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Don't Forget Serum in the Diagnosis of Human Bocavirus Infection

To the Editor —We read with great interest the article of Martin et al [1] on the role of human bocavirus (HBoV) in children's respiratory infections. HBoV was studied by polymerase chain reaction (PCR) in nasal swab samples obtained from 119 previously healthy children aged 6–24 months and attending three day care centers at enrollment. During a mean follow-up time of 12 months, HBoV infection was detected at least once in 59% of the children, and HBoV infection was associated with 33% of the episodes of respiratory illness; 72% were mixed infections with other viruses, and no association was found with any respiratory symptom or manifestation. At enrollment, HBoV infection was found in 44% of the 45 asymptomatic children, and there was no significant difference between the symptomatic and asymptomatic children in either HBoV presence or viral load. Martin et al [1] reported neither the diagnoses, clinical manifestations, nor the severity of the cases included, but most cases were obviously mild upper respiratory infections.

In the editorial commentary [2], Williams highlighted the study design, a prospective follow-up of a cohort, including both symptomatic and asymptomatic children at enrollment, and also the use of sensitive PCR tests for other viruses. The results of Martin et al [1], in agreement with reports reviewed in the commentary [2], raised the question whether HBoV infection contributes to the pathogenesis of a specific clinical syndrome or whether it is even a respiratory pathogen. Martin et al documented extended and intermittent HBoV shedding by regular samplings for up to 75 days. In another recent study, shedding of HBoV was documented for up to 142 days in children with lower respiratory infections [3]. Several seroepidemiologic studies have demonstrated that HBoV infection is ubiquitous at ages 6 months to 4 years, after which there appears to be widespread immunity [2]. Thus, prevalent HBoV shedding was expected in the study cohort. In light of this, a method distinguishing primary HBoV infection from virus shedding should be a crucial element of the study design.

We have introduced immunoglobulin M (IgM) and G (IgG) enzyme immunoassays (EIA) for the diagnosis of HBoV infections [4], and subsequently a HBoV-IgG-avidity EIA [5]. The diagnosis of HBoV infection could be confirmed by immunoblotting in 59% [6] and by EIA in 71% [4] of wheezing children if HBoV had been found by PCR in nasopharyngeal aspirates (NPA) and in 92% if HBoV had been found by PCR in blood samples. In these studies, the serodiagnostic findings coincided with the presence of viral DNA in blood (viremia) and in NPA at a high load, as well as with the presence of HBoV as a single infecting virus [4, 6], and we concluded that viremia is an excellent marker of a primary infection [6–8], as was also concluded in a recent controlled study with over 1300 children [9]. Since viremia coincided with the time of symptoms, these results suggested that HBoV is a causative agent of acute wheezing in children. Secondary infections and even reactivations of silent long-term infections are, at least in theory, possible [1, 3, 5]. However, whether, or to what extent, the frequent HBoV-PCR positivity in nostrils [1] is a useful marker of HBoV infection is an open question. Even mere mucosal HBoV contamination is easy to envision for a ubiquitous pathogen among infants and toddlers in a day care setting.

Serological verification of actual infection is needed to circumvent the PCR-related problems of virus shedding and mucosal contamination, and to disclose the association of HBoV infection with disease. Indeed, by using the EIA tests, we witnessed serological evidence of acute HBoV infection in 12 (12%) of 101 children with radiologically confirmed community-acquired pneumonia. The HBoV infection was single in 58% of the cases [10].

Martin et al [1] and William [2] concluded that the frequency of HBoV infection implies a need for additional studies with new approaches. The use of antibody assays and HBoV-DNA detection in serum samples may be the answer to their question.

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