

Rhinovirus and Asthma Exacerbations



Joshua L. Kennedy, MD^{a,b,c,*}, Sarah Pham, MD^a, Larry Borish, MD^{d,e,f}

KEYWORDS

• Allergy • Asthma • Genetics • IgE • Rhinovirus

KEY POINTS

- Most asthma exacerbations in children and adolescents are associated with development of a rhinovirus (RV) infection.
- These RV-mediated exacerbations seem to require concomitant exposure to a bystander allergen to which the asthmatic is highly sensitized.
- Asthmatics can be genetically prone to RV-mediated exacerbations.
- Targeting IgE and type 2 inflammation–promoting cytokines can mitigate the likelihood of developing RV-induced asthma exacerbations.

INTRODUCTION

Asthma is an increasing public health concern with more than 8% of children and adults now having this condition.^{1,2} Asthma exacerbations, or loss of symptom control that includes increased cough, wheezing, and difficulty breathing, provide the

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^a Department of Pediatrics, University of Arkansas for Medical Sciences, 13 Children's Way, Slot 512-13, Little Rock, AR 72202, USA; ^b Department of Internal Medicine, University of Arkansas for Medical Sciences, 13 Children's Way, Slot 512-13, Little Rock, AR 72202, USA; ^c Arkansas Children's Research Institute, University of Arkansas for Medical Sciences, 13 Children's Way, Slot 512-13, Little Rock, AR 72202, USA; ^d Department of Medicine, University of Virginia Health Systems, MR4 Building Room 5041, 409 Lane Road, Charlottesville, VA 22903, USA; ^e Department of Microbiology, University of Virginia Health Systems, MR4 Building Room 5041, 409 Lane Road, Charlottesville, VA 22903, USA; ^f Carter Immunology Center, University of Virginia Health Systems, MR4 Building Room 5041, 409 Lane Road, Charlottesville, VA 22903, USA

* Corresponding author. University of Arkansas for Medical Sciences, 13 Children's Way, Slot 512-13, Little Rock, AR 72202.

E-mail address: kennedyjoshual@uams.edu

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greatest morbidity to asthmatics and can lead to hospitalizations and, rarely, to death. Importantly, in 2016, ~54% of children² and ~45% of adults¹ with a diagnosis of current asthma reported having 1 or more asthma exacerbations. Although an exact mechanism/causal relationship is not clear, rhinovirus (RV) infections have been extensively linked to asthma exacerbations. From 60% to 80% of children with asthma exacerbations seen in the emergency department (ED) have a concomitant RV infection.^{3,4}

This article evaluates the evidence regarding the association of RV infections with asthma exacerbations. Further, it examines the effects of genetic polymorphisms on the generation of viral-induced asthma exacerbations and discusses the role of the atopic host in the relationship between exacerbations and RV infections. Because of the overwhelming evidence linking RV infection and asthma exacerbations, the ultimate goal is to gather potential mechanisms concerning how this virus can cause such chaos in asthmatics and to speculate on potential therapeutics that may improve outcomes in the future.

THE EVIDENCE THAT RHINOVIRUS INFECTION CAUSES ASTHMA EXACERBATIONS

Viral respiratory infections are the most common triggers for exacerbations of asthma, with human RV, particularly subtypes A and C, being the most frequent.⁵ Hospital admission rates for asthma exacerbations in school-aged children correlate with the seasonal increase of RV infections in the fall and again in the spring, with similar peaks observed in adults.⁶ However, RV infections are ubiquitous and can occur throughout the year. Many of these infections do not cause exacerbations, and some remain completely asymptomatic.⁷ This lack of a consistent association has led to a debate as to whether RV infection is causal or is merely associated in asthma exacerbations.

The Con: Rhinovirus Is Associated with Asthma Exacerbations

In the context of asthma exacerbations, there is ongoing debate as to whether RV infections are the sole cause, are synergistic with other factors, or are merely associated with exacerbations. For example, studies have detected the presence of RV in patients who are asymptomatic or have minimal symptoms. In one prospective study, 126 infants were followed for the first 2 years of life.⁸ Among these subjects, RV was the most predominant virus detected, regardless of the presence of symptoms. In the Early Unbiased Risk Assessment of Pediatric Asthma (EUROPA) prospective case-control follow-up study, 140 symptomatic and 96 asymptomatic children were selected from a birth cohort and were followed for 3 years (November 2009 through December 2012).⁹ RV-A and RV-C were detected with similar prevalence between symptomatic (which included both wheezing and nonwheezing children) and control children. Of note, RV-B was detected significantly more in the control group.⁹ Improved detection techniques using polymerase chain reaction (PCR) and more regular screening may lead to recognition of an even greater prevalence of indolent RV infection in the asymptomatic population.

When examining RV infections in the setting of experimental challenge models, studies have suggested that RV may not cause asthma exacerbations. In one of the first studies to examine this, 21 adult asthmatics were exposed to RV,¹⁰ and their symptoms, spirometry measurements, and histamine challenges were assessed before RV exposure, daily while symptomatic, and 3 weeks post-RV exposure. The results showed no significant changes in spirometry or histamine sensitivity, either as a whole group or when subcategorized by asthma severity.

The Pro: Rhinovirus Causes Asthma Exacerbations

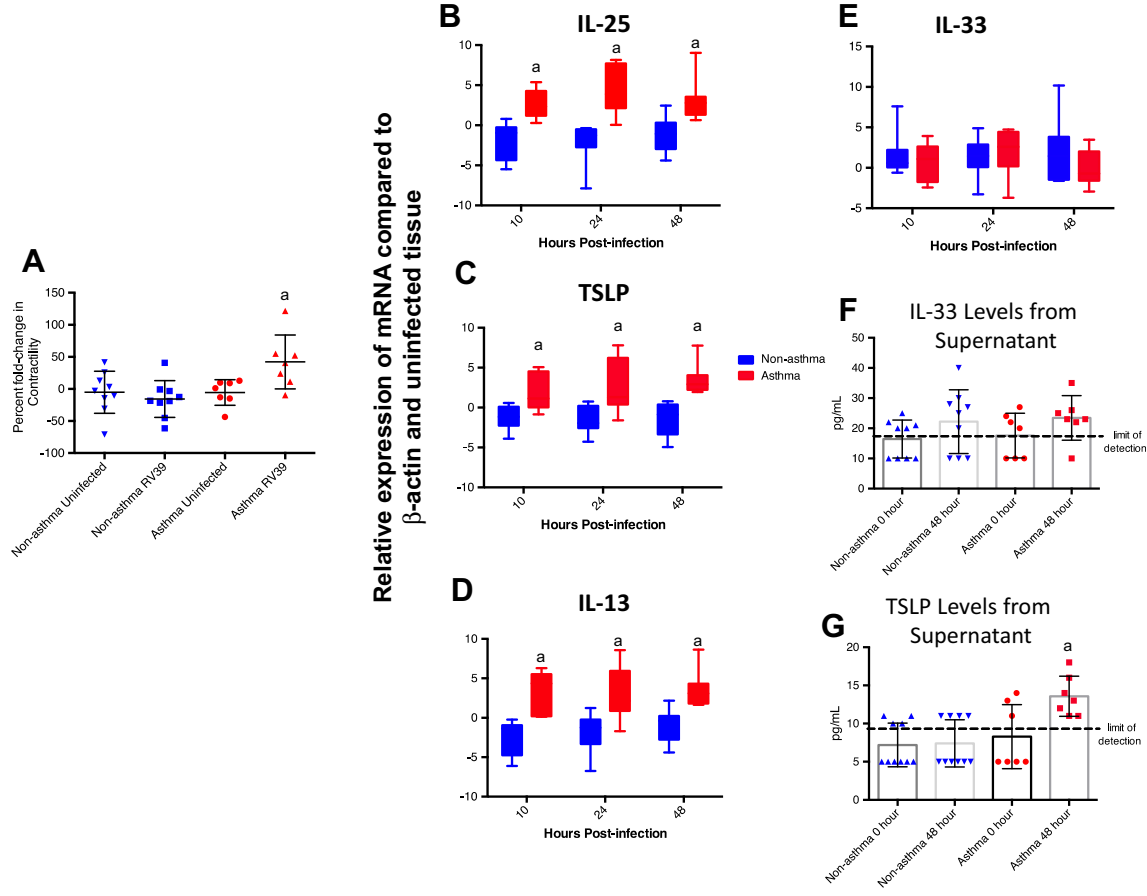
In contrast, many other studies have shown a causal relationship between exposure to RV and asthma exacerbations or, alternatively, objective evidence of increased airways hyperresponsiveness (AHR). In a prospective study following subjects from the same household, 1 with asthma and 1 without, subjects had similar frequency of RV infections, although the asthmatics developed greater lower respiratory symptoms during the infection.^{11,12} Other studies have shown increased susceptibility and symptoms, specifically during RV-C infections in children with asthma. For example, in one study, the frequency of RV-C infections was much higher in the asthma population than in the community as a whole, suggesting that asthmatic children are more susceptible to infection with RV-C. The same study showed that subjects with RV-C had higher asthma severity scores than children with RV-A or RV-B.¹³

More direct evidence of a causative role of RV in acute exacerbations of asthma has been established in the experimental RV infection model.^{14–16} In a study by Zambrano and colleagues,¹⁴ patients with asthma and high total immunoglobulin (Ig) E levels (>371 IU/mL) infected with RV-A16 had increased methacholine sensitivity by day 4 of the study, and that increase remained evident through day 21. These subjects experienced significantly worse lower respiratory symptoms than their control counterparts. Another experimental infection study exposed subjects with asthma on inhaled corticosteroids (ICS) to RV-A16. Subjects had increased symptoms with a mean period between peak cold and peak asthma symptoms of 2.1 (0.3–3.9) days.¹⁵ There was also increased β -agonist use, suggesting loss of symptom control; however, these asthmatics did not experience a reduction in lung function postinoculation. The investigators suggest that long-term ICS use might inhibit this process. In a more recent study, 10 adult atopic asthmatics and 15 controls were infected with RV-A16¹⁶ and bronchial biopsies were taken at 14 days before infection, 4 days after, and 6 weeks postinfection. There were no significant differences in the number of neutrophils at baseline between asthmatics and controls. In asthmatics, the change in number of epithelial and subepithelial neutrophils from baseline to day 4 was significantly higher. Those asthmatics who had higher epithelial neutrophil counts had a significantly larger decrease in forced expiratory volume in 1 second postinfection.

Recently, *in vitro* studies of human precision-cut lung slices (PCLS) from 7 asthmatics and 9 control lungs infected with RV-A39 showed increased AHR (asthma mean, 35% change in AHR after infection; nonasthma mean, 17.7% change in AHR after infection; $P < .05$)¹⁷ (Fig. 1A). These studies also found differences in the inflammatory responses generated by asthmatic tissue compared with controls, specifically related to type 2 (T2) inflammation in the asthmatic tissue, which is discussed further later. To our knowledge, this study is the first to show direct evidence of AHR to RV in asthma tissue *ex vivo*.

GENETIC SUSCEPTIBILITIES LEADING TO ASTHMA EXACERBATIONS AS RELATED TO RHINOVIRUS INFECTION

Although it may be difficult to connect genetic predisposition with a future outcome such as asthma exacerbation risk, researchers have recently shed light on mechanisms whereby this might be the case. Specifically, several candidate genes have been identified that provide potential associations between genetic polymorphisms and viral respiratory illness outcomes, including asthma exacerbations. Some of these genes (eg, *STAT4*, *JAK2*, *MX1*, *VDR*, *DDX58*, and *EIF2AK2*) are important in antiviral and innate immune responses and, as such, might impart susceptibility to respiratory viruses, increase infection severity, and lead to virus-induced asthma exacerbations.^{18,19}



Studies have highlighted the importance of one particular gene in contributing to RV-induced asthma exacerbations: the genetic variant of the transmembrane protein cadherin-related family members 3 (*CDHR3*), which has been identified as the RV-C receptor.²⁰ In a Swedish study, 122 wheezing subjects and 94 controls (ages 6–48 months) were seen both during acute episodes for wheeze and at a follow-up visit 2 to 3 months later.²¹ The genotype AA/AG at the *CDHR3* gene was significantly overrepresented in wheezing children; moreover, children with this genotype sought emergency care because of respiratory symptoms at a significantly higher rate. The AA/AG genetic variant results in an amino acid change (Cys529Tyr) in the CDHR3 protein, at a site that is associated with increased binding, internalization, and subsequent replication of RV-C strains. As such, these findings suggest a mechanism for greater susceptibility to, and symptoms during, RV-C infection that could drive exacerbations of asthma. The same outcome of this *CDHR3* gene mutation was replicated in early-onset asthmatics in a different population. In this retrospective study of 2 cohorts (distinguished by geographic location: 967 healthy and 814 asthmatic adults in Tsukuba and 994 healthy and 591 asthmatic adults in Hokkaido), a greater number of early-onset asthmatics (≤ 10 years of age) had the A (Cys529Tyr) allele.²² When only atopic individuals from both cohorts were examined, the association between the *CDHR3* variant and early-onset asthma reached significance. These findings tie together the importance of genetic susceptibility to RV infection in combination with allergy (and by extension T2 status) in the generation of asthma exacerbations.

THE ROLE OF ALLERGY IN RHINOVIRUS-ASSOCIATED ASTHMA EXACERBATIONS

As mentioned, 60% to 80% of children who are seen for asthma exacerbations have a concomitant RV infection^{3,4}; however, almost all (ie, $\geq 85\%$) are also allergic.²³ It is reasonable to speculate that transient increases in exposure to allergen are not a convincing explanation of most attacks. However, almost all the evidence regarding the effects of RV relates primarily to allergic patients. In a study of Costa Rican children, the relationship of dust mite allergy and severe asthma exacerbations in the context of RV infection was positively correlated.²⁴ Ninety-six acutely wheezing children, 65 stable asthmatics, and 126 controls were enrolled through the ED. Multiple allergen-specific IgE antibodies were measured, and IgE to dust mite (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, or *Blomia tropicalis*) allergens were the most commonly detected. In this population, the probability of acute wheezing was significantly associated with increasing IgE titers to dust mite, and this probability substantially increased if the subject was RV positive during the exacerbation (Fig. 2, Table 1). These data produced a remarkable positive odds ratio of 30

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Fig. 1. RV39 infection of human PCLS from asthma donors. (A) Comparison of carbachol (CCh)-induced airway responsiveness in donors with and without asthma before and after infection with RV39. RV39 infection causes airway hyperresponsiveness to CCh only in PCLS from donors with a history of asthma. (B–E) Interleukin (IL)-25, TSLP, IL-13, and IL-33 gene expression from RV39-infected PCLS. There are significant increases in the expression of IL-25, TSLP, and IL-13 in the PCLS from asthma donors compared with controls without asthma. (F, G) IL-33 and TSLP protein levels in supernatants from RV39-infected PCLS in donors with and without asthma. There are significantly increased TSLP protein levels in those donors with a history of asthma after infection with RV39. ^a $P < .05$. mRNA, messenger RNA. (Adapted from Kennedy JL, Koziol-White CJ, Jeffus S, et al. Effects of rhinovirus 39 infection on airway hyperresponsiveness to carbachol in human airways precision cut lung slices. *J Allergy Clin Immunol* 2018;141(5):1888; with permission.)

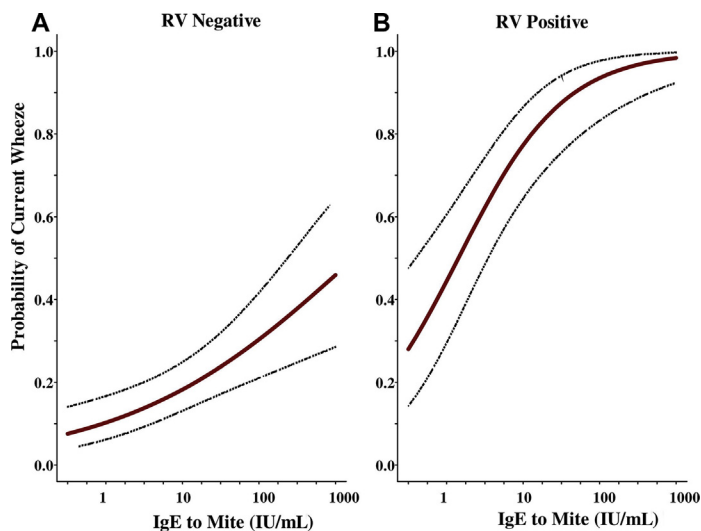


Fig. 2. Probability of current wheezing based on increasing titers of IgE to *D pteronyssinus* in children with (A) negative tests for RV and (B) positive tests for RV. The presence of high titers of specific IgE to dust mite in combination with RV leads to greatly increased risk for current wheezing. (From Soto-Quiros M, Avila L, Platts-Mills TA, et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J Allergy Clin Immunol* 2012;129(6):1504; with permission.)

($P<.001$), arguing that, in the presence of sufficient allergic sensitization to the dust mite, an RV infection virtually ensured development of an asthma exacerbation sufficiently severe to require urgent care.

The findings of potential synergy between RV infection, allergic sensitization, and asthma exacerbations were further confirmed in controlled trials using omalizumab (anti-IgE) to treat severe or moderately severe asthma.^{25,26} Omalizumab used to treat

Table 1 Odds ratio for wheezing based on positive tests for rhinovirus and titers of immunoglobulin E antibodies to dust mite (<i>Dermatophagoides pteronyssinus</i>)								
Titer of IgE Antibodies to Mite	n	<0.35 IU/mL		0.35–17.4 IU/mL		≥17.5 IU/mL		
		PCR–	PCR+ (A/C) ^a	PCR–	PCR+ (A/C) ^a	PCR–	PCR+ (A/C) ^a	
Current wheeze	95	5	4 ^b (2/2)	8	16 (3/10)	20	42 (8/30)	
Stable asthma	63	12	2 (0/1)	12	5 (1/2)	31	1 (0/1)	
Control	123	60	13 (6/4)	31	2 (1/1)	14	2 (1/1)	
Nonwheezing children ^c	186	73	15 (6/5)	43	7 (2/3)	45	3 (1/2)	
Odds Ratio ^d	—	3.89 (0.9–16), $P = .07$		12.3 (3.8–39), $P < .001$		31.5 (8.3–108), $P < .001$		

^a Number in brackets indicates the number of subjects positive for group A and group C strains of RV.

^b Two of these 4 children had IgE antibody to *B tropicalis*: (24.3 and 1.66 IU/mL).

^c Stable asthma combined with nonasthmatic controls.

^d Odds ratio for wheezing among RV-positive (real-time PCR) compared with RV-negative subjects. Adapted from Soto-Quiros M, Avila L, Platts-Mills TA, et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J Allergy Clin Immunol* 2012;129(6):1503; with permission.

inner-city children had a striking effect in preventing the increase in acute episodes of asthma that occurred in May and September. As previously noted, those months coincide with the season for which allergen exposure is highest and viral infections are prevalent. As also mentioned earlier, during experimental RV challenge, patients with higher IgE levels (>371 IU/mL) have significant changes in bronchial hyperreactivity as judged by methacholine testing and increased symptom severity. Together, these observations strongly suggest that omalizumab likely has a role in mitigating RV-induced exacerbations of asthma. However, controlled trials of anti-IgE treatment before RV challenge, which are ongoing (ClinicalTrials.gov: NCT02388997) will be needed to understand the exact interaction between IgE-mediated allergy and RV-induced exacerbations.

MECHANISMS OF RHINOVIRUS-INDUCED EXACERBATIONS OF ASTHMA RELATED TO ALLERGY

Current research suggests a differential response in asthmatics that consists of cytokines that could bias an allergic response, including interleukin (IL)-25, thymic stromal lymphopoietin (TSLP), and IL-33. In one study, mice that were sensitized to ovalbumin before experimental RV-1B infection showed significantly increased IL-25 messenger RNA (mRNA) levels (28-fold higher than noninfected, allergen-sensitized mice at 10 hours postinfection).²⁷ Higher IL-25 mRNA levels were associated with increased levels of the T2 cytokines IL-4 and IL-13 in bronchoalveolar lavage fluid 10 hours postinfection and IL-5 at 24 hours postinfection. Moreover, when this group of mice was treated with a monoclonal antibody to block the IL-25 receptor, levels of IL-4, IL-5, and IL-13 decreased and were similar to controls. The researchers from this study corroborated a similar role for IL-25 in human asthmatics, showing that when 28 asthmatics and 11 controls were experimentally infected with RV-A16, asthmatics showed significantly increased levels of IL-25 compared with the baseline before infection.

In the studies mentioned earlier using human PCLS, a role for IL-25 and TSLP was suggested in the increased AHR afforded to human airways after RV infection.¹⁶ In asthmatic tissue, not only was gene expression of IL-25, TSLP, and IL-13 significantly increased at 10, 24, and 48 hours postinfection but TSLP protein release was also significantly increased at 48 hours postinfection (Fig. 1B–G). In other studies, TSLP has been induced by both RV infection and double-stranded RNA in the lungs of allergic mice²⁸ and in human bronchial epithelial cells.²⁹ Further, TSLP is increased in the nasal passages of young children with RV infection.³⁰ These findings provide supporting evidence that epithelial generation of T2 cytokines (such as IL-13) leads to increased AHR in the setting of RV infection.

IL-33 has a vital role in the induction and effector phases of type 2 immune responses, and, as such, it is important in many allergic diseases, including asthma, atopic dermatitis, and allergic rhinitis.³¹ Genetic polymorphisms of both the IL-33 gene and its receptor are strongly linked to asthma, suggesting atopic individuals may be genetically predisposed to secrete more and respond better to IL-33, especially during allergen challenge.³² In a recent study by Jackson and colleagues,³³ experimental RV inoculation and bronchoalveolar lavage sampling of human subjects revealed induction of IL-4, IL-5, IL-13, and IL-33 in the airways of asthmatics. Peripheral blood T and ILC2 cells from the same subjects cultured with the supernatants of RV-infected bronchial epithelial cells also induced these cytokines, and this process was entirely dependent on IL-33.^{34,35}

FUTURE THERAPEUTIC OPTIONS FOR PATIENTS WITH VIRAL-INDUCED EXACERBATIONS OF ASTHMA

Given the studies that show a muted allergic response in asthmatic patients treated with biologics directed against IgE, it is reasonable to expect lower severity of viral-induced exacerbations because of the lesser T2-biasing response. One such biologic, omalizumab, effectively blocks the activity of much of the circulating IgE by targeting its binding to the high-affinity receptor-binding site on IgE. As a result, omalizumab therapy improves asthma impairment, risk, and degree of control, as shown by reduction in days with asthma symptoms, reduction in exacerbations and hospitalizations, and reduced need for ICS to maintain control.²⁶ More importantly, as previously noted, the seasonal peaks of asthma exacerbations seen in spring and fall were nearly eliminated in the omalizumab treatment group compared with the control. This association remained in spite of similar detection of viruses throughout the year in both the treatment and control groups.²⁶ However, because the treatment group reported a significantly decreased number of exacerbations, this further supports the previously discussed synergistic association between viral infections and allergen responses during asthma exacerbations.

In addition to biologics directed against IgE, additional pharmacologic agents have also been developed. Given the central importance of TSLP to RV-mediated asthma exacerbations, it is reasonable to speculate that this agent would also attenuate the presence and severity of exacerbations. A monoclonal antibody to TSLP (tezepelumab) has been evaluated in both an allergen challenge model³⁵ and in severe uncontrolled asthmatics and was shown to significantly improve asthma control and prevent exacerbations while decreasing eosinophil and exhaled nitric oxide levels.³⁶ Human monoclonal antibodies to IL-25 and IL-33 are currently also being developed as asthma therapeutics, and the central importance of these cytokines to RV-mediated exacerbations in preclinical studies supports their potential to improve symptoms during RV infections. For example, as previously discussed, blockade of the IL-25 receptor in murine models correlated with decreased T2 biasing response during RV infections.²⁷ Similarly, in an in vitro study using human asthma bronchial epithelial cells experimentally infected with RV-A16, antibodies to IL-33 resulted in attenuated T2 cytokine production.³³ In summary, these studies support the premise that biologics directed against TSLP, IL-25, and IL-33 could be additional therapeutic targets for prevention of viral-induced asthma exacerbations.

SUMMARY

In recent years, significant progress has been made toward improving asthma control; however, despite these best efforts, there continues to be significant morbidity and, tragically, mortality from asthma. RV is ubiquitous and typically causes only minor upper respiratory symptoms in the general population. However, RV causes asthma exacerbations, especially in the presence of another impetus, especially allergy. Because exacerbations do not happen in every asthmatic with an RV infection, it is possible that exacerbations may be related to the genetic background of the host, occur in the context of a concomitant allergen exposure, or require altered immune responses to the virus that lead to greater inflammation and loss of asthma control. In allergic patients, mechanisms of the host immune response seem to bias toward increased allergic inflammation and worsening AHR. Given these responses, there are several possible treatments available and even more being developed that should improve the ability to control exacerbations related to RV infection.

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