Inflammatory and Bronchospastic Factors in Asthma Exacerbations Caused by Upper Respiratory Tract Infections

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Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine, Sendai, Japan, 1Virus Center, Clinical Research Division, Sendai National Hospital, Sendai, Japan, and 2Department of Pulmonary Medicine, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

YASUDA, H., SUZUKI, T., ZAYASU, K., ISHIZUKA, S., KUBO, H., SASAKI, T., NISHIMURA, H., SEKIZAWA, K. and YAMAYA, M. Inflammatory and Bronchospastic Factors in Asthma Exacerbations Caused by Upper Respiratory Tract Infections. Tohoku J. Exp. Med., 2005, 207 (2), 109-118 — It is still uncertain how viral respiratory infections cause acute exacerbations of bronchial asthma, although several mechanisms have been proposed. We studied the relationship between the airway narrowing and the inflammatory and bronchospastic factors in peripheral venous blood and urine, in 30 patients with asthma at the exacerbations caused by upper respiratory tract infections (URTIs). Acute exacerbations caused decreases in peak expiratory flow rate (PEFR) in all 30 patients with asthma. Asthma exacerbations caused the rises in serum levels of interleukin-6, soluble intercellular adhesion molecule-1 and eosinophil cationic protein, concentrations of urinary leukotriene E4 and plasma histamine, compared with those in patients with asthma at a stable condition and those in 30 control subjects (p < 0.05). The values of PEFR at the exacerbations correlated with the levels of these factors. Treatment with oral glucocorticoids reversed the decreases in PEFR and the increases in these factors. At the onset of URTIs, rhinovirus and influenza type A virus were identified in 13 and 7 patients, respectively. Each of parainfluenza virus, adenovirus, and enterovirus was identified in one patient. These findings suggest that respiratory viral infections may cause acute asthma exacerbations via the production of mediators that induce inflammation and bronchospasm.

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Acute respiratory infections, including rhinoviruses (RVs), adenoviruses, respiratory syncytial viruses and influenza viruses, induce asthma exacerbations (Minor et al. 1976; Nicholson et al. 1993). Although several mechanisms have been proposed, it is still uncertain how viral respiratory infections cause an attack of wheezing in patients with asthma.

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RV infection induces the production of several cytokines such as interleukin (IL)-1 and IL-6 in airway epithelial cells (Terajima et al. 1997; Yamaya 2002) and human mast cells (Hosoda et al. 2002), and increases IL-6 in nasal washing (Zhu et al. 1996). Respiratory virus infections also induce the production of intercellular adhesion molecule-1 (ICAM-1) in the airway epithelial cells (Terajima et al. 1997). RV infected-lymphocytes release factors that activate monocytes to induce interferon (IFN)-γ production (Gern et al. 1996). Serum eosinophil cationic protein (ECP) is known as a marker of activated eosinophils (Venge et al. 1999), which release several chemical mediators, reactive oxygen species and proteins such as major basic proteins. Activated eosinophils induce the injury of airway epithelium (Holgate 1997), and RV infection causes activation of eosinophil chemotaxis (Furukawa et al. 2004) and eosinophilic infiltration in the bronchial mucosa (Fraenkel et al. 1995). These cytokines, adhesion molecules and ECP are known to mediate various inflammatory and immunoregulatory effects (Akira et al. 1990; Holgate 1997; Furukawa et al. 2004), and may play an important role in the pathogenesis of respiratory viruses infections.

Leukotriene (LT) and histamine are important factors associated with the pathogenesis of bronchial asthma (Barnes et al. 1988; Sekizawa 1994). Influenza virus infection increases basophil LTC4 release (Huftel et al. 1992). Infection of respiratory viruses, including influenza virus and RV, also activates histamine release from peripheral blood basophils (Chonmaitree et al. 1988; Huftel et al. 1992) and human mast cells (Hosoda et al. 2002). Furthermore, RV infection increases bronchial responsiveness to histamine (Gern et al. 1997), and histamine content in bronchoalveolar lavage fluid in allergic subjects (Calhoun et al. 1994).

Increased circulating serum levels of IL-6 (Hashimoto et al. 1994; Yokoyama et al. 1995), soluble intercellular adhesion molecule-1 (sICAM-1) (Montefort et al. 1994) and ECP (Niimi et al. 1998), and concentrations of urine leukotriene E4 (LTE4) (Oosaki et al. 1997) and plasma histamine (Calhoun et al. 1991) have been reported in symptomatic acute asthma (Montefort et al. 1994; Yokoyama et al. 1995; Oosaki et al. 1997; Niimi et al. 1998), in children with acute respiratory infection (Hashimoto et al. 1994), and in experimental RV infection in allergic subjects after antigen bronchoprovocation (Calhoun et al. 1991). However, the relationship between the airway narrowing and the increases in these factors has not been studied in patients with asthma exacerbations caused by spontaneously developed upper respiratory tract infections (URTIs).

To study the inflammatory and immunoregulatory factors in the asthma exacerbations caused by URTIs, we examined serum concentrations of inflammatory cytokines, sICAM-1 and ECP in patients with asthma during acute exacerbations with URTIs. Furthermore, to demonstrate the increases in mediators that induce bronchospasm, we measured the levels of urine LTE4 and plasma histamine in such patients.

**MATERIALS AND METHODS**

One hundred sixty seven asthmatic patients were recruited from patients treated in 3 public hospitals in Miyagi Prefecture. Thirty of 167 patients were defined as having a clinical cold and acute exacerbations between April 2000 and March 2004, and were studied. Asthma was defined as a clinical history of symptoms including dyspnea, wheeze, cough, or chest tightness, and documented reversible airflow limitation, according to American Thoracic Society criteria (American Thoracic Society 1987) and the Global Initiative for asthma (GINA) guidelines (U.S. Department of Health and Human Services 2002). Before exacerbations of asthma, all 30 patients were in a stable condition. The patients were taking regular treatment with inhaled glucocorticoids (beclomethasone dipropionate 200-400 μg daily) and daily long acting bronchodilators (procaterol hydrochloride 50 to 100 μg/day and theophylline 200 to 400 mg/day), and were moderate in severity assessed on the basis of GINA guidelines (U.S. Department of Health and Human Services 2002). This study was approved by the Tohoku University Ethics Committee, and informed consent was obtained from each patient.

To examine the relationship between URTIs and acute asthma, the asthmatic patients were asked to judge the severity of the following 8 symptoms (Jackson et al. 1958): sneezing, rhinorrhea, nasal obstruction, sore throat,
cough, headache, malaise, and chillness. Each symptom was assigned a severity score of 0 to 3 corresponding to a report of symptom severity of absent, mild, moderate, or severe. Subjects who had a total symptom score of at least 6 and either at least 3 days of rhinorrhea or the subjective impression that they had a cold were defined as having a URTI (Jackson et al. 1958).

To compare the differences between patients with acute asthma without URTIs, we also studied the levels of these factors in 30 patients with acute asthma without the symptoms of URTIs. All 30 patients without the symptoms of URTIs were atopic, as determined by the presence of specific serum IgE antibody level over 250 U/l against at least one common inhalant allergen or a positive skin reaction to a battery of standard antigens. In contrast, in 30 patients with asthma exacerbations with URTIs, 14 patients were atopic and other 16 patients were non-atopic.

To isolate viruses from the asthmatic patients with URTIs, 13 different viruses (influenza type A, B, and C, paramyxovirus, adenovirus, RV, respiratory syncytial virus, mumps virus, poliovirus, Coxsackie B virus, herpes simplex virus, cytomegalovirus, and enterovirus) were screened for using throat swabs from each patient, and viruses were identified using methods described previously (Numazaki et al. 1987). Furthermore, RVs were identified with reverse transcription-polymerase chain reaction (RT-PCR) methods described previously (Johnston et al. 1993) using either throat swabs, nasal discharges or throat gargles with 10 ml of distilled water. Virus identification was performed at the visit to the hospitals due to a clinical cold and acute exacerbation, and 21 days of treatment with oral glucocorticoids when patients showed evidence of clinical improvement.

Peripheral venous blood samples were collected to measure serum concentrations of IL-1β, IL-4, IL-5, IL-6, tumor necrosis factor (TNF)-α, sICAM-1 and ECP by a specific enzyme-linked immunosorbent assay (ELISA). Contents of urinary LTE₄ and plasma histamine were measured with high-performance liquid chromatography-enzyme immunoassay (HPLC-EIA) methods (Oosaki et al. 1997) and with high-performance liquid chromatography (HPLC) methods (Yamatodani et al. 1985). Levels of serum cytokines, sICAM-1 and ECP, urinary LTE₄ and plasma histamine were measured in 30 asthma patients at the stable condition, at the admission due to exacerbations of asthma and at 21 days of treatment with oral glucocorticoids when patients showed evidence of clinical improvement, and in 30 healthy control subjects.

Thirty patients had presented themselves for emergency treatment due to exacerbations of asthma after having a clinical cold. All patients had the symptoms of either dyspnea or wheeze within 3 days after the beginning of symptoms of the URTIs as described in detail in the Results section. Patients were admitted to the hospital within 24 h after the beginning of exacerbations of asthma. They were assessed as to the severity of symptoms and given physical examinations at the admission to the hospital. The inhalation of β2 agonists had an incomplete or poor effect on symptoms and physical findings, and oral glucocorticoid treatment (prednisolone 40 mg daily) was started in all patients according to a stepwise approach for asthma therapy based on the GINA guidelines (U.S. Department of Health and Human Services 2002). Peak expiratory flow rate (PEFR) was measured with a peak flow meter (Personal Best, Health Scan, Cedar Grove, NJ, USA). A pulmonary function test was performed in 30 patients with bronchial asthma during the stable period before exacerbation and in 30 healthy control subjects. PEFR was also measured before and at the admission due to exacerbations of asthma, and at 1, 2, and 3 weeks of treatment with oral glucocorticoids in 30 patients with bronchial asthma.

Results are reported as means ± S.E.M. Statistical analysis was performed using two-way analysis of variance (ANOVA), and followed by the Newman-Keuls test. Significance was accepted at p < 0.05.

**RESULTS**

Physical characteristics and pulmonary function test results in 30 patients during the stable period before exacerbation and in 30 healthy control subjects are shown in Table 1. In the 30 control subjects there was no history of respiratory and cardiovascular disease. None of these 30 control subjects were receiving long-term medication.

Thirty patients had presented themselves for emergency treatment due to exacerbations of asthma after having a clinical cold. All patients had the symptoms of either dyspnea and wheeze within 3 days after the beginning of symptoms of the URTIs including rhinorrhea in 28 patients (93%), nasal obstruction in 18 patients (60%), chillness in 18 patients (60%), sneezing in 13 patients (43%), sore throat in 12 patients (40%), cough in 9 patients (30%), headache in 4 patients
(13%), or malaise in 2 patients (7%). Patients were admitted to the hospital within 24 h after the beginning of exacerbations of asthma. Acute asthma exacerbations caused decreases in PEFR in all patients. On the other hand, within 21 days of treatment with oral glucocorticoids when patients showed evidence of clinical improvement, the PEFR values returned to levels similar to those before the exacerbations (Fig. 1). The values of PEFR during acute asthma exacerbations (228 ± 12, means ± S.E.M., n = 30) were significantly lower than those before the exacerbations (418 ± 17, p < 0.01), and those after 21 days of treatment with oral glucocorticoids when patients showed evidence of clinical improvement (424 ± 18, p < 0.01).

With RT-PCR methods, RVs were identified in 13 patients at the onset of asthma exacerbations (7 patients from nasal discharge, 3 patients from throat swabs and 3 patients from throat gargles) (Table 2). With a microplate method, influenza type A virus was identified in 7 patients at the onset of asthma exacerbations (Table 2). In addition, each of parainfluenza virus, adenovirus and enterovirus was identified in one patient (Table 2). Furthermore, only one virus was identified in each

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**Table 1. Physical characteristics and baseline pulmonary function test results**

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Age (yrs)</th>
<th>Sex M/F</th>
<th>Atopy Atopic/Non-atopic</th>
<th>FVC (% pred)</th>
<th>FEV1 (% pred)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
<td>59 ± 5</td>
<td>16/14</td>
<td>113 ± 5</td>
<td>102 ± 4</td>
</tr>
<tr>
<td>Asthmatics</td>
<td>30</td>
<td>58 ± 5</td>
<td>14/16</td>
<td>98 ± 5</td>
<td>84 ± 5</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.M.

M, male; F, female; FVC, forced vital capacity; FEV1, forced expiratory volume in one second.

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Fig. 1. Time course changes in peak expiratory flow rate (PEFR) in asthmatic patients (n = 30) before acute asthma exacerbations (baseline) and after treatment with oral glucocorticoids. ↑: the start of treatment of acute asthma exacerbations with oral glucocorticoids. Medians and ranges are indicated by open circles with bars. Significant differences from baseline are indicated by ** p < 0.01. Significant differences from acute asthma exacerbations are indicated by * p < 0.05 and ++ p < 0.01.
patient, and no patients had more than one virus identified. In contrast, no virus was identified after 21 days of treatment with oral glucocorticoids when patients showed evidence of clinical improvement.

Serum levels of IL-6, sICAM-1 and ECP (Fig. 2) as well as concentrations of urinary LTE₄ and plasma histamine (Fig. 3) in asthmatic patients were observed during acute asthma exacerbations and returned to levels similar to those in control subjects after 21 days of treatment with oral glucocorticoids when patients showed evidence of clinical improvement. During acute asthma exacerbations, serum levels of IL-6 (10.4 ± 2.0 pg/ml, n = 23), sICAM-1 (397 ± 26 ng/ml, n = 23) and ECP (16.1 ± 2.0 μg/ml, n = 23) as well as concentrations of urinary LTE₄ (464 ± 90 pg/ml, n = 23) and plasma histamine (0.52 ± 0.7 ng/ml, n = 23) in patients with objective evidence of virus infection did not differ from those in all the asthmatic patients studied (n = 30, p > 0.20).

In contrast to a variety of other respiratory pathogens including influenza and adenovirus (Jacoby et al. 1988), cytotoxicity of epithelial cells does not appear to play a major role in the pathogenesis of RV infections (Stanway 1994; Fraenkel et al. 1995). Therefore, we examined

### Table 2. Virus identification from asthma patients with URTIs

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Positive results</th>
</tr>
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<tbody>
<tr>
<td>Rhinovirus</td>
<td>13</td>
</tr>
<tr>
<td>Influenza A</td>
<td>7</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>1</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>1</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>1</td>
</tr>
</tbody>
</table>

URTIs, upper respiratory tract infections.

![Fig. 2. Serum levels of IL-6 (A), soluble ICAM-1 (sICAM-1) (B) and ECP (C) in control subjects (Control, n = 30) and patients with bronchial asthma (n = 30) at a stable condition (Stable), during exacerbations (Exacerbations) and after 21 days of treatment with oral glucocorticoids when patients showed evidence of clinical improvement (Recovery). Mean values ± S.E.M. are indicated by closed circles with error bars. NS, not significant.](image)
the differences in the factors in asthma exacerbations between patients with RV infection and patients with other viruses (Table 3). In patients with RV infection during exacerbations, serum levels of IL-6, sICAM-1 and ECP, concentrations of urinary LTE_4 and plasma histamine were significantly lower than those in patients with virus infection of other than RV during exacerbations (Table 3).

We also examined the levels of these factors in atopic patients with acute asthma without the symptoms of URTIs. Increases in serum levels of IL-6, sICAM-1 and ECP as well as concentrations of urinary LTE_4 and plasma histamine were also observed in patients with acute asthma without the symptoms of URTIs compared with the levels in control subjects (Table 4). Furthermore, serum levels of IL-6, sICAM-1 and ECP as well as concentrations of urinary LTE_4 and plasma histamine did not differ between patients with acute asthma

Table 3. Factors in asthma exacerbations with infection of rhinovirus or other viruses

<table>
<thead>
<tr>
<th></th>
<th>IL-6 (pg/ml)</th>
<th>sICAM-1 (ng/ml)</th>
<th>ECP (μg/l)</th>
<th>LTE_4 (pg/mg·creatinine)</th>
<th>Histamine (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma exacerbations</td>
<td></td>
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<td></td>
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<tr>
<td>with RV (n = 13)</td>
<td>5.3 ± 0.8</td>
<td>347 ± 22</td>
<td>10.5 ± 1.1</td>
<td>257 ± 27</td>
<td>0.35 ± 0.04</td>
</tr>
<tr>
<td>Asthma exacerbations</td>
<td></td>
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<tr>
<td>with other viruses (n = 10)</td>
<td>17.0 ± 3.5*</td>
<td>406 ± 48*</td>
<td>23.5 ± 3.1*</td>
<td>734 ± 174*</td>
<td>0.74 ± 0.13*</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.M.
IL-6, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1; ECP, eosinophil cationic protein;LTE_4, leukotriene E_4; RV, rhinovirus.
*p < 0.05; compared with RV infection.
without the symptoms of URTIs and patients with acute asthma with URTIs (Table 4).

Serum levels of IL-1β, IL-4, IL-5 and TNF-α were under the limit of detection of the assay both during acute asthma exacerbations and after 21 days of treatment with oral glucocorticoids when patients showed evidence of clinical improvement.

The values of PEFR at the exacerbations significantly correlated with serum levels of either IL-6 (n = 30, r = −0.81, p < 0.001), sICAM-1 (n = 30, r = −0.89, p < 0.001) or ECP (n = 30, r = −0.82, p < 0.001). Furthermore, the values of PEFR at the exacerbations significantly correlated with either urinary LTE_4 concentrations (n = 30, r = −0.67, p < 0.001) or plasma histamine concentrations (n = 30, r = −0.79, p < 0.001).

**DISCUSSION**

In the present study, we have demonstrated that acute exacerbations with URTIs caused decreases in PEFR in all 30 patients with asthma. Asthma exacerbations caused rises in serum levels of IL-6, sICAM-1 and ECP, concentrations of urinary LTE_4 and plasma histamine, compared with those in patients with asthma at a stable condition and those in 30 healthy control subjects. The values of PEFR at the exacerbations significantly correlated with serum levels of either IL-6, sICAM-1 or ECP. Furthermore, the values of PEFR at the exacerbations significantly correlated with either urinary LTE_4 concentrations or plasma histamine concentrations. Treatment with oral glucocorticoids reversed the decreases in PEFR and the increases in these factors. The increased plasma histamine levels in asthma patients during the exacerbations is consistent with that in the antigen bronchoprovocation after RV infection (Calhoun et al. 1991). During acute asthma exacerbations with URTIs, serum levels of IL-6, sICAM-1 and ECP as well as concentrations of urinary LTE_4 and plasma histamine in patients with objective evidence of virus infection did not differ from those in all the patients studied. At the onset of URTIs, RV and influenza type A virus were identified in 13 and 7 patients, respectively. Furthermore, each of parainfluenza virus, adenovirus and enterovirus was identified in one patient. These findings suggest that respiratory viral infections might be associated with an increased production of mediators that induce inflammation and bronchospasm, cytokines and adhesion molecules in acute asthma exacerbations.

Furthermore, increases in serum levels of IL-6, sICAM-1 and ECP as well as concentrations of urinary LTE_4 and plasma histamine were also observed in patients with acute asthma without the symptoms of URTIs. The levels of these factors at the exacerbations caused by URTIs did not differ from those in patients with acute asthma without obvious URTIs. The levels of these factors are consistent with the data as previously described in acute asthma without obvious URTIs (Montefort et al. 1994; Yokoyama et al. 1995;
Increased IL-6 levels in serum, bronchoalveolar lavage fluid or nasal secretions have been reported in asthma patients during exacerbations or after antigen challenge (Yokoyama et al. 1995). Likewise, RV infection increased IL-6 levels in nasal secretions (Zhu et al. 1996), and in lung epithelial cells (Zhu et al. 1996; Terajima et al. 1997) and basophils (Hosoda et al. 2002). Increased serum IL-6 levels during asthma exacerbations by URTIs in this study were consistent with previous reports in children with acute respiratory infection (Hashimoto et al. 1994).

IL-6 not only induces B-cell differentiation and antibody production but is also capable of stimulating T-cell activation (Akira et al. 1990). IL-6 acts as an endogenous pyrogen and stimulates the acute phase response (Akira et al. 1990). Therefore, IL-6 may relate to fever, rhinorrhea, systemic symptoms and airway inflammation as seen in colds (Fraenkel et al. 1995).

Levels of sICAM-1 are reported to increase in the serum and sputum of patients with acute bronchial asthma, bronchopulmonary dysplasia, and other inflammatory and immune disorders (Chihara et al. 1994; Montefort et al. 1994). Likewise, respiratory virus infections increase ICAM-1 in airway epithelial cells (Terajima et al. 1997; Yamaya 2002) and in vascular endothelial cells (Golden-Stanfield et al. 1993). RV infection also induces the lymphocyte accumulation in airway submucosa, suggesting the possibility of circulating leukocytes activation (Fraenkel et al. 1995). Furthermore, virus-activated T cells induce shedding of ICAM-1, and circulating sICAM-1 is suggested to be a sensitive marker of T-cell activation in choriomeningitis (Christensen et al. 1995). Because intercellular adhesion molecule (ICAM)-1 is the receptor for a major group of RVs (Greve et al. 1989), binding of RV to ICAM-1 on T-cells is thought to activate the T-cell function (Stanciu and Djukanovic 1998). Up-regulation of ICAM-1 could increase susceptibility to major group RVs (Greve et al. 1989) and lead cells adjacent to infected cells to infection when viruses are released from the cells originally infected. Furthermore, ICAM-1 expression in the lung cells is suggested to have an important role in the pathogenesis of asthma (Pilewski and Albelda 1995). Therefore, increased serum sICAM-1 levels in this study might relate to ICAM-1 expression in airway inflammation and subsequent asthma exacerbations.

Eosinophil cationic protein (ECP) is one of the granular proteins derived from eosinophils. The granular proteins are cytotoxic, and cause damage to the bronchial epithelium, bronchial hyperresponsiveness and worsening of asthma (Bjorndottir et al. 1995). The serum level of ECP is known to be a marker of activated eosinophils in patients with bronchial asthma (Venge et al. 1999). Increased serum ECP levels in asthma patients in the present study are consistent with the levels in a previous report in symptomatic asthma patients (Niimi et al. 1998).

There is considerable evidence that the peptidoleukotrienes (LTs) are major mediators in bronchial asthma (Barnes et al. 1988; Holgate 1997). LTs have been shown to induce potent airway smooth muscle contraction in asthma patients (Barnes et al. 1988; Holgate 1997). LTE₄ is a stable product of LTs and is considered to be an index of systemic LTs production in men (Barnes et al. 1988). In the present study, urinary LTE₄ levels increased during asthma exacerbations caused by URTIs. The urinary LTE₄ levels in the present study were consistent with a previous study on spontaneous asthma attacks (Oosaki et al. 1997). Therefore, respiratory virus infections might induce LTs production in the airway or in blood circulation, and production of LTs might be, at least in a part, associated with the virus infection-induced asthma exacerbations.

In patients with RV infection during exacerbations, serum levels of IL-6, sICAM-1 and ECP, concentrations of urinary LTE₄ and plasma histamine were significantly lower than those in patients with infection of viruses other than RV during exacerbations, including influenza virus and adenovirus. The reasons are uncertain. However,
in contrast to a variety of other respiratory pathogens including influenza and adenovirus (Jacoby et al. 1988), cytotoxicity of epithelial cells does not appear to play a major role in the pathogenesis of RV infections (Stanway 1994; Fraenkel et al. 1995). The strong effects of influenza virus and adenovirus on the cells (Jacoby et al. 1988; Stanway 1994) might be associated with the increased serum and urine levels of the factors.

In summary, the present study shows increases in serum levels of IL-6, sICAM-1 and plasma histamine during acute asthma exacerbations caused by URTIs. These factors may relate to the airway inflammation and narrowing, and development of asthma exacerbations caused by respiratory virus infections.

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