Bovine Parainfluenza-3 Virus

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KEYWORDS

• Bovine parainfluenza-3 virus • Parainfluenza • Paramyxovirus
• Enzootic pneumonia • Bovine respiratory disease complex

HISTORICAL PERSPECTIVE

Bovine parainfluenza-3 virus (bPI_3V) was first isolated in the United States by workers at the US Department of Agriculture laboratory in Beltsville, Maryland, from the nasal discharge of cattle with shipping fever, and initially called myxovirus SF-4[1] in the August 1, 1959 issue of the *Journal of the American Veterinary Medical Association*. In the same issue, other workers at the University of Illinois, together with collaborators at the National Institutes of Health in Bethesda, Maryland, reported[2] on the apparent second isolation of the virus, and gave it its current name based on serologic relationships with the HA-1 strain of human parainfluenza or human parainfluenza-3 virus (hPI_3V)[3] in the then newly designated parainfluenza virus group.[4] Based on growth in the same cultured cells, ability to agglutinate erythrocytes from the same species, and essentially identical patterns of hemagglutination inhibition (HI) and virus neutralization (VN) activities by hyperimmune rabbit and chicken sera raised against the respective viruses, it was proposed that these 2 viruses were different strains of the same viral species, although, based on preliminary unpublished experiments, it was mentioned that "cattle may be relatively insusceptible to infection with the human strain."[3]

In the 1960s, growth characteristics, including differences among isolates, were described in detail. During this period and thereafter, bPI_3V was found to be endemic in cattle populations worldwide. In the 1970s and 1980s most of the seminal work on the pathogenesis of bPI_3V infections, documentation of interisolate genetic and antigenic differences, as well as the development and testing of parenteral and intranasal vaccines were completed. There have been few published studies on bPI_3V in the last 20 years. Work on bPI_3V since the last review of the agent in the *Veterinary Clinics of North America* in 1997[5] has focused on the viral variation and the possibility of cross-species transmission. Because of its endemicity, inclusion in commonly used combination vaccines, and the common failure to pursue or obtain specific etiologic diagnoses in field cases of respiratory disease, it has become a forgotten virus,

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much like its human counterpart, hPI_3V, which continues to a major clinical infection in infancy and childhood.[6] One purpose of this review is to emphasize that relegation to this status is unwarranted.

VIRUS CHARACTERISTICS

bPI_3V is in the genus Respirovirus of the subfamily Paramyxovirinae, order Mononegavirales, of the family Paramyxoviridae. In addition to bPI_3V, the Respirovirus genus includes the genetically and antigenically related human parainfluenza viruses types 1 and 3 (hPI_1V and hPI_3V, respectively) and Sendai virus of mice (mPI_1V).[6] Like other parainfluenza viruses (PIV), the spherical to pleomorphic 150- to 200-nm bPI_3V virion consists of a nucleocapsid surrounded by a lipid envelope that derives from the plasma membrane of the cell from which it buds.[6] bPI_3V has a single-stranded, nonsegmented, negative-sense RNA genome of 15,456 nucleotides that comprise 6 genes (N-P-M-F-HN-L) that encode for 9 proteins. The conserved N or nucleoprotein, in association with the phosphoprotein (P) and large (L) proteins, together with the genome forms the nucleocapsid or ribonucleoprotein (RNP) core of the virus, which is characteristically helical in form. The P and L proteins, whether associated with the N protein or free in the cytoplasm, are always found in a complex and comprise the viral RNA polymerase that is essential for the transcription of viral mRNA and replication of genomic RNA. The conserved, nonglycosolated matrix, or M protein, is the most abundant viral protein in an infected cell. It is located on the inner face of the envelope and is essential in virus assembly, budding, and release of progeny virions.[7] The homotetrameric hemagglutinin-neuraminidase (HN) and the homotrimeric fusion (F) glycoproteins are in the envelope and mediate attachment to, and penetration of, the host cell, respectively. The domains of these transmembrane proteins that are exposed to the extracellular milieu induce protective antibody responses. The nonstructural, or accessory, V, C, and D proteins result from RNA editing or insertion of G nucleotide residues into the P gene by the viral polymerase. This editing, which results in alternative reading frames, is characteristic of the Paramyxovirinae, and allows 1 gene to encode multiple proteins. The V, C, and D proteins are believed to affect inhibition of interferon α/β in Respirovirus-infected cells.[6]

Studies conducted in the 1960s showed that bPI_3V can grow in cells of bovine, porcine, and human origin in vitro, and that this growth was associated with a cytopathic effect characterized by plaque formation, syncytia, and eosinophilic intracytoplasmic inclusion bodies.[8–10] Subsequently, differences in plaque morphology and syncytium formation were reported among bPI_3V isolates.[11,12] Differences in neuraminidase activity, which are somewhat assay dependent, were reported[11–14] among isolates. These differences have been associated with differences in infectivity in vivo; isolates with strong neuraminidase (activity) being able to infect younger calves.[15] Using polyclonal sera in hemagglutination inhibition tests no antigenic differences in the HN protein were reported among bPI_3V isolates,[9,10] but, in contrast with initial findings,[3] this technique revealed antigenic differences between human and bovine PI_3V isolates,[16] the disparity in results apparently being related to the source of sera that were used. Application of monoclonal antibodies in the 1980s and 1990s documented differences among bPI_3V isolates,[16,17] primarily in epitopes, in the envelope glycoproteins HN and F, and significant antigenic differences between human and bovine PI_3V isolates.[18,19]

There are few bPI_3V genome sequence data.[20–23] Available data[20–23] indicate a high level of genomic conservation among bPI_3V isolates tested, the proteins of which, except for the P protein, exhibit 95% or greater identity.[23] There is substantial amino