Human Bocavirus in Children

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Key Words: human bocavirus (HBoV), new viruses, respiratory infections, gastroenteritis (Pediatr Infect Dis J 2010;29: 557–558)

DISCOVERY

Human bocavirus (HBoV) was first detected using nonspecific gene sequencing of specimens from human subjects with respiratory illness. Viral, bacterial, and human genetic sequences were identified in 2 libraries of specimens collected at different times of year. Among the genetic sequences of many known pathogens was a parvovirus clone, which was not parvovirus B19. Bovine parvovirus and canine minute virus were the closest genetic relatives to the newly discovered parvovirus, and thus, it was called “human bocavirus” (bo for bovine and ca for canine). Although HBoV was initially described with a single genotype, 2 closely related variants have subsequently been identified and designated as “HBoV2” and “HBoV3.”

EPIDEMIOLOGY

Conventional epidemiologic descriptions of pathogens include surveillance using culture to detect acute infections and/or serologic studies to describe previous infections. HBoV has presented unique challenges that have led to a slow accrual of epidemiologic data. Until recently, there was no permissive cell line in which to grow the virus, so the description of “acute infections” has been limited to detection of viral deoxyribonucleic acid (DNA). Such descriptions are limited because the presence of DNA could represent acute infections, prolonged shedding of live virus, or inactive virus. In addition, there is no universally accepted polymerase chain reaction (PCR) assay for HBoV, which could lead to study-to-study variability in sensitivity and specificity. While noting the weaknesses of relying on nucleic acid detection, most studies of children have detected HBoV DNA in approximately 5% to 15% of those with symptoms of respiratory infection, although a high rate of codeletion of other viral pathogens is almost universally noted.

Serologic assays are most often based on neutralization of viral antigens. Because no cell culture system was initially available, the production of antigen has occurred by cloning structural genes into other expression vectors. The selection of the different genes and vectors led to variable rates of “seroprevalence.” Insect cell-based antigen production has been used by several investigators demonstrating HBoV-specific antibodies in 5% of children 6 months of age and in all samples of children aged 6 to 9 years. Using similar insect cell-based HBoV antibody detection, high rates of seroconversion in children and persisting antibodies in adults have been verified by multiple investigators.

Combined serologic evidence and nucleic acid detection data suggest that children are exposed to HBoV relatively frequently. HBoV detection is most frequent in children younger than 5 years, with the highest rates occurring during winter and early spring.

CLINICAL SPECTRUM

Although the epidemiologic data show that HBoV is a virus that can be frequently detected in children and to which an immune response is mounted, its role as a pathogen has been controversial. Because HBoV was first recognized in subjects with respiratory symptoms, it was suspected to be a respiratory pathogen, although proving causation has been difficult for 2 reasons. First, the presence of DNA in the airway neither proves that the organism is causing disease nor that its tropism is the airway. Second, when a full panel of viral diagnostics is applied to the sample, other viral pathogens are present in approximately 78% of samples testing positive for HBoV, with a common range of 50% to 60% codeletions described by different investigators. Although upper respiratory symptoms are frequently described in association with HBoV, lower respiratory tract involvement is more variable. HBoV has been detected in 0% to 76% of subjects with lower respiratory tract illness, with some data suggesting it may be an important factor in asthma exacerbations. Of course, conclusions about symptoms attributable to HBoV should be tempered by the fact that most studies have included a population of subjects recruited solely based on the presence of such symptoms, which could exaggerate the frequency that a symptom is truly associated with the pathogen.

To elucidate the role of HBoV in respiratory infections, several studies have compared subjects experiencing respiratory illnesses to controls, and the presence of symptoms is more common in those with HBoV than in those without. The presence of HBoV DNA in respiratory tract secretions is associated with an exacerbation of asthma symptoms, but it is not clear if it is a cause or a marker of exacerbation.

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DOI: 10.1097/INF.0b013e3181e0747d
symptoms with asymptomatic controls and present conflicting data. HBoV DNA was identified in 44/369 (12%) of symptomatic children and 2 of 85 (2%) of the matched controls in one series and in 5% of symptomatic children, and none of the asymptomatic controls in another, suggesting that HBoV is truly a respiratory pathogen. Conversely, 2 different study groups found no difference in the rates of HBoV detection in symptomatic and asymptomatic children. It is possible that variability in the age of study subjects, season, and geographic location may have led to such heterogeneity, although the significance of HBoV in children with and without respiratory symptoms awaits clarification.

Early descriptions of the association between HBoV in the airway and the presence of diarrhea suggested that there may be gastrointestinal tropism. Subsequently, HBoV DNA has been described in up to 9% of diarrheal stools, although other gastrointestinal pathogens are often simultaneously detected. In a case-control study, no difference in the rates of detection of HBoV DNA in stool of children with and without diarrhea was observed. HBoV2 is detected more frequently than HBoV in stool, although causality has not been established.

HBoV DNA has been detected in immunocompromised patients with fever, respiratory tract illness, hepatitis, gastrointestinal illness, and central nervous system disease, although it is unclear what etiologic role HBoV plays as a sole pathogen in immunocompromised hosts.

**PATHOGENESIS**

HBoV DNA has been most often detected in the airway and to a lesser extent, the stool, suggesting a primary respiratory or possibly a gastrointestinal tropism. In addition, HBoV DNA has also been detected in the blood, particularly in the presence of higher viral loads in the airways. HBoV DNA has not been detected in samples of the bone marrow, brain, heart, lymph nodes, or spleen, and it has not been associated with in utero infections. However, HBoV DNA has been isolated from approximately one-third of tonsil and adenoid tissue specimens. Because HBoV DNA can be present each time a child is tested sequentially for >4 months after it is first identified, it is not known whether the presence of HBoV in tonsillar tissue represents persistence, latency, or prolonged shedding.

The lack of permissive cell lines has limited the ability to describe the pathogenesis of HBoV. Recently, in vitro HBoV infection of pseudostratified epithelial cells was accomplished, with confirmation of virus uptake, transcription, and replication. This model not only helps to support the concept that HBoV is a respiratory pathogen but also allows for detailed analysis of viral processes and virus/host interactions as well as the significance of the frequent finding of coinfection of HBoV and other respiratory pathogens.

**DIAGNOSIS**

HBoV is not isolated in standard viral culture cell lines, and there are currently no commercially PCR or serologic assays available. In special circumstances, HBoV DNA may be identified by a research laboratory, although the results must be interpreted with caution given the lack of standardization, possibility for laboratory contamination, and high rates of codetection of other pathogens. A correlation between a high quantitative viral load and the lack of codetection of other viruses has been described and may be helpful in identifying HBoV as the causative pathogen.

Although serologic assays are neither standardized nor commercially available, the presence of HBoV-specific IgM along with acute and convalescent anti-HBoV IgG has been described as a sensitive method to detect acute infections.

**TREATMENT**

Neither in vitro nor in vivo antiviral therapy has been described for HBoV. Any risk of future antiviral treatment would have to be weighed against the potential benefits for this virus, which is frequently detected in the presence of other viral pathogens and which is most often associated with benign respiratory and gastrointestinal symptoms.

**CONCLUSION**

HBoV has been most frequently associated with respiratory, and to a lesser extent, gastrointestinal symptoms. The role that HBoV plays as a pathogen has been questioned because of very frequent codetection of other viral pathogens. However, children with respiratory illness that have higher viral loads, viremia, seroconversion, and lack of other viral pathogens are consistently described, suggesting a true role in respiratory infection. Testing for HBoV is currently limited to research settings and no specific treatment is available.

**REFERENCES**