

CONTAGIOUS COMMENTS

Department of Epidemiology

CHANGING TIMES: THE “NEW” RESPIRATORY VIRUSES

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Every winter our practices and hospitals are inundated with sneezing, wheezing, and coughing young children, most of who seem to have an acute respiratory virus infection. All too frequently however the etiologic agent is not identified, greatly frustrating us all! Not only is failure to provide a viral diagnosis unsatisfying, “virus-negative” patients tend to receive more antibiotics, have increased ancillary testing, and longer lengths of stay than individuals with a confirmed etiology.

We have always understood why some respiratory tract specimens fail to yield virus. Many receive a limited virology work-up because the slower results of viral culture rarely benefit short-stay patients. Some respiratory viruses, such as the rhinoviruses and human coronaviruses 229E and OC43, influenza C, and the parechoviruses are either difficult or impossible to cultivate. A handful of specimens also contain “virus-like” pathogens such as *M. pneumoniae* which do not grow in viral culture. Finally, about 10% of all specimens are poorly-collected and cannot yield a virus under the best of circumstances!

Over the last 5 years, however, another reason has emerged! At least 3 “new” viruses have been discovered, which taken together may cause a significant proportion of respiratory tract disease in children. This table lists our current understanding of the respiratory viruses, with the newly-discovered agents described in greater detail below.

RESPIRATORY VIRUSES – 2007

PREVIOUSLY-KNOWN		NEWLY-DISCOVERED
Readily-Detected	Fastidious or Not Detected	
Respiratory Syncytial Virus	Rhinoviruses	Human metapneumovirus
Influenza Virus A, B	HCoV OC43 & 229E	HCoV NL-63 & HKU1
Parainfluenza virus	Influenza C	Bocavirus
Adenoviruses	Parechoviruses	
Enterovirus (summer)		

HUMAN METAPNEUMOVIRUS

In 2001, Dutch researchers applied a new pathogen discovery technique, randomly-primed PCR, to poorly-growing paramyxovirus-like isolates collected from children over a 20 year period. All isolates were found to be a single virus type most closely related to turkey rhinotracheitis virus. This “new” virus was the first human pathogen in the *Metapneumovirus*

genus, so it was named human metapneumovirus (HMPV). Serologic studies show that HMPV has circulated for at least 50 years and probably did not recently “hop” from an animal reservoir into humans. Genetically, it most closely resembles RSV. There are 2 major subgroups (A and B) and at least 4 genotypes, all of which cause illnesses of similar symptoms and severity. Asymptomatic carriage is uncommon, so the causal role of HMPV in human disease is relatively certain. The relationship of HMPV to other known human paramyxoviruses is shown below:

Family Paramyxoviridae	
Sub-Family: <u>Paramyxovirinae</u>	Sub-Family: <u>Pneumovirinae</u>
Genus: Respirovirus	Genus: Pneumovirus
Species: Parainfluenza 1&3	Species: RSV
Genus: Rublavirus	Genus: Metapneumovirus
Species: Parainfluenza 2&4	Species: HMPV A&B
Species: Mumps	
Genus: Morbillivirus	
Species: Measles	
Genus: Henipavirus	
Species: Hendra, Nipa	

Respiratory tract disease is the major manifestation, with both lower (LRTI) and upper respiratory tract (URTI) infections described. Most infections occur in children, are mild to moderate in severity, and self-limited. Recurrent infections occur throughout life and in healthy individuals tend to be mild or asymptomatic.

The incidence of HMPV-associated LRTIs in children ranges from 5-15% or somewhat higher depending on the year and geographic location. HMPV infections are indistinguishable from those caused by RSV, although symptoms can be milder and the mean age of infection is slightly older. Overall HMPV appears to be second only to RSV as a cause of bronchiolitis and of viral pneumonia requiring hospitalization and intensive care stays in young children. Secondary bacterial infections are uncommon.

Risk factors for severe LRTIs in children, like those for RSV, include prematurity, very young age, underlying cardiopulmonary disease, and immune system defects. Recently, HMPV has been detected in CSF and brain of several patients with encephalitis, suggestive of spread beyond the respiratory tract. Severe LRTI in adults is associated with advanced age and cardiopulmonary disease. HMPV has been detected in exacerbations of COPD. In younger adults, HMPV can present as influenza. Dyspnea is more likely in elderly adults. Infections in

immunocompromised hosts at any age can be prolonged. Some are severe and lead to death.

HMPV also causes 5-15% of all cases of URTI in children and a slightly lesser percentage in adults. A small but significant amount of acute otitis media is HMPV-associated. The virus has also been linked to exacerbations of asthma and wheezing in all ages, although rhinoviruses may be a more frequent cause. HMPV is perhaps the most significant pathogen in lung transplant patients with respiratory symptoms.

The virus has been found worldwide and on every continent. Sporadic infections occur year-round but peak every winter and spring in temperate climates, coincident with or immediately following the RSV season. Both HMPV subgroups usually co-circulate in varying proportions by locale. Due to seasonal overlap, co-infections of HMPV with RSV, and to a lesser extent other respiratory viruses, can occur. It is unclear whether these dual infections result in more severe disease. Formal transmission studies are lacking but the virus probably spreads by direct or close contact with contaminated secretions, like RSV. The incubation period is 3-5 days, with viral shedding in healthy children lasting about a week. Nosocomial infections are reported. Over 90% of children are infected by 5 years of age. Current treatment is supportive and includes hydration and careful clinical assessment, with supplemental oxygen and mechanical ventilation if necessary. Ribavirin is active *in vitro* against HMPV, but is unlikely to be helpful *in vivo* due to the exuberance of the immune response. A humanized monoclonal antibody for HMPV prophylaxis is likely to be developed for high-risk infants, as has been done for RSV.

Since the virus grows poorly, it must be detected by non-culture assays. In our laboratory, HMPV infections are diagnosed in two ways. HMPV is routinely detected in our respiratory virus direct immunofluorescence stain panel. Since the direct HMPV stain was introduced late last year, over 100 cases have been identified; making HMPV the second most common respiratory virus of this winter. The most sensitive assay, however, is HMPV PCR. This test is available at TCH and in reference laboratories. We recommend PCR for detection of HMPV in direct stain-negative respiratory tract specimens, tissue, or other fluids from hospitalized patients with severe illness.

HMPV At A Glance

- Paramyxovirus family
- 5-15% of all LRTI & URTI
- Symptoms RSV-like in children
- Detection: Direct stain or PCR

HUMAN CORONAVIRUSES

The coronaviruses are large, enveloped viruses that cause a variety of illnesses in animals and in humans. Two serotypes, OC43 and 229E, have been known since the 1980's to cause 10-30% wintertime colds in humans, as well as sinus infections, some LRTIs, and asthma exacerbations. Considerable interest in the human coronavirus (HCoV) family was generated when the

severe acute respiratory syndrome (SARS) coronavirus abruptly appeared in 2002, probably by "jumping" from an animal reservoir (most likely bats) to humans. It then caused an epidemic, affecting more than 8,000 people in 29 counties with nearly 800 deaths. It was subsequently eliminated by infection control efforts, but great interest in HCoVs persisted.

Coronavirus Family

Group 1a: No human members	Group 2a: OC43, HKU1
Group 1b: 229E, NL63	Group 2b: SARS

NL63

In 2003 another human coronavirus, NL63, was independently detected by 2 different research groups in the Netherlands, using a molecular pathogen discovery method with respiratory tract specimens of hospitalized infants, children, and immunosuppressed adults. Subsequently it has been found worldwide. NL63 is most closely related to 229E, from which it probably diverged in the 11th century. What sets NL63 apart from 229E (and to a lesser extent OC43) is that infections tend to be more severe, with hospitalization in a larger percentage of patients. A link of NL63 to Kawasaki Disease was also proposed, but is unlikely based on studies performed at TCH and elsewhere. Incidence of NL63 infection in symptomatic hospitalized children is reported to be 1-10%. We found the virus in 7% of such specimens submitted to TCH from Kawasaki Disease and control patients with various respiratory tract illnesses. LRTIs associated with NL-63 are reported in elderly and immunocompromised and can be severe. One death (in an elderly Canadian man) is reported.

NL63 causes disease predominately in the winter months in temperate climates. Serosurveys indicate that most infections are acquired before age 8 and are more common than infection with 229E. Up to half of all infections occur in combination with other common respiratory viruses. Prolonged shedding, a characteristic of all coronaviruses, can occur for more than 3 weeks following the initial infection, even after symptoms have abated. Symptoms can be mild to severe, ranging from fever, cough, sore throat, and rhinitis, to croup, bronchiolitis, and pneumonia. Croup is a common manifestation. Several studies now indicate that NL63 may be a more frequent cause of croup than parainfluenza virus! For example, a recent study of children under age 3 found 45% of children with NL63 infection had croup, compared to only 6% of children infected with other viruses.

HKU1

HKU1 coronavirus was first detected in 2005 in an adult with chronic pulmonary disease from Hong Kong. Subsequently it has been found in other elderly patients and in children with URTI and LRTI. Respiratory symptoms include rhinorrhoea, fever, cough, and wheeze. Disease manifestations include bronchiolitis and pneumonia. The virus has also been found in stool, suggesting it may also cause diarrhea. Febrile seizures may also occur. Hepatitis was noted in one patient. Most patients with HKU1 infections have underlying diseases, suggesting that the virus may aggravate their conditions, resulting in hospitalization.

The exact incidence of HKU1 is still to be determined, but it appears to be less than for NL63. In the only study of US children, 1% of patients were positive for the virus.

Currently detection of NL63 and HKU1 by RT-PCR is available in at least one commercial laboratory. Several companies are also developing molecular assays for both viruses.

NL63 & HKU1 At A Glance

- Coronavirus family
- Disease in 1-5% of patients with NL63, 1% (?) with HKU1
- NL63: croup, other URTI & LRTI
- HKU1: URTI, LRTI, possibly gastroenteritis
- Detection: Commercial or research laboratories

BOCAVIRUS

Parvoviruses are tiny, single-stranded DNA viruses that infect many animal and arthropod species. They replicate exclusively in the nucleus of dividing cells and are typically recovered from the respiratory tract, gut, hematopoietic cells, or placenta and fetus. Until recently, the only parvovirus thought to be pathogenic for humans was B19, the etiologic agent of erythema infectiosum (Fifth disease).

In 2005, a second parvovirus pathogenic for humans, human bocavirus (HBoV), was detected by Sweden investigators using molecular pathogen discovery techniques and pooled human nasopharyngeal aspirates from children with respiratory tract symptoms. So far, HBoV is the only human member of the *Bocavirus* genus, so named because it includes the related but distinct bovine and canine minute parvoviruses. There are at least 2 HBoV genetic “clusters,” but whether they are separate genotypes is unclear.

Parvovirus Family

Subfamily: Parvovirinae – infects birds and mammals

Genus: Erythrovirus

Species: B19

Genus: Bocavirus

Species: **Bocavirus**

Subfamily Densoviruses –disease mostly in arthropods

HBoV has been detected in a wide range (1-19%) of specimens from individuals with acute respiratory tract disease. A remarkably-high (>50%) rate of co-infection with other viruses has been observed in some studies. Bacterial co-infection is also described. Co-infected specimens tend to have lower HBoV loads than single infections, so quantitative PCR may be necessary to differentiate carriage of the virus from disease. Asymptomatic carriage however, was infrequent in the only study to include a substantial number of healthy controls.

The relative importance of HBoV and its disease spectrum are still unknown. Infants and children under 3 years of age are most often affected. In one report, HBoV was the third most common

virus detected in children behind RSV and HMPV, although not all viruses were evaluated. Currently, HBoV may be associated with up to 24% of cases of URTI, 11-26% of cases of bronchiolitis, and 17-33% of cases of pneumonia in otherwise healthy children. Up to 20% of children with wheezing requiring hospitalization may be infected with HBoV. A link with otitis media is reported. Not surprisingly, the same populations at high risk of severe RSV disease are also at risk of severe HBoV LRTI and hospitalization. Exacerbations of asthma and paroxysmal cough resembling whooping cough are also reported. The mode of transmission and duration of viral shedding are unknown, although the reported duration of symptoms is 2 days - \geq 20 days. Nosocomial infections occur. Consequences for adults and immunocompromised patients are unknown, although there is one case report of severe case of HBoV in an adult with cancer. No deaths have been reported.

HBoV is found globally, but its circulation pattern is controversial. Both sporadic and seasonal activity peaking during fall-spring in temperate climates are described. Intriguing features setting HBoV somewhat apart from other respiratory viruses include its association with diarrhea (up to 29% in one study) and possibly rash. The presence of viral DNA in over 50% of acute sera and a lesser percentage in convalescent specimens, particularly in patients with high viral loads in the respiratory tract, may also be unique. Whether viremia indicates that extension of HBoV disease beyond the respiratory tract, including infection of the fetus as with B19, remains unknown.

Until the role of the virus is more clearly defined and the need for quantitative PCR are clarified, routine testing for HBoV is neither recommended nor available

HBoV At a Glance

- Parvovirus Family
- Incidence, spectrum of infection yet to be defined.
- Co-infections frequent.
- Diarrhea and wheezing may be prominent symptoms
- Detection: Research. Quantitative PCR may be required

CONCLUSIONS AND FURTHER READING

It is now clear that many “new” respiratory viruses have been circulating for decades, and that we simply were unaware of them! It is highly likely that most of the respiratory viruses infecting children will be defined soon. Initially molecular testing will be required for their detection, but with time, simpler assays may become available, as has been the case with HMPV. One thing is certain – the times in virology are certainly are a’ changing!

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