

1 **Title:**

2 Understanding the Association of Human Rhinovirus with Asthma

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MINIREVIEW

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Cosby A. Stone, Jr. and E. Kathryn Miller

25

Abstract

27

Human rhinoviruses are ubiquitous seasonal pathogens. They have known associations

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with first onset of wheezing illnesses in children, and with asthma exacerbations in all

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ages of patients. It is not yet certain whether human rhinoviruses play a direct role in the

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pathogenesis of asthma by activating deleterious inflammatory responses or if they only

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serve as a catalyst to accelerate the disease in genetically predisposed individuals.

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There have been previously demonstrated reductions in development of the asthmatic

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phenotype with passive immunization against respiratory syncytial virus, though in the

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case of rhinovirus, there are barriers to effective vaccine development such as the lack

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of a common antigenic target due to alterations of surface markers amongst subtypes. It

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remains to be determined whether certain subtypes of human rhinovirus are more

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“asthmagenic” and therefore worthy of greater attention as vaccine candidates, but

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several studies have suggested that RV-C and certain RV-A strains may be more

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strongly linked with asthma.

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44 **Introduction**

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46 Human rhinoviruses (RVs), which are among the most ubiquitous viral pathogens in
47 humans, were originally discovered in the 1950s. RVs produce disease in all parts of
48 the world, and typically have seasonal peaks in spring and fall in geographic regions with
49 temperate climates. RVs typically infect the upper respiratory tract, and the most
50 common clinical manifestations include rhinitis or nasal congestion, though up to 15% of
51 patients infected with RVs may be asymptomatic (1). More recently, RVs have been
52 implicated in more serious respiratory disease including dyspnea,
53 laryngotrachobronchitis, exacerbations of chronic obstructive pulmonary disease
54 (COPD), bronchitis, pneumonia, and bronchopneumonia. For example, infant
55 bronchiolitis has historically been attributed to respiratory syncytial virus (RSV) infection
56 (2, 3), but recent studies implicate rhinovirus as another important cause of bronchiolitis
57 (2, 4-6). Papadopoulos et al demonstrated that RSV and RV were recovered from 72%
58 and 29%, respectively, of virologically confirmed cases of acute bronchiolitis in infants,
59 and that RVs were associated with more severe disease than RSV in this population (7).
60 RVs have also been detected outside of the respiratory tract from patients with
61 symptoms including fever, febrile convulsion, otitis media, gastroesophageal reflux
62 disease, pericarditis, dyspnea, apnea, and a variety of other potentially life threatening
63 conditions.

64

65 RV's are non-enveloped viruses with capsids that express four viral proteins, VP1, VP2,
66 VP3, and VP4. These proteins are arranged in overlapping fashion to form an
67 icosahedral structure, with VP1, VP2, and VP3 expressed on the surface of the capsid,
68 and VP4 somewhat hidden beneath, just overlying the viral genome. Three genetically
69 distinct RV species, RV-A, RV-B, and RV-C, have been described. RV-A and RV-B

70 were distinguished from one another in the early 1990s based on the activities of
71 antiviral compounds(8), and these distinctions were further refined through molecular
72 analysis; RV-C has only been recognized since 2009(9). There are currently 74 known
73 subtypes of RV-A, 26 subtypes of RV-B, and at least 50 subtypes of RV-C(10).
74 Assignment of a RV to a given species is based on sequences of the VP4/VP2 or VP1
75 proteins (11). In most RVs, binding and fusion of the viral particle is mediated by
76 attachment to ICAM-1(12), which binds to a pocket groove of the VP-1 protein(13). Other
77 subtypes of RVs bind to LDL receptor family receptors. There are additional receptors
78 for RV-C that are currently unknown which appear to be distinct from the other known
79 receptors(14), but one of them appears to be CDHR3, a cadherin-related family member
80 protein identified in a genome wide association study as being strongly associated with
81 severe asthma exacerbations(15). Upon attachment to the cell, the virion particle is
82 internalized in an endosome, where the subsequent drop in pH causes uncoating of the
83 virus's positive sense strand of RNA and release of that RNA from the endosome,
84 leading to translation of viral proteins, replication of viral RNA via formation of negative
85 sense complementary strands that allow for transcription of further mRNA-like positive
86 strands, and assembly of new viral particles. Newly assembled virus is released through
87 epithelial cell lysis, shedding viral particles onto neighboring cells(10).

88

89 In general, RV-A and RV-C are the dominant species found circulating among humans,
90 and are significantly more common than RV-B. RV-A and RV-C generally do not peak
91 during the same season, suggesting that these species could interfere with one
92 another's activity, or that there is cross-protection from previous infection(16).

93

94 **Human Rhinoviruses and Asthma**

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96 More than 80% of pediatric asthma is diagnosed before five years of age (17), and a
97 consensus statement from the Environmental and Occupational Respiratory Diseases
98 Interest Section, of the American Academy of Allergy, Asthma & Immunology identified
99 five crucial host factors that could increase the probability of developing asthma in
100 infants and remain areas for further inquiry. These include: 1) lower lung volumes at
101 birth, 2) the presence of atopic disease, 3) greater intensity of mucus secretion when
102 infected with a viral pathogen during infancy, 4) neutrophilic pathways that induce airway
103 hyperresponsiveness to infection, and 5) differential production of type I and III
104 interferons in response to a variety of viral infections, including RVs, during infancy(18,
105 19). (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880817/>)

106

107 There is substantial evidence linking RVs to wheezing illness, bronchiolitis, and
108 exacerbations of asthma in adults, children, and infants(18, 20-28). One group linked
109 RV's and asthma epidemiologically, based on an association between the development
110 of bronchiolitis during RV season and a subsequent diagnosis of childhood asthma;
111 significantly, however, this study did not include virologic testing (29). Iwane et al
112 studied children <5 years of age hospitalized with acute respiratory illnesses compared
113 to healthy clinic control patients and demonstrated RV-A detection rates among children
114 >24 months old to be 8.1% in the hospitalized group and 2.2% in the control group (P =
115 .009), and among children >6 months old, RV-C detection rates of 8.2% and 3.9%,
116 respectively (P = .002), with hospitalization diagnoses of asthma or wheezing being
117 more common among RVs than other viruses(30). Piotrowska et al found that infection
118 with RV was an important determinant for the likelihood of children <2 years of age being
119 hospitalized for wheezing illness, at rates similar to RSV(31).

120

121 Importantly, acute RV-induced wheezing during infancy has been associated with
122 increased risk for recurrent wheezing and subsequent childhood asthma. (3, 32).
123 Jackson et al (2008) demonstrated that infants of atopic families who wheeze with RVs
124 in the first three years of life are more likely to develop asthma by age six than those
125 who wheeze with RSV (OR for RV=9.8, RSV =2.6). Further, 90% of children who
126 wheezed with RV in the third year of life developed asthma by six years of age (3, 28)
127 The association of RVs with bronchiolitis (25, 33, 34), wheezing in infancy and later
128 childhood(35), and asthma exacerbations suggests that RVs may be associated with the
129 pathogenesis of asthma. Having shown earlier that RV-induced wheezing predicts
130 subsequent asthma development, Jackson et al have more recently hypothesized that
131 initial allergic sensitization leads to the propensity for RV-related wheezing to occur. In a
132 sequentially monitored birth cohort, they showed that children transitioned from allergic
133 sensitization to wheezing illness at higher ratios if they were exposed to rhinoviruses in
134 between(36).

135

136 **Risk Factors for Severe Rhinovirus Infection:**

137

138 There are several epidemiologic risk factors known to predict the likelihood of having a
139 more severe outcome with rhinovirus infection. The presence of bronchopulmonary
140 dysplasia has been noted to increase the incidence of severe rhinovirus infection in very
141 low birth weight infants, whereas breastfeeding decreases the incidence(37). Active
142 smoking is known to increase the likelihood of severe asthma exacerbation caused by
143 rhinovirus in adults(38), and in children, prenatal and postnatal secondhand smoke
144 exposure has long been known to predispose to increased respiratory infections and
145 increase hospitalizations for lower respiratory tract infections(39, 40). A history of
146 maternal atopy and asthma also increases the risk for severe rhinovirus infection in their

147 offspring(41). Finally, more frequent exposure to pathogens in settings such as daycare
148 leads to increased infection rates of all types of respiratory pathogens(42), and
149 rhinoviruses are more commonly associated with severe outcomes when compared to
150 most other viruses acquired in daycare(43).

151

152 **Host- Pathogen Interactions and the Onset of Wheezing and Asthma**

153

154 Evidence supports the concept that certain individuals are predisposed to the
155 development of wheezing illness by genetic and environmental factors(44), and that viral
156 infections acquired during early infancy and childhood are often the initial triggers for
157 these illnesses.(35) For example, studies of RSV using genetic variance and direction of
158 causation models in twins demonstrated that wheezing illness may reflect genetic
159 susceptibilities of the host (45). Elevated total IgE level(46) and sensitization to dust
160 mite(47) or other allergens(48) have been shown to influence the likelihood of wheezing
161 with rhinovirus, adding evidence that allergic individuals may have a different response
162 to infection.

163

164 In mouse models of allergic airway inflammation, RV infection has been demonstrated to
165 induce increased levels of eotaxin, IL-4, and IL-13. Bronchoalveolar lavage performed in
166 these animals also showed increased infiltration of the respiratory tract with eosinophils,
167 macrophages, and neutrophils compared to controls (49). RVs have also been shown to
168 stimulate the synthesis of a variety of factors that can influence airway remodeling, such
169 as vascular endothelial growth factor(50), nitric oxide(51), and transforming growth factor
170 beta(52) during in vitro experiments with cultured human epithelial cells(53). Human
171 volunteers with allergic disease and mild asthma, who were experimentally inoculated

172 with human RV-16, had a reduced forced expiratory volume in 1 second (FEV1) and
173 potentiated airway inflammation after provocation(54).

174

175 **Rhinoviruses, Asthma and Differential Interferon Production by the Host**

176

177 There is a debate on the role of interferon production, specifically Type III interferons, in
178 the development of wheezing in response to upper respiratory infections. Some groups
179 have shown impaired Th-1 responses and deficient IFN- γ production in human subjects
180 with asthma, and went on to suggest that deficient antiviral defenses might play a role in
181 the pathology of RV-initiated asthma(55-57). Baraldo et. al noticed that, compared to
182 healthy controls, asthmatics showed decreases in both Type I and Type III interferons
183 when challenged with RV type 16, regardless of their atopic status; and noted that with
184 decreases in IFN- λ there was a correlation with increased serum IgE (58, 59).
185 Other groups have suggested a different viewpoint, that Type III interferons such as IFN-
186 λ increase Th-2 type responses. One group studied school-aged children with
187 underlying asthma and upper respiratory symptoms and found that increased wheezing
188 and wheezing severity were associated with elevated, not depressed, levels of nasal
189 wash IFN- λ_1 . Moreover, the association between wheezing and RV infections
190 disappeared when levels of IFN- λ_1 were accounted for in the statistical analysis as a
191 covariate(60). Pritchard et al have noted that Type I interferons, α and β , secreted by
192 plasmacytoid dendritic cells, are an important brake in both controlling RVs and in
193 preventing a deleterious Th-2 response(61). The same group recently reported an
194 increase in Th-2 cytokines, specifically IL-5 secretion, by peripheral blood mononuclear
195 cells (PBMC) when both RV and the Type III interferon IFN- λ was present, and
196 attenuation of Th-2 secretion when IFN- β was present(62). They went on to check the
197 PBMC of 22 asthmatic patients and noted multiple abnormalities in the expression of

198 Type I interferons via pathways of reduced expression of intra-cellular signaling
199 molecules including interferon regulatory factors (IRF1, IRF7), NF- κ B family members
200 (p50, p52, p65 and I κ B α) and STAT1, and by reduced responsiveness to TLR7/TLR8
201 activation(63). Their hypothesis is that failure of Type I interferon function either by
202 deficient production or poor receptor and downstream performance leads to failure of
203 suppressing Th-2 phenotypic response from RV specific memory T cells (63). Taking
204 this hypothesis one step further, Djukanović et al have noted in randomized controlled
205 trials that by administering the Type I interferon, IFN- β , via nebulization that response to
206 viral URIs do not progress to wheezing disease in asthmatics(64).

207

208 **Progress toward rhinovirus vaccination.** Studies with RSV have shown that passive
209 immunization with monoclonal antibodies can reduce the probability of developing
210 asthma(65). Given the strong association between early RV infection and subsequent
211 wheezing illness and asthma, the concept of developing an RV vaccine that would
212 similarly reduce the likelihood of developing asthma has attracted considerable attention.
213 Unfortunately, there are over 150 RV subtypes, (66) and little cross protection afforded
214 among subtypes after infection(67). The amino acid sequences of antigenic sites
215 expressed on VP1 and other surface proteins have high intraspecies variability, but
216 vaccination of mice with either VP2 plus VP4 antigens with adjuvant or VP1 antigens
217 along with adjuvant have produced cross-species neutralizing IgG antibodies(68, 69). It
218 is known that high homotypic antibody levels reduce symptoms on re-exposure to a
219 previously experienced strain(70), but it has been very difficult to generate cross-reactive
220 neutralizing antibodies in humans up to this point. Interest remains in vaccination as a
221 strategy if certain RV subtypes can be consistently shown to be more “asthmagenic”,
222 similar to the way that targeted HPV vaccination has been implemented(71).

223

224 **Closing Comments.** The association of rhinovirus infection with the onset of wheezing
225 illness in children and exacerbations of asthma continues to be an important area for
226 research in host-pathogen interactions. Certain features of infection with rhinovirus,
227 including stimulation of IL-4, IL-13, and eotaxin production; immigration of inflammatory
228 cells such as eosinophils, macrophages and neutrophils; and subsequent increases in
229 factors thought to be important for airway remodeling such as vascular endothelial
230 growth factor, nitric oxide, transforming growth factor beta, and fibroblast growth factor
231 would all point to the possibility that rhinovirus infection is an “asthmagenic” infection.
232

233 Host factors that predispose to an asthmatic response, such as impaired Th-1 responses
234 and variations in host interferons expressed in response to rhinovirus infection, have
235 been observed in subjects with subsequent asthma. When coupled with clinical
236 knowledge that children with lower lung volumes and atopic phenotypes are more likely
237 to develop asthma, it can sometimes seem that rhinovirus infection is simply the
238 revelation of an inevitable progression for certain children. Perhaps, though, rhinovirus
239 infection and the subsequent response to it are a modifiable risk factor.

240

241 Though creating a universal RV vaccine is currently quite difficult to achieve, due to the
242 wide variety of RV subtypes and poor cross-protection from prior heterologous
243 infections, ongoing research in rhinovirus subtypes and subsequent risk of asthma
244 development, as well as treatments aimed towards patients with alterations in interferon
245 response to viral infection, may be fruitful pathways toward rational interventions that
246 could impact the development of asthma in early childhood and reduce overall disease
247 burden. Given the enormous economic impact of caring for patients with asthma,
248 estimated at 56 billion dollars per year in 2007(72) there is substantial financial and

249 social incentive to identify the pathogenic mechanisms leading to the development of
250 asthma, and to develop better approaches for preventing and treating this disease.

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