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Viral Diversity in Asthma

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Asthma is a heterogeneous inflammatory disease of the airways characterized by reversible airway obstruction, airway hyperresponsiveness, inflammatory cell infiltration, thickening of the lamina reticularis, and the accompanying symptoms of chest tightness, wheezing, coughing, and shortness of breath.\(^1,2\) Asthma now affects an estimated 16.4 million adults and 7.0 million children (7.3% and 9.4% of the population, respectively) within the United States\(^3,4\) and is additionally indicated as a “contributing factor” in nearly 7000 deaths each year.\(^5\)

Whereas chronic asthma results from the daily inhalation and response to allergen (eg, dust, pollen, animal dander) and is by and large successfully managed by the individual, acute asthma attacks or exacerbations are precipitated primarily by respiratory viral infections and frequently require immediate medical intervention. In the United States alone, severe asthma exacerbations lead to over 400,000 hospitalizations each year, at a cost of one-third of the total $11.5 billion in annual asthma-related health care expenditures.\(^6\)

Although the exact mechanism(s) by which respiratory viral infection causes asthma exacerbation remains to be determined, the respiratory viruses implicated in exacerbations have themselves been largely identified and well characterized (Table 1). Traditionally associated with acute respiratory illness (ARI) or symptoms of the “common cold,” the respiratory viruses implicated in asthma exacerbations predominantly possess RNA genomes with a distinct genome organization (positive [+] or negative [−] sense), virus particle (virion) morphology (enveloped or nonenveloped), host cell receptor interaction, and well-defined annual or seasonal prevalence.

**KEYWORDS**

- Asthma
- Exacerbation
- Respiratory
- Newly identified virus

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### Table 1
Human respiratory viruses associated with asthma exacerbations

| Genus  | Virion Morphology | Species or Subtypes | Cell Receptor(s) | Highest Seasonal Prevalence | % of Virus-Related Asthma Exacerbation |
|--------|-------------------|---------------------|------------------|-----------------------------|---------------------------------------|
| **RNA Viruses** | | | | | |
| **Picornaviruses** | | | | | |
| HRV (rhinovirus) | ss +ve | Nonenveloped Icosahedral | A, B, C A–D | ICAM-1, VLDL-R ICAM-1, Coxsackievirus adenovirus receptor (CAR), α/β integrins | Spring, Autumn Variable | 20–80 |
| HEV<sup>a</sup> (enterovirus) | ss +ve | Nonenveloped Icosahedral | A–D | ICAM-1, Coxsackievirus adenovirus receptor (CAR), α/β integrins | Variable | |
| **Paramyxoviruses** | | | | | |
| RSV (respiratory syncytial virus) | ss –ve | Enveloped Pleomorphic | A, B | Heparan sulfate (HS)(?) | Late autumn–winter | 5–50 |
| HMPV (metapneumovirus) | ss –ve | Enveloped Pleomorphic | (A, B?) | Integrin αvβ1 | Late winter–spring | 2–13 |
| PIV (parainfluenzavirus) | ss –ve | Enveloped Pleomorphic | 1, 2, 3, 4a, 4b | Sialic acid–containing oligosaccharides | Mostly winter | 1–8 |
| **Orthomyxoviruses** | | | | | |
| IFAV (influenzavirus) | ss –ve | Enveloped Pleomorphic | Various | Glycans with α2,6 or α2,3 sialic acid–galactose linkages (subtype/host dependent) | Winter | 1–9 |
| IFBV | ss –ve | Segmented Pleomorphic | | | | |
| IFCV | ss –ve | Segmented Pleomorphic | | | | |
| **Coronaviruses** | | | | | |
| HCoV-229E | ss +ve | Enveloped Pleomorphic | Alphacoronavirus<sup>^</sup> | CD13 (aminopeptidase N) Angiotensin-converting enzyme (ACE)-2 | Autumn, winter | 1–4 |
| HCoV-NL63 | ss +ve | Enveloped Pleomorphic | Betacoronavirus<sup>^</sup> | 9-O-acetylated sialic acid moieties TD | Winter, spring, summer | |
| HCoV-OC43 | ss +ve | Enveloped Pleomorphic | Alphacoronavirus<sup>^</sup> | CD13 (aminopeptidase N) Angiotensin-converting enzyme (ACE)-2 | Autumn, winter | |
| HCoV-HKU1 | ss +ve | Enveloped Pleomorphic | Alphacoronavirus<sup>^</sup> | CD13 (aminopeptidase N) Angiotensin-converting enzyme (ACE)-2 | Autumn, winter | |
### DNA Viruses

| Virus                | Structure |Envelope | CAR, HS-glycosaminoglycans, CD86, various integrins | Season       | Incidence |
|----------------------|-----------|---------|----------------------------------------------------|--------------|-----------|
| AdV (adenovirus)     | ds linear | Nonenveloped icosahedral | A–F | Winter, spring | <7 |
| HBoV (bocavirus)     | ss circular | TD (most likely nonenveloped icosahedral) | 1–3(?) | TD | Winter | 6–13(?) |
| WuPyV (WU polyomavirus) | ds circular | TD (most likely nonenveloped icosahedral) | TD | Spring, autumn, winter | TD |
| KIPyV (KI polyomavirus) | ds circular | TD (most likely nonenveloped icosahedral) | TD | TD | TD |

Newly identified viruses (NIVs) are underlined.

* Human enteroviruses including: Coxsackieviruses and other enteroviruses associated with acute respiratory illness; ss, single-stranded; +ve, positive sense; −ve, negative sense; ds, double-stranded; (?), research ongoing; ^, genera of the subfamily Coronavirinae; TD, to be determined.
The full extent of respiratory virus involvement in exacerbation has recently been revealed in asthma studies with the implementation of molecular methods of viral detection, specifically the reverse transcriptase polymerase chain reaction (RT-PCR). Molecular methods of viral detection have superior sensitivity and specificity compared with cell culture–based methods and additionally allow for the improved identification of multiple viruses (and other pathogens), revealing the role of dual or multiple infections play in asthma exacerbations. Indeed, molecular methods have also been invaluable in identifying new respiratory viruses, the majority of which were described after the emergence of the severe acute respiratory syndrome-associated coronavirus (SARS-CoV) that prompted research into the etiology of ARI. These “newly identified viruses” (NIVs) including human metapneumovirus (HMPV; described pre-SARS), the human rhinovirus (HRV) species C (HRV-Cs), human coronaviruses (HCoVs)-NL63 and -HKU1, human bocavirus (HBoV), and the KI and WU polyomaviruses (KIPyV and WUPyV) are now the focus of intense research, and their involvement in asthma exacerbations is slowly beginning to be determined. Because those respiratory viruses most associated with exacerbations—the HRVs, respiratory syncytial virus (RSV), and HMPV—are reviewed elsewhere in this issue by Miller and colleagues, this review discusses some of the other respiratory viruses implicated in childhood and adult asthma exacerbations, including additional RNA viruses and those with DNA genomes. By also encompassing some of the recently described NIVs, this article illustrates the diversity that exists in virus-related asthma exacerbations.

INFLUENZA VIRUSES

Influenza viruses (IFVs) are probably the best known of all the respiratory viruses, due to their ability to cause annual epidemics and potential pandemics of serious respiratory disease. IFVs pose the greatest risk of morbidity and mortality to young children and the elderly, and as such have been the focus of repeated public health and vaccination campaigns. However, despite their potential to cause serious respiratory illness in otherwise healthy individuals, most asthma studies describe relatively low levels of IFVs in exacerbations, accounting for approximately 1% to 9% of all virus-related asthma exacerbations (see Table 1).

IFVs constitute the family Orthomyxoviridae and are segmented—single stranded (ss) RNA viruses. The IFV virion has a pleomorphic envelope derived from host cell membranes and incorporates 3 viral encoded surface proteins: hemagglutinin (HA), neuraminidase (NA), and matrix protein 2 (M2). Under the envelope and encased within the matrix protein (M1), the core of the IFV virion contains the ribonucleoprotein complex, consisting of the viral RNA segments, polymerase proteins (PB1, PB2, and PA), and the nucleoprotein (NP).

There are 3 types of IFVs, -A (IFAV), -B (IFBV), and -C (IFCV), which are divided further in subtypes and strains based on the combination of HA and NA proteins (eg, H1N1, H3N2). IFAV and IFCV have subtypes known to infect both animals (eg, birds, pigs) and humans, whereas IFBV is predominately a human virus. Although all types of IFVs can cause ARI in humans, IFAV and IFBV subtypes and strains are of the most prominent in the annual epidemics or “flu season” that occurs during the winter months.

IFVs initiate infection via the HA protein attaching to sialic acid (SA) linked to galactose (Gal) sugars on the terminal ends of host cell surface glycans. It has been determined that the HA interaction is dependent on the sialic acid-galactose linkages, with HA from subtypes that infect humans recognizing α2,6 linkages (SAα2,6Gal), whereas

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HA from subtypes infecting other animals mostly recognize α2,3 linkages (SAα2,3Gal).17,18

Although IFVs are implicated in 1.9% to 6.6% of wheezing illnesses in children7,10,12,13 and have been detected in 9.8% of asthmatic adults during emergency department (ED) visits,15 uncertainty remains as to whether IFVs are specifically responsible for the production of asthma exacerbations.19,20 The main contention arises from the role that vaccination has played in preventing exacerbations. Because, unlike other respiratory viruses, vaccines against IFV subtypes and strains are available and asthmatics frequently have increased vaccination rates due to their at-risk status during flu season, IFV-related exacerbations should be reduced or indeed eliminated among asthmatic children and adults.21,22 However, some studies have shown that despite their three- to fourfold greater odds of having an influenza vaccination (as reported by parents), asthmatic children have higher rates of IFV-related hospital visits23 and that vaccination does not affect the number, duration, or severity of IFV-related asthma exacerbations compared with placebo.24 Other similar studies have shown that influenza vaccination also fails to reduce severe and fatal complications in adults with asthma and chronic obstructive pulmonary disease (COPD).20

The association of IFVs with exacerbations in vaccinated asthmatics questions the efficacy of seasonal influenza vaccines in this group and also suggests a role for other respiratory viruses in IFV-related exacerbations. If influenza vaccinations are effective, then it is likely that IFV-related exacerbations are caused by infection with another respiratory virus, such as those that peak in prevalence during the same time as IFVs (eg, RSV and HMPV). However, if influenza vaccination of asthmatics fails to reduce IFV-proven exacerbations (ie, by RT-PCR during symptomatic illness) then alternative vaccination strategies may be required to increase efficacy. Ensuring that comprehensive respiratory virus testing is employed during both influenza vaccination and asthma studies and that vaccination rates among asthmatics remain high, the contention over vaccination and IFV-related exacerbations will be better clarified.

Some recent studies focusing on ARI suggest that infection with other respiratory viruses, particularly HRVs, may actually provide “protection” against IFV infection.25,26 Although such claims remain to be fully substantiated, viral competition may be a contributing factor in the relatively low rates of IFV-related asthma exacerbations being reported. It remains to be determined whether the asthmatic phenotype preferentially facilitates infection with respiratory viruses other than IFVs or whether, owing to vaccination in the wider community, the overall prevalence of IFVs is reduced making infection with another “uncontrolled” respiratory virus more likely.

The association of IFVs with asthma exacerbation is complicated by the emergence of more virulent pandemic strains, such as the novel 2009 swine-origin IFAV H1N1 (S-OIV), which may pose a greater risk to asthmatics than seasonal strains.27 Although the full impact of S-OIV remains to be determined, initial studies have indicated that among both children and adults hospitalized with RT-PCR–identified S-OIV, asthma accounted for the largest percentage (28%) of all underlying medical conditions.27 However, it is unclear whether S-OIV evokes a specific immune response among asthmatics or whether, owing to increased awareness of this particular strain, asthmatics were more likely to seek medical care when respiratory symptoms initially began.

HUMAN CORONAVIRUSES

HCoVs were initially described in the 1960s in studies aiming to determine the etiologic agent responsible for ARI, but gained notoriety after the emergence of SARS-CoV in 2003. Since that time, 2 additional HCoVs have been described in ARI studies,
indicating that there are several HCoVs potentially associated with respiratory illness in humans. Because of the severity of associated illness, this review excludes SARS-CoV and focuses solely on the 4 HCoVs associated with ARI and currently implicated in 1% to 4% of virus-related asthma exacerbations: HCoV-OC43, HCoV-229E, and the NIVs, HCoV-NL63 and HCoV-HKU1 (see Table 1).  

HCoVs are classified within the Family Coronaviridae, subfamily Coronavirinae, with the Genus Alphacoronavirus containing HCoV-229E and HCoV-NL63 and the Genus Betacoronavirus containing HCoV-OC43 and HCoV-HKU1. HCoVs possess a +ssRNA genome, which is associated with nucleocapsid (N) phosphoprotein within the core of a host cell–derived enveloped virion. The HCoV virion also comprises 3 viral encoded proteins (S, E, and M), and characterization has indicated that binding to host cell receptors is mediated predominately via the spike (S) glycoprotein, with each HCoV employing a specific host cell receptor during infection (see Table 1). The virion of Betacoronavirus also contains a hemagglutinin (HE) protein, which is thought to be involved in either host-receptor interactions or release of virus from infected cells.

The molecular and receptor interaction differences existing between HCoVs are reflected in their seasonal prevalences. Studies of ARI have indicated that HCoV-NL63 can be detected in the spring, summer, or winter whereas HCoVs -HKU1, -OC43, and -229E infections mainly occur during the autumn and winter months.

A recent study of HCoVs -NL63, -OC43, and -229E also found fluctuations occurring between their yearly prevalence.

The clinical impact of each HCoV also appears to vary, but all present the greatest disease burden within the childhood population. In a retrospective study of clinical samples taken over a 20-year period from young children (median age 14.5 months), the percentage of lower respiratory tract illness (LRTI; including asthma exacerbations and bronchiolitis) associated with any HCoV, HCoV-NL63, or HCoV-OC43 was estimated to be 4.6%, 2.6%, and 1.9%, respectively. Although this study failed to include HCoV-HKU1 in the testing panels, other studies have associated HCoV-HKU1 with wheezing illness in children.

Among asthmatic adults, HCoVs have been detected during both ED visits and well-defined episodes of exacerbation prompted by ARI. Atmar and colleagues reported that HCoVs were detected in 21 of 148 ED visits during a 2-year study of 122 asthmatic adults, and Kistler and colleagues reported detections of HCoVs, OC43, HKU1, and NL63 in asthmatic adults with ARI, of which HCoV-NL63 occurred most in episodes of exacerbations.

Despite being associated with ARI, HCoV-229E appears to be the HCoV least associated with asthma exacerbations. Recent studies using RT-PCR have failed to find HCoV-229E in either adult or childhood episodes of asthma exacerbation. Although some previous studies detected HCoV-229E in asthmatic children, detection occurred with HCoV-OC43 and individual HCoV detection rates were not reported, despite the investigators using HCoV-OC43- and HCoV-229E–specific primers and antibodies. Another early study of asthmatic adults detected HCoV-229E through analysis of paired sera in 12 instances where exacerbation could be objectively measured. However, HCoV-299E detections could not be associated with a peak expiratory flow rate (PEFR) mean decrease of greater than 50 L/min. The reason for the lack of HCoV-229E detections in asthma exacerbations remains unclear.

PARAINFLUENZA VIRUSES

Parainfluenza viruses (PIVs) are primarily associated with bronchiolitis and laryngotracheobronchitis or croup, in children younger than 4 years of age. PIVs also pose
a serious risk to immunocompromised individuals, and outbreaks of viral pneumonia among transplant recipients and patients undergoing chemotherapy have occurred.\textsuperscript{41,42} The PIVs consist of 4 serotypes (1–4) and 2 subtypes (4a and 4b), and as a group are responsible for 1% to 8% of virus-related asthma exacerbations (see Table 1).\textsuperscript{7,10,12,13,29,43}

Like RSV and HMPV, PIVs are nonsegmented \(-\) ssRNA viruses belonging to the family \textit{Paramyxoviridae}.\textsuperscript{44} PIVs 1 to 3, 4a, and 4b are classified within 2 of the 5 genera of the subfamily \textit{Paramyxovirinae}, genus Respirovirus (PIV-1 and PIV-3) and genus \textit{Rubulavirus} (PIV2 and PIV-4a and -4b).\textsuperscript{45} In contrast to the G glycoprotein encoded by RSV and HMPV, PIVs encode a hemagglutinin-neuraminidase (HN) glycoprotein, which interacts with gangliosides (sialic acid–containing oligosaccharides) on target host cells during infection.\textsuperscript{46,47}

Seasonal and yearly prevalence of PIVs have been shown to vary among the serotypes. PIV-1, -2, and -4 have the highest prevalence in the autumn and winter months whereas PIV-3 occurs mostly in the spring and summer. Peaks in PIV-1 prevalence have been shown to occur biennially. PIV-2 prevalence exhibits some yearly variation and PIV-3 is consistently detected each year. PIV-4 is the least prevalent of all PIVs.\textsuperscript{42}

Although each PIV has the potential to cause respiratory illness in any age group, PIVs 1 to 3 appear to be more associated with a particular clinical presentation at certain ages. PIV-1 is associated with croup in children 1 to 4 years old, PIV-2 with bronchiolitis in the age group younger than 1 year, and PIV-3 is more associated with viral pneumonia in individuals older than 15 years.\textsuperscript{42}

Studies of asthmatic children have revealed that each PIV type plays a different role in the production of asthma symptoms. In studies where the incidence of each individual PIV is described, PIV-1 is detected in 1.4% to 2.9%, PIV-2 in 1.4%, PIV-3 in 2.9% to 6%, and PIV-4 in up to 1.9% of wheezing illnesses.\textsuperscript{12–14,43} Although PIVs are largely considered as a single group in adult asthma studies, PIVs are still detected in episodes of exacerbation. Atmar and colleagues\textsuperscript{15} detected PIVs 1 to 3 in 16 of 138 episodes of ARI in asthmatic adults, with at least one infection each of PIV-2 and PIV-3 resulting in an ED visit, and Nicholson and colleagues\textsuperscript{40} detected 5 cases of PIV1-3 in asthmatic adults, 3 of which had instances of a PEFR mean decrease of greater than 50 L/min.

### ADENOVIRUSES

Adenoviruses (AdVs) comprise a large group of DNA viruses that are known to cause a wide variety of clinical syndromes including diarrhea, keratoconjunctivitis, and hemorrhagic cystitis.\textsuperscript{48,49} However, AdVs are best known as a primary cause of ARI and, particularly in young children, have been implicated in the production of more severe LRTI. Fifty-one AdV serotypes have been identified, and as a group AdVs are associated with up to 7% of virus-related asthma exacerbations (see Table 1).\textsuperscript{7,10,13,29,43}

AdVs are classified within the family \textit{Adenoviridae}, genus \textit{Mastadenovirus}, and divided into species A through G based on biochemical and biophysical properties, hemagglutination reaction, and sequence identity. The AdV virion is a nonenveloped icosahedral capsid consisting of 240 hexon and 12 penton polyproteins or capsomers. A long fiber protein protrudes from each of the 12 penton capsomers and contains a terminal “knob” domain, which interacts with host cell receptors.\textsuperscript{49} AdVs have been shown to employ a diverse variety of cell receptors, including coxsackie-adenovirus receptor (CAR), heparan sulfate glycosaminoglycans, CD86, and an array of cell surface integrins.\textsuperscript{50}

Although each serotype exhibits some variation, AdVs are detected primarily during the winter and spring months.\textsuperscript{10,48} Of all the serotypes, AdV-1, -2, -5, and -6 are the
most common cause of ARI.\textsuperscript{51,52} However, similar to other respiratory viruses (eg, RSV subtype detections reported by Lee and colleagues\textsuperscript{12} versus Matthew and colleagues\textsuperscript{14}), location can affect the predominance of a given serotype, with AdV-4, -7, and -5 being the most frequently detected in ARI studies conducted in the United States.\textsuperscript{52,53}

As with most respiratory viruses, AdV infections occur primarily in infants and children, and it is within these populations specifically that AdVs have been associated with more serious respiratory illness.\textsuperscript{48,52,54–56} In an 8-year study of children younger than 2 years hospitalized with LRTI, Larranaga and colleagues\textsuperscript{55} detected AdV at a rate of 8.6\% (sole detections), second only to RSV (26.3\%), and predominately in patients with pneumonia and wheezing bronchitis (69.8\%). The investigators also typed the AdV isolates and determined that the species B and C were most frequently detected among their population and that serotype-7h was particularly associated with a longer duration of hospitalization. Although this study employed culture-based methods of detection, more recent studies employing PCR for AdV detection describe comparable detection rates (0.4\%–7\%) in episodes of childhood wheeze and asthma exacerbations.\textsuperscript{7,10,13,29,43}

An interesting aspect of the association of AdV with asthma was described in a study of asymptomatic asthmatic children conducted by Marin and colleagues.\textsuperscript{56} These investigators reported that AdV DNA was detected in 78.4\% of the asthmatic group but in only 5\% of the nonasthmatic control group. This study also described HRV and RSV detection rates in the asthmatic group of 32.4\% and 2.7\%, respectively, despite none of the participants experiencing respiratory symptoms for the duration of the study (3 weeks). However, a confounding aspect of this study is that the subjects were classified as having mild asthma that was well controlled (fluticasone 100–250 $\mu$g daily) in the 6 months before the start of the study. Nevertheless, the disparity in viral detection between the asthmatic and control groups may imply some mechanism of either persistence in asthmatics or an association with the long-term compliance of glucocorticoid therapy and inhibition of symptoms during respiratory virus infection.

**HUMAN BOCAVIRUSES**

Human bocaviruses (HBoV) were discovered in 2005 by Allander and colleagues\textsuperscript{57} in pooled nasopharyngeal aspirates obtained from children with LRTI. Further characterization in ARI-focused studies has revealed that HBoV is frequently associated with ARI in both children and adults, with detection rates of 1.5\% to 19\%.\textsuperscript{58–61} In addition, HBoV has been associated with wheezing and gastrointestinal illness predominately in children younger than 2 years.\textsuperscript{57,61–75} However, the exact role of HBoV in respiratory and other illnesses remains ambiguous, with a high overall codetection rate with other respiratory viruses being described (median 42.5\%) and the detection of HBoV DNA in serum, urine, and lymph node samples.\textsuperscript{60,61,66,76,77}

HBoV is a parvovirus, a single-stranded DNA virus of the family Parvoviridae, genus *Bocavirus*.\textsuperscript{65} The genome, which requires host cell DNA polymerases for replication, encodes 2 structural (VP1 and VP2) and 2 nonstructural (NS1 and NP1) proteins.\textsuperscript{65} Although HBoV has only recently been propagated in cultured cells and its host cell interactions remain to be determined,\textsuperscript{78} initial studies have found that HBoV shares similar virion morphology with other paroviruses, a nonenveloped icosahedral capsid consisting of 60 copies of each structural protein.\textsuperscript{79} Recently, 2 viruses related to HBoV have been identified, namely HBoV-2 and HBoV-3, but it is unknown whether these are unique viral entities or closely related genotypes of the same virus.\textsuperscript{80,81} While
the epidemiology of HBoV is still being determined, ARI studies have shown that HBoV infection occurs primarily during the winter, with a smaller peak in spring.\textsuperscript{65,74,82} Several studies have indicated that HBoV is associated with severe respiratory disease in children, particularly in those hospitalized with asthma and other wheezing illnesses.\textsuperscript{29,65} A study conducted by Vallet and colleagues\textsuperscript{83} of children aged 2 to 15 years hospitalized for asthma detected HBoV in 13\% of children with asthma exacerbations compared with only 2\% in children with stable asthma, suggesting HBoV plays a causative role in the development of exacerbations. Similar findings were reported by Nadji and colleagues,\textsuperscript{84} who detected HBoV at a rate of 6\% in children younger than 10 years with asthma exacerbations, and Garcia and colleagues,\textsuperscript{69} who reported that wheezing was seen in more than 50\% of children in whom HBoV was the sole virus detected.

Although HBoV is more often detected in symptomatic than healthy individuals, high levels of codetection with other respiratory viruses, particularly picornaviruses and IFVs, confounds HBoV’s role in respiratory illness.\textsuperscript{25,65} Although a study of infants younger than 12 months hospitalized with bronchiolitis found that dual infections of RSV and HBoV were associated with higher clinical severity scores and longer length of hospitalization than infants with a single HBoV or HRV and HBoV dual infections,\textsuperscript{85} most studies have found that coinfection of HBoV with another respiratory virus does not alter the severity or duration of associated illness.

**POLYOMAVIRUSES**

In 2007, 2 novel human polyomaviruses (PyVs) were described, the KI polyomavirus (KIPyV) by Allander and colleagues\textsuperscript{86} and the WU polyomavirus (WUPyV) by Gaynor and colleagues.\textsuperscript{87} Initially identified in nasopharyngeal aspirates obtained from individuals with respiratory illness, further characterization has revealed KIPyV and WUPyV are detected in 2.6\% and 6.2\% of ARI cases, respectively, suggesting these NIVs have a causative role in respiratory illnesses.\textsuperscript{88–91} However, similar to HBoV, a high rate of codetection (>80\%) with other respiratory viruses and detection in other tissue types currently confounds any direct association of KIPyV and WUPyV with ARI and other illnesses.\textsuperscript{92}

PyVs are classified in the single genus *Polyomavirus* of the family *Polyomaviridae*, and contain histone-associated circular dsDNA genomes encoding 3 structural (VP1, VP2, VP3) and 2 nonstructural (large-T and small-T antigens) proteins.\textsuperscript{87,93} As with some other NIVs (eg, HRV-C, HCoV-HKU1), KIPyV and WUPyV cannot be grown using current cell culture systems. This drawback has postponed identification of host cell receptor interactions and determination of virion morphology, although the latter is believed to be similar to the nonenveloped icosahedral configuration of other PyVs.\textsuperscript{93} KIPyV and WUPyV characterization in retrospective ARI-focused studies has determined that they exhibit a year-round prevalence, with the greatest peaks in detections occurring in the spring, autumn, and winter months.\textsuperscript{90,94–96} Although no studies have yet looked specifically for KIPyV and WUPyV during episodes of asthma exacerbations, wheezing illness and other more serious LRTI have been reported in patients positive for KIPyV and WUPyV. Bialasiewicz and colleagues\textsuperscript{90} showed that 15\% of KIPyV-positive and 23\% of WUPyV-positive patients had symptoms of bronchiolitis, and Payungporn and colleagues\textsuperscript{96} found that 11 of 15 combined KIPyV and WUPyV sole detections originated in children younger than 1 year with pneumonia. However, the overall high codeletion rates (35\%–80\%) described in these studies again indicates the need for further clarification of the role of KIPyV and WUPyV in respiratory illness.
An interesting aspect of the previously described human PyVs is their ability to establish a form of latency (ie, low-level persistent infection) and undergo reactivation when an infected individual’s immune system experiences stress (eg, infection, inflammation, or immune suppression). While characterization of the host-virus interactions of KIPyV and WUPyV is still continuing, Sharp and colleagues have proposed that they may also reactivate during illness, as evidenced by mutations in the transcriptional control region of KIPyV and WUPyV genomes detected in autopsy tissue from immunosuppressed individuals. Given our incomplete knowledge about the role of KIPyV and WUPyV in respiratory illness, it may be plausible that the high codection rates observed in ARI studies are not the result of bona fide dual infections, but rather may be caused by infection with another respiratory virus evoking an immune response that reactivates latent KIPyV and WUPyV.

Although Sharp and colleagues did not observe the high frequency of transcriptional control region mutations in KIPyV and WUPyV genomes detected from respiratory samples, a seroepidemiology study by Nguyen and colleagues may provide evidence of KIPyV and WUPyV reactivation during ARI. These investigators observed that the proportion of KIPyV- and WUPyV-seropositive individuals increased at around 4 years of age, a finding that they speculated was the result of KIPyV and WUPyV exposure during school attendance. However, they conceded that the serum obtained for their study originated from 2 tertiary referral hospitals and was likely from individuals with underlying medical conditions. Given that ARI represents the most common reason for hospital visits and admissions among school-aged children, and that the incidence of other respiratory virus infections also increases among this age group, the KIPyV and WUPyV antibody detected may not be that produced in response to initial exposure, but rather antibody produced during KIPyV and WUPyV reactivation evoked by infection with another ARI-causing respiratory virus. Indeed, Nguyen and colleagues reported that a high proportion of adults were KIPyV- and WUPyV-seropositive which, considering the nature of the study cohort (ie, hospital-based), may not indicate preexisting immunity but again KIPyV and WUPyV reactivation during illness. Future community-based studies will no doubt determine when initial KIPyV and WUPyV exposure occurs and will better elucidate the relationships that exist between ARI, viral codetections, and KIPyV and WUPyV reactivation.

SUMMARY

This review focuses on some of the less common respiratory viruses currently implicated in both childhood and adult asthma exacerbations. Although the respiratory viruses covered here have a lesser, or in the case of NIVs, an as yet uncharacterized involvement in the development of exacerbation compared with the “usual suspects” (eg, HRV, RSV, HMPV), they exemplify the diversity that exists in virus-related exacerbations. The implementation of more sensitive methods of virus detection and the identification and characterization of NIVs in future asthma studies will further expand our understanding of viral diversity and the mechanisms underlying development of asthma exacerbations during respiratory virus infection.

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