

# PORCINE ADENOVIRUS



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## SUMMARY

### Etiology

- Porcine adenovirus (PAdV) is a non-enveloped DNA virus in the genus *Mastadenovirus*, family *Adenoviridae*. There are currently three porcine species and five serotypes recognized: PAdV-A (serotypes 1-3); PAdV-B (serotype 4); and PAdV-C (serotype 5).

### Cleaning and Disinfection

- PAdVs can survive in the environment for days to weeks.
- Bleach, formaldehyde, alcohol and phenolic compounds are effective disinfectants for PAdV. PAdV-5 (belonging to PAdV-C), has been successfully inactivated using 0.85% salt solution or 1M MgCl<sub>2</sub> solution heated at 50°C for 1 hour. Heating to 56°C for greater than ten minutes can also inactivate adenoviruses.

### Epidemiology

- Adenoviruses are relatively host-specific and pigs are the only known hosts for PAdV. Experimentally, human AdVs are able to infect pigs.
- PAdVs are not known to infect humans.
- The geographic distribution of PAdVs is not fully known, although the virus is suspected to be widespread in domestic swine populations.
- Serological surveys from Canada and England in the 1960s–1970s indicated that up to 60% of swine test positive for anti-PAdV antibodies. However, current seroprevalence data is lacking. The virus rarely causes death.

### Transmission

- The major routes of PAdV transmission are fecal-oral and inhalation. Virus has also been detected in swine kidneys post-mortem, making exposure to urine a suspected route of transmission. Because PAdV is stable in the environment, fomites are also a potential source of virus.

### Infection in Swine/Pathogenesis

- PAdV generally causes subclinical infections, and is commonly isolated from the gastrointestinal tract of normal swine. However, PAdV can induce enteritis and has been isolated in association with encephalitis, nephritis, respiratory disease, and reproductive disorders.

## **Diagnosis**

- PAdV is easily cultured. PAdV can be detected in fecal and intestinal culture using negatively stained, transmission electron microscopy (TEM). Immunofluorescence antibody (IFA) assays, complement fixation, direct fluorescence antibody (FA), and gel diffusion precipitation tests are all capable of detecting PAdV antigen and can be useful in confirming infection.
- A rise in anti-PAdV antibody in the presence of clinical disease is suggestive of clinical disease. Serological methods include virus neutralization or indirect fluorescent antibody testing.

## **Immunity**

- Most adult swine are seropositive to adenovirus and antibodies are presumably protective.
- There is no vaccine for PAdV. Information on cross-protection between strains is unavailable.

## **Prevention and Control**

- There is no treatment for PAdV infection.
- Standard industry biosecurity practices should be in place to limit fecal contamination and virus transmission.

## **Gaps in Preparedness**

- PAdV is not thought to be a major threat to the United States swine industry. However, recent seroprevalence data is lacking and further studies could help determine the potential impact of PAdVs on swine production.

## OVERVIEW

Porcine adenovirus (PAdV) is a ubiquitous virus with a worldwide distribution and is considered a low grade pathogen in domestic swine. PAdV is a non-enveloped, DNA virus in the genus *Mastadenovirus* of the family *Adenoviridae*. PAdV can be isolated from intestines during cases of moderate enteric disease, but more commonly results in subclinical infections. Most adult swine are seropositive for anti-PAdV antibodies, indicating that the virus is widespread but has a low incidence of disease. PAdV has also been isolated in cases of nephritis and respiratory disease, and is thought to contribute to reproductive disorders.

Currently, there are three porcine species and five serotypes in the *Mastadenovirus* genus. Porcine adenovirus A is composed of porcine adenovirus serotypes 1-3 (PAdV 1-3). Serotype 4 (PAdV-4) belongs to porcine adenovirus B and serotype 5 (PAdV-5) belongs to porcine adenovirus C. PAdV-4 is the most commonly isolated serotype and has been associated with enteritis, nephritis, encephalitis and pneumonia. Serotypes can be differentiated using cross-neutralization assays. PAdV is stable in the environment for ten days. It is resistant to ether and chloroform but can be inactivated using 0.85% salt solution or 1M MgCl<sub>2</sub> solution heated to 50°C for 1 hour. Beach, formaldehyde, alcohol and phenolic compounds are also effective disinfectants for PAdV.

PAdV is endemic in most conventional swine herds throughout the world and infection is mostly asymptomatic. Swine are the only known hosts of porcine adenoviruses and there have been no reports of zoonotic transmission from swine to humans; however, human adenoviruses have been able to experimentally infect swine. Adenovirus was first isolated in swine in 1964 from a rectal swab of a pig with diarrhea. Through the remainder of the 1960s and the 1970s, serological surveys in Canada and England indicated many adult swine have anti-PAdV antibodies. However, the serologic prevalence of PAdV has not recently documented and the current distribution of PAdV is unclear. PAdV-induced clinical disease has been documented in several states in the United States, Belgium, Japan and the United Kingdom.

Fecal-oral or fecal-nasal transmission of PAdV is most common. PAdV is stable in the environment, so transmission via fomites is also likely. Once ingested, PAdV undergoes intranuclear replication, primarily in the short blunt villous enterocytes and lymphoid tissue located in the distal jejunum and ileum. The most common clinical sign associated with PAdV infections is intermittent, yellow, watery diarrhea. Animals appear depressed, emaciated, and severely dehydrated. Occasionally diarrhea is accompanied by vomiting. Post-mortem findings include thin walled distal small intestine and enlarged mesenteric lymph nodes. Yellow, watery contents may be present in the small and large intestines. Upon histologic examination, the villi are short and blunt in the distal jejunum and ileum. Intranuclear inclusion bodies are present in the enterocytes of the affected villi.

PAdV is easily cultured in cell lines of porcine origin; primary and continuous kidney cells, primary thyroid cells, and primary testicular cells are most commonly used. PAdV can be identified from fecal and intestinal culture using negatively stained, transmission electron microscopy (TEM), immunohistochemical staining or virus isolation. Alternatively, immunofluorescence antibody (IFA) assays, complement fixation, direct fluorescence antibody (FA), and gel diffusion precipitation tests are all capable of detecting PAdV antigen and can be useful in confirming infection. Although polymerase chain reaction (PCR) assays have been developed for detection of PAdV in the environment, they are not currently utilized in the clinical diagnosis of PAdV.

As PAdV rarely results in clinical illness, little information is available on immunity post-infection. PAdV not considered to be a major threat to the United States swine industry; it is a low grade pathogen

and infections are generally asymptomatic. There is no specific treatment for PAdV-induced disease and no vaccine is available.

## LITERATURE REVIEW

### 1. Etiology

#### 1.1 Key Characteristics

Porcine adenovirus (PAdV) is a non-enveloped, DNA virus with an icosahedral capsid, belonging to the family *Adenoviridae* in the genus *Mastadenovirus*.<sup>1</sup> Adenovirus was first isolated in swine from a rectal swab of a pig with diarrhea in 1964.<sup>2</sup>

#### 1.2 Strain Variability

There are currently three recognized porcine species and five serotypes within the *Mastadenovirus* genus. Serotypes can be differentiated using cross-neutralization assays.<sup>3</sup>

- Porcine adenovirus A is composed of porcine adenovirus 1-3 (PAdV 1-3). PAdV-1 and PAdV-3 have been isolated from diarrheic swine, and PAdV-2 and PAdV-3 have been isolated from normal swine.
- Porcine adenovirus B has only one serotype, porcine adenovirus 4 (PAdV-4),<sup>1</sup> the most commonly isolated serotype. PAdV-4 has been isolated from pigs with enteritis, nephritis, encephalitis and pneumonia.<sup>4</sup>
- Porcine adenovirus C is comprised of porcine adenovirus 5 (PAdV-5).<sup>1</sup> PAdV-5 has been isolated from the brain of a newborn pig and from nasal secretions from pigs with respiratory disease.<sup>5,6</sup>

Recently, two novel PAdVs have been identified. Strain PAdV-WI was identified in swine facility pen wash water and has been proposed as a prototype of a new *Mastadenovirus* species.<sup>7</sup> A second strain, PAdV-SVN1, was isolated in cultures of normal porcine urothelial cells (from the bladders of domestic pigs), and has genetic similarity to PAdV-WI.<sup>8</sup>

Experimentally PAdVs have also been used in gene transfer research and as vectors in vaccine research.<sup>5</sup> For example, a recombinant PAdV-3 vector has been generated for potential gene transfer to human cells.<sup>9</sup> PAdV-3 and -5 have been investigated as vectors for transmissible gastroenteritis virus and classical swine fever virus vaccines.<sup>10</sup>

### 2. Cleaning and Disinfection

#### 2.1 Survival

Adenoviruses are able to survive in the environment for at least ten days.<sup>11</sup> Following a manure spill, porcine adenovirus was detectable 18 days later 5.6 km downstream.<sup>12</sup> Heating to 56°C for greater than ten minutes can inactivate adenoviruses.<sup>1</sup>

#### 2.2 Disinfection

PAdV is stable in acidic conditions (pH 3–4) and not susceptible to ether or chloroform. Bleach, formaldehyde, alcohol and phenolic compounds are effective disinfectants for PAdV.<sup>2,6,11</sup> PAdV-5 has been successfully inactivated using 0.85% salt solution or 1M MgCl<sub>2</sub> solution heated at 50°C for 1 hour.<sup>6</sup>

### 3. Epidemiology

#### 3.1 Species Affected

Adenoviruses are relatively host-specific. Swine are the only known hosts for PAdV.<sup>5</sup> Human adenoviruses have been able to experimentally infect swine.<sup>13,14</sup> The *Mastadenovirus* genus also includes adenovirus species that infect humans, bovines, canines, equines, murines, ovines, and tree shrews.<sup>1</sup>

### **3.2 Zoonotic Potential**

There is no known zoonotic transmission of PAdV to humans.<sup>5</sup> Adenoviruses generally have a specific and restrictive host range.<sup>1</sup>

### **3.3 Geographic Distribution**

In the 1960s–1970s, several serological surveys showed that PAdVs were widespread in Canada and England. However, the serologic prevalence of PAdV has not been documented recently and the current distribution of PAdV is unclear.<sup>5</sup> Natural PAdV-induced infections associated with nephritis have been documented in the United States (Georgia and South Dakota)<sup>4</sup> and Belgium.<sup>15</sup> Natural PAdV-induced infections associated with respiratory disease have been reported in Japan,<sup>6</sup> and clinical enteritis has been seen in the United States (Kentucky and Tennessee)<sup>16</sup> and the United Kingdom.<sup>2</sup>

### **3.4 Morbidity and Mortality**

There is little data on adenovirus-related morbidity and mortality rates. Studies from England in the 1960s reported seroprevalence rates of 25–53% and 50–60%.<sup>17,18</sup> Serological surveys of swine in Quebec found lower prevalence rates ranging from about 15% to 18%.<sup>19,20</sup> In one documented PAdV-induced disease outbreak, a morbidity rate of 30% was reported. Animals 14 days of age experienced diarrhea with occasional vomiting and no sows showed clinical signs of infection.<sup>21</sup> PAdV-induced infections rarely result in death.<sup>16</sup>

## **4. Transmission**

Transmission of PAdV is primarily through fecal ingestion or inhalation.<sup>5</sup> However, as PAdV has been detected in kidneys post-mortem, urinary-oral and urinary-nasal should also be considered as viable routes of transmission.<sup>4</sup> PAdV is stable in the environment, so transmission via fomites is likely.<sup>5</sup>

## **5. Infection in Swine/Pathogenesis**

Once ingested, PAdV undergoes intranuclear replication, primarily in the short blunt villous enterocytes and lymphoid tissue located in the distal jejunum and ileum.<sup>3,5</sup> In an experimental study, PAdV-3 viral particles were detected 24 hours to 16 days post-inoculation in enterocytes. It was determined that destruction of the epithelium and shortening of the villi correlated with the presence of PAdV-3 in the nucleus of these cells. Viral antigen was found 24 hours and up to 45 days in some animals. However, antigen detection at day 45 post-inoculation did not coincide with morphologic changes in the epithelium. Tonsils were sporadically infected, and frequently at later stages, indicating a possible viremia of PAdV-3.<sup>22</sup>

In experimental studies, diarrhea ensues three to four days post-inoculation and persists for three to six days.<sup>21,22</sup> During natural infection, diarrhea has been documented in some instances for three to five days and others persisted for one to three weeks.<sup>16,21</sup> Pre-weaned piglets one to four weeks of age are primarily affected.<sup>16</sup>

### **5.1 Clinical Signs**

The most common clinical sign associated with PAdV infections is intermittent, yellow, watery diarrhea.<sup>16,21</sup> Animals appear depressed, emaciated, and severely dehydrated.<sup>16</sup> Occasionally diarrhea is accompanied by vomiting.<sup>21</sup> Natural infection usually occurs in piglets one to four weeks of age and sows are not clinically affected by PAdV. Generally, PAdV-induced gastrointestinal disease is found secondary to other clinical signs.<sup>5</sup>

Rarely, nephritis is documented in association with PAdV. In reported cases, affected animals were four to eight months of age. The presenting problem on these farms was chronic, purulent bronchopneumonia and PAdV nephritis was an incidental finding that likely did not contribute to the clinical presentation.<sup>4</sup>

PAdV-5 has been isolated in cases of respiratory disease with sneezing, nasal discharge and coughing.<sup>6</sup> PAdV is also thought to contribute to reproductive disorders, primarily those resulting in abortion.<sup>11</sup>

## **5.2 Postmortem Lesions**

In clinical cases of PAdV-induced diarrhea, the wall of the distal small intestine is thin and mesenteric lymph nodes enlarged.<sup>16,21</sup> Yellow, watery contents can be present in the small and large intestines.<sup>21</sup> Upon histologic examination, the villi are short and blunt in the distal jejunum and ileum. Intranuclear inclusion bodies are present in the enterocytes of the affected villi. Infiltration of the lamina propria in these areas is made up of histiocytes, plasma cells, and lymphocytes.<sup>16,21</sup>

Animals experimentally infected with PAdV-3 strain 6618 had similar gross lesions as those found in natural infections. This included thin intestinal walls with yellow watery contents. Mesenteric lymph nodes were also enlarged and edematous. Occasionally, pulmonary lesions were found on apical lobes. Similar lesions as those found in natural infections were also seen histologically including intranuclear bodies in enterocytes of affected villi with infiltration of the lamina propria. Focal gliosis and non-purulent perivascularitis was observed in the brain of some animals. The liver revealed some hepatocyte vacuolization with neutrophilic infiltration. Lungs were congested with interstitial pneumonia and some hydropic degeneration of bronchial epithelium.<sup>21</sup>

In documented cases of PAdV-induced nephritis, the connective tissue surrounding renal tubules contained multifocal accumulations of lymphocytes and plasma cells. Some eosinophilic, necrotic epithelial cells were present in the lumen of medullary tubules, and sloughed tubular epithelial cells contained intranuclear bodies.<sup>4</sup>

## **6. Diagnosis**

### **6.1 Clinical History**

PAdV should be considered as a differential in cases of diarrhea in pre-weaning aged piglets.<sup>16</sup>

### **6.2 Tests to Detect Nucleic Acids, Virus, or Antigens**

PAdV is easily cultured in cell lines of porcine origin; primary and continuous kidney cells, primary thyroid cells, and primary testicular cells are most commonly used.<sup>5</sup> Cytopathic effects can be seen two to five days post-inoculation.<sup>3,5</sup> Intranuclear bodies can be seen in infected tissue samples; however, PAdV identification techniques should be used to confirm diagnosis.<sup>5,21</sup> PAdV can be detected in fecal and intestinal culture using negatively stained, transmission electron microscopy (TEM).<sup>4</sup>

Immunofluorescence antibody (IFA) assays, complement fixation, direct fluorescence antibody (FA), and gel diffusion precipitation tests are all capable of detecting PAdV antigen and can be useful in confirming infection.<sup>2-5,11</sup> Although polymerase chain reaction (PCR) assays have been developed for detection of PAdV in the environment, they are not currently utilized in the clinical diagnosis of PAdV.<sup>5</sup>

### **6.3 Tests to Detect Antibody**

A rise in anti-PAdV antibody in the presence of clinical disease is suggestive of causation of clinical disease.<sup>5</sup> Serological methods include virus neutralization or indirect fluorescent antibody testing.

### **6.4 Samples**

#### *6.4.1 Preferred Samples*

Preferred samples from diarrheic animals are the distal ileum and the jejunum.<sup>16,22</sup> PAdV antigen has also been successfully identified using fecal samples of infected animals.<sup>5</sup>

#### *6.4.2 Oral Fluids*

The use of oral fluids as a diagnostic specimen has not been evaluated for PAdV.

## **7. Immunity**

### **7.1 Post-exposure**

Viral antigen has been found in enterocytes up to 45 days post-infection, which is suggestive of long-term shedding. PAdV has been successfully isolated from the brain, nasal tissue, pharynx, lung and intestine 48 days after experimental inoculation. Most adult serum and rectal swabs are positive for anti-PAdV antibodies.<sup>5,16</sup>

### **7.2 Vaccines**

There is no vaccine for PAdV.

### **7.3 Cross-protection**

Information on cross-protection between strains is unavailable.<sup>5</sup>

## **8. Prevention and Control**

There is no specific treatment or vaccine for PAdV-induced infection.<sup>11</sup> PAdV is a low grade pathogen and rarely results in mortality. Swine industry biosecurity practices, including cleaning and disinfection, should be in place to limit transmission of the virus.

## **9. World Organization for Animal Health (OIE) Terrestrial Animal Health Code**

PAdV is not included in the 2015 OIE Terrestrial Animal Health Code. There are no restrictions for importation of animals from countries or zones infected with PAdV.

## **10. Gaps in Preparedness**

PAdV is a low grade pathogen that likely presents little threat to the swine industry. However, recent seroprevalence data is lacking and further studies could help elucidate the potential impact of PAdVs on swine production.

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