%, respectively.

IgG concentration ($P = .022$ with the Spearman test) (Figure 4). No correlation was found between oral steroids and serum IgG concentrations. Receiver operating characteristic curves have been created according to the length of stay and the steroid duration to know the reliability of serum IgG concentrations as a predictive biomarker of exacerbation severity. For the length of stay prediction (≤3 days or >3 days), the best sensitivity and specificity of IgG concentrations are 80.00% and 50.00%, respectively, for a cutoff value of 11.05 g/L (see Figure E1*A*, in this article's Online Repository at www.jaci-inpractice.org). Regarding the steroid duration prediction (≤5 days or >5 days), for a cutoff value of 9.99 g/L, the best sensitivity and specificity of IgG concentrations are 62.07% and 66.67%, respectively (Figure E1*B*). If a positive virus sample is combined with the IgG serum concentrations, for a cutoff of 10.75 g/L, the best sensitivity and specificity of the length of stay prediction are 79.17% and 61.11%, respectively. Regarding a cutoff of 11.05 g/L, the best sensitivity and specificity of the steroid duration prediction are 82.76% and 55.00%, respectively (Figure 5).

DISCUSSION

Patients with asthma with a positive nasopharyngeal viral sample had a lower serum IgG concentration, at the time of

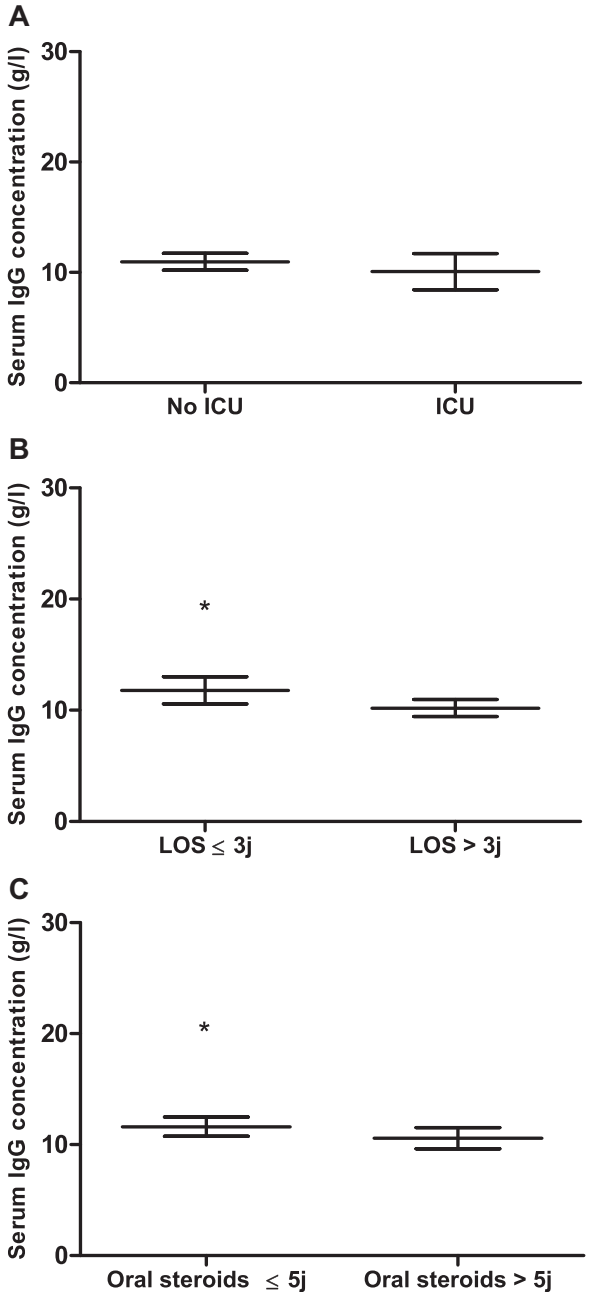

FIGURE 3. Comparison of blood IgG concentrations (**A**) between patients hospitalized in the ICU and those not hospitalized in the ICU, (**B**) between patients hospitalized for 3 days or less and those hospitalized for more than 3 days, and (**C**) between patients treated during 5 days or less with oral corticosteroids and those treated during more than 5 days. *ICU*, Intensive care unit; *LOS*, length of stay. $^{*}P < .05$.

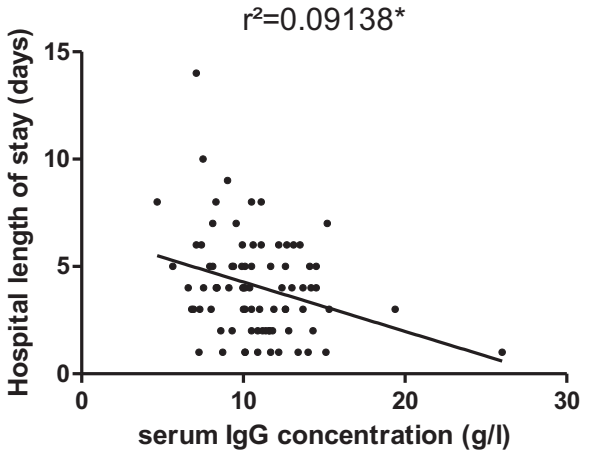

FIGURE 4. Scatter plots with regression line showing the relationship between the serum IgG concentrations and the hospital length of stay. $^{*}P = .0058$ using linear regression.

exacerbation, than those with a negative viral sample. Moreover, the median serum IgG concentration was lower in patients hospitalized for more than 3 days as well as in those who were given oral steroids for more than 5 days compared with their counterparts.

In our study, the epidemiology of viruses found in patients hospitalized for asthma exacerbations was similar to data observed in the literature. Indeed, herein, rhinovirus was the most frequently observed pathogen (38%). This virus is known to be more often associated with asthma exacerbations in children,[20-22] and some works suggest that it is also the most incriminated virus in severe asthma exacerbations in adults.[13,23,24] Our patients also presented with other viruses such as myxovirus influenzae. Myxovirus influenza, particularly influenza A H1N1, is responsible for a significant morbidity and mortality in patients with asthma.[25-27] Enterovirus appears to be less frequently found in the literature.[28] In our cohort, enterovirus was always found in coinfection with rhinovirus and this represented 5 of 10 patients who had coinfections. The 5 remaining patients were coinfected with rhinovirus/myxovirus influenza A (n = 3), metapneumovirus A and B/myxovirus influenza A H1N1 (n = 1), adenovirus/myxovirus influenza A (n = 1), and coronavirus 229E/myxovirus influenza A (n = 1). No relationship between coinfection and serum IgG concentrations or the severity of exacerbations was found.

No demographic differences were found between the patients with positive virus samples and those with negative virus samples. However, although the difference was not statistically significant, patients with a positive virus sample were slightly younger compared with their negative counterparts (43.5 vs 50.5 years, respectively). The lack of significance is probably due to the small sample size. It is well known that asthma exacerbation in young people is associated with virus infections.[29] Body mass index appears to be a bit higher in patients with positive virus samples compared with patients with negative virus samples (29 kg/m^2 vs 25 kg/m^2, respectively), but the difference is also not significant. The risk of viral infections in obese patients with asthma has been identified elsewhere in the literature. Indeed, asthma and obesity have been found as independent risk factors of pandemic influenza hospitalization.[30] In our study, more patients in the positive virus group required intensive care although there was no significant difference. Data from the literature suggest that respiratory viruses may trigger severe asthma exacerbations, particularly in young people.[31]

The link between viral infections and asthma exacerbations is widely recognized and the impairment of viral immunity may

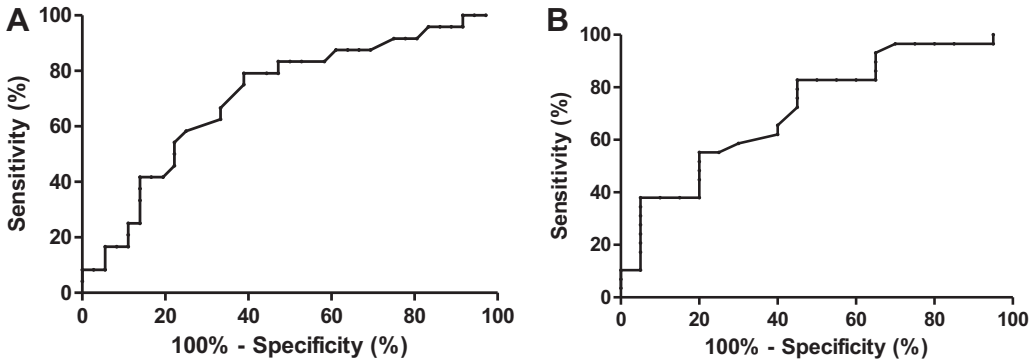

FIGURE 5. Receiver operating characteristic curve analysis of serum IgG concentrations combined with a positive virus sample for (**A**) the prediction of a length of stay duration of more than 3 days (for a cutoff value of 10.75 g/L, sensitivity and specificity are 80.0% and 40.5%, respectively) and (**B**) the prediction of a steroid duration of more than 5 days (for a cutoff value of 11.05, the best sensitivity and specificity are 82.76% and 55.00%, respectively).

partly explain the development of viral infections in patients with asthma.[32,33] In influenza infections, IgG has been identified as being particularly involved in protecting the respiratory tract against viruses and its role seems to be superior to that of IgA.[34] Rhinovirus-specific IgG appears to prevent and control reinfection and a high concentration of specific IgG antibodies is correlated with the attenuation of respiratory symptoms and a reduction in viral shedding.[35] A decrease in specific viral antibodies in patients with asthma has been suggested.[36] However, in another study, higher antibody responses to rhinovirus have been shown in patients with asthma compared with controls without asthma.[37] Given the study conducted by Johnston et al[10] on rhinovirus involvement in asthma exacerbations in children, we may also speculate that the admitted patients had less exposure to school-age children in the past and therefore had not generated a sufficient antibody response to the current virus(es). Other mechanisms beyond adaptive immunity dysfunction are involved in virus-induced asthma exacerbations. Indeed, an altered innate immune antiviral response has been observed in patients with asthma compared with those without asthma.[38-40] Our study does not add a mechanistic explanation for the low level of serum IgG in patients with a positive virus sample.

Our results may suggest that serum IgG concentrations at the time of asthma exacerbation would be a marker of severity. Indeed, patients with a hospitalization length of more than 3 days or a steroid course of more than 5 days show lower IgG concentrations at the time of exacerbation. Among patients with stable COPD, reduced total IgG levels have been linked to an increased risk of exacerbations and hospitalizations.[41] In that study, patients with serum IgG level of less than 7 g/L had a higher risk of COPD exacerbations compared with patients with the highest quartile of serum IgG. We assessed the predictive ability of serum IgG concentrations as a biomarker of exacerbation severity. However, it does not seem to be a useful predictor based on modest sensitivity and poor specificity. If we combine serum IgG concentrations and a positive virus sample, the prediction of exacerbation severity was not improved, and further studies are needed to specifically assess IgG level as a marker of severity in asthma exacerbations. The prediction of next hospitalizations with IgG levels would also be interesting, but we cannot answer this question with our study because it was not designed to answer this question. However, we may speculate that a low IgG level particularly at baseline would predispose patients to virus infection and consequently increase their risk of hospitalization.

Our study does have several limitations. The difference in IgG concentrations between patients with positive and negative viral samples is statistically significant, but it remains uncertain whether this difference is clinically relevant or not. More robust studies on the role of IgG are needed. In addition, the change in IgG concentrations or other immunoglobulins over time was not assessed in our study. We did not measure IgG in patients in a stable condition. It would have been interesting to know if the IgG decline is transient or longer-lasting. Indeed, in patients with COPD, low IgG serum concentrations at baseline seem to be associated with more severe exacerbations per year.[41] However, in this study, no virus analysis was performed. Finally, our study is based on multiplex PCR for virus identification. Nevertheless, the list of viruses, though very extensive, is not exhaustive; therefore, emerging viruses cannot be ruled out.

CONCLUSIONS

The results of our study show that serum IgG level was significantly lower when severe asthma exacerbations were associated with a positive viral sample. Serum IgG levels were lower in patients with a longer length of stay and when a course of oral steroids was prescribed for a longer duration. Further studies are requested to know the exact usefulness of IgG concentrations as a severity marker of severe asthma exacerbations. The understanding of immunologic mechanisms of viral infection in severe asthma exacerbations may be an interesting lead for the development of new therapies in patients for whom severe exacerbations are a source of significant morbidity and mortality.

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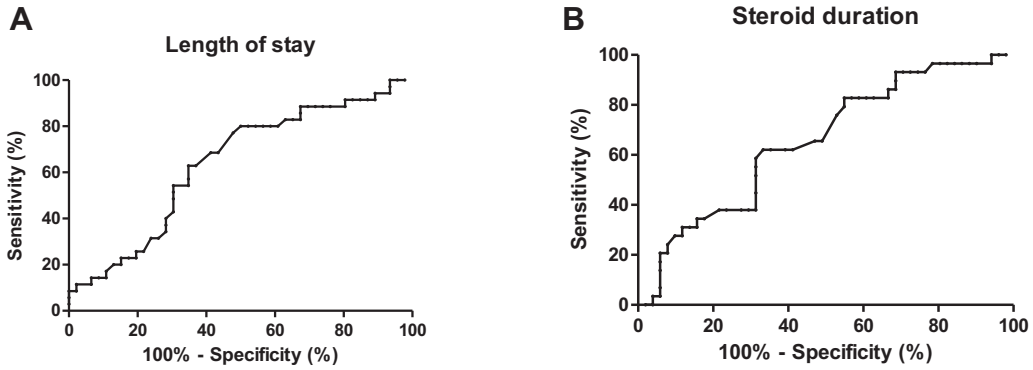

FIGURE E1. Receiver operating characteristic curve analysis of serum IgG concentrations for (**A**) the prediction of a length of stay of more than 3 days (for a cutoff value of 11.05 g/L, the best sensitivity and specificity are 80.00% and 50.00%, respectively) and (**B**) the prediction of a steroid duration of more than 5 days (for a cutoff value of 9.99 g/L, the best sensitivity and specificity are 62.07% and 66.67%, respectively).