Animal Adenoviruses

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Amit Gaba, Lisanework E. Ayalew, and Suresh K. Tikoo

Abstract

Since the first report on adenoviruses in the early 1950s, more than a hundred serotypes of this virus have been reported from reptiles, fish, mammalian, and avian species. These viruses exhibit different lineages based on the differences noticed in the genes located in the terminal regions. Adenoviruses are grouped into five genera including *Mastadenovirus, Aviadenovirus, Atadenovirus, Siadenovirus*, and *Ichtadenovirus.* Recently, a sixth genus, *Testadenovirus*, is proposed to include adenoviruses from turtles. Bats have been identified as prospective reservoir hosts of emerging and re-emerging diseases and playing an important role in the evolution of adenoviruses. This chapter details the information on epidemiology, clinical signs, pathology, diagnosis, prevention, and control aspects of various species-specific adenoviruses affecting bovine, ovine, porcine, canine, and equine that are reported from both healthy animals and those suffering from diarrhea and pneumoenteritis. There is no specific treatment or vaccine available for adenoviruses.

Keywords

Adenoviruses · Classification · Genome · Pathology · Diagnosis · Vaccines

A. Gaba
VIDO-InterVac, University of Saskatchewan, Saskatoon, SK, Canada

L. E. Ayalew
VIDO-InterVac and Veterinary Pathology Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK, Canada

Veterinary Pathology Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, SK, Canada

S. K. Tikoo (✉)
VIDO-InterVac, University of Saskatchewan, Saskatoon, SK, Canada

Vaccinology & Immunotherapeutics Program, School of Public Health, University of Saskatchewan, Saskatoon, SK, Canada
e-mail: Suresh.tik@usask.ca

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1.1 Prologue

Adenovirus was first isolated in 1953 from human adenoids (Enders et al. 1956). Since then, over 120 adenovirus serotypes have been isolated from mammals, birds, reptiles, and fish. Although adenoviruses infect a wide variety of animal species, most of these are involved with mild clinical infections. Unlike human adenovirus, animal adenoviruses are usually species specific. Although overall capsid structure and organization of adenovirus genome has remained largely unchanged, there are differences in the proteins encoded by selected regions of adenovirus genome. Interestingly, compared to genes located in the central region of genome, which are involved in virion capsid formation, DNA encapsidation, and DNA replication, the genes located in the terminal regions show distinct differences and may define distinct lineage (Davison et al. 2003).

1.1.1 Classification

Adenoviruses are members of *Adenoviridae* family. Based on the genome organization, phylogenetic relations including presence of conserved and unique genes, the adenoviruses are grouped into five genera including *Mastadenovirus, Aviadenovirus, Atadenovirus, Siadenovirus*, and *Ichtadenovirus* (Davison et al. 2003) (Fig. 1.1). Recently, a sixth genus, *Testadenovirus*, is proposed to include adenoviruses from

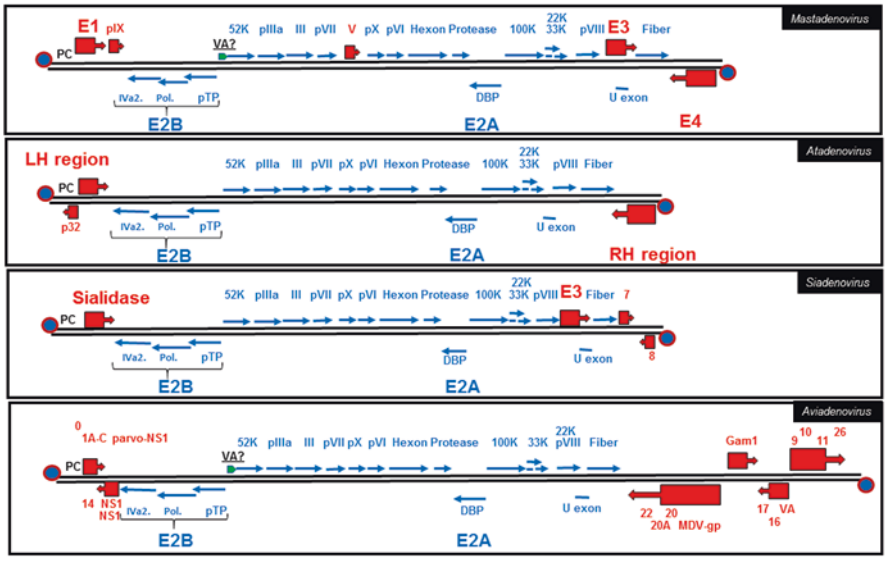

Fig. 1.1 Schematic diagram of adenovirus genomes of different genera. (Adapted from Davison et al. 2003). The common genes are depicted in blue text (⟶); unique genes are depicted in red text (➡) PC (cis-acting DNA packaging signal(s)); Terminal protein (TP) (●). E (early). The arrow heads show the direction of transcription

turtles (Order Testudines) (Doszpoly et al. 2013). Members of all genera share 16 genes [DNA polymerase (pol), terminal protein (TP), DNA binding protein (DBP), 52 K, IVa2, pIIIa, III, pVII, pX, pVI, hexon, protease, 100 K, 33 K, pVIII, and fiber].

Members of *Mastadenovirus* infect mammals and contain genus-specific proteins (protein IX, protein V, and few proteins encoded by E1, E3 and E4 regions). Members of *Atadenovirus* infect different hosts (ruminants, birds, reptiles, and marsupial) and (a) contain genome with high AT content and (b) encode genus-specific proteins p32 and LH3 but (c) do not contain genes encoding protein IX and protein V (Gorman et al. 2005).

Members of *Aviadenovirus* infect avian host (chicken, goose, turkey, and falcon) and (a) contain genomes of 43–45 kb (Kaján et al. 2012) with short inverted terminal repeats (ITRs) and (b) two fiber proteins per vertex of icosahedral virion capsid but (c) does not contain genes encoding protein IX, protein V, and E3 region proteins (Grgić et al. 2011). Members of *Siadenovirus* infect various hosts (reptiles, frogs, and turkeys) and (a) contain short genomes with short ITRs and (b) a viral gene encoding sialidase and (c) do not contain E1, E3 and E4 regions and genes encoding proteins IX and V (Davison et al. 2003). Members of *Ichtadenovirus* infect fish (white sturgeon) and contain the longest genome identified in all adenoviruses. Interestingly, unlike members of the other genera, the homologue of fiber gene appears to be located at the left end of the genome (Kovacs et al. 2003).

1.1.2 Virion Structure

Adenovirus is a non-enveloped icosahedral particle of 65–90 nm diameter in size (Fig. 1.2a), which contain a double-stranded linear genome of 26–48 kb (Kovacs et al. 2003). The ends of the genome contain inverted terminal repeats ranging from 36 bps to over 200 bps. In addition, a terminal protein (TP) is covalently attached to

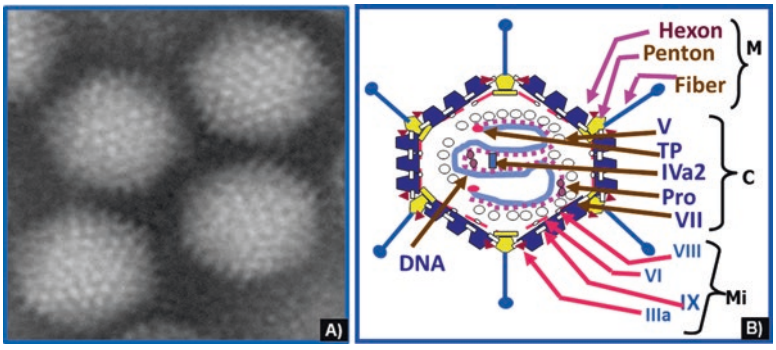

Fig. 1.2 (**a**) Electron micrograph of bovine adenovirus-3, a member of *Mastadenovirus*. (**b**) Schematic diagram of cross section of adenovirus virion. (Adapted from Russel et al. 2009.) *M* major capsid proteins, *Mi* minor capsid proteins, *C* core proteins, *Pro* protease, *TP* terminal protein

5′ ends of the genome, which is required for viral DNA replication (protein-primed DNA replication). Adenovirus genomes can encode between about 23 and 46 proteins (structural, core, and nonstructural). The icosahedral virion capsid contains major structural proteins (hexon, penton, fiber), minor structural proteins (IIIa, VI, VIII, IX), and core proteins (V, VII, Mu, TP, IVa2, cysteine protease) (Fig. 1.2b).

1.1.3 Adenovirus Life Cycle

Like other viruses, the adenovirus initiates attachment to host cell by interaction of fiber protein with cellular receptor. Following virus attachment, interaction of penton to cell surface receptors (e.g., integrins) activates rearrangement of actin cytoskeleton and initiates receptor-mediated virus endocytosis using clathrin-coated pits, which requires GTPase dynamin and adaptor protein 2 (Meier and Greber 2004). Stimulation of endosome acidification due to proton pump action leads to partial uncoating of viral capsid proteins. The exposure of lytic portion of protein VI by adenovirus protease cleavage induces disruption of endosomal membrane and results in microtubule motor protein dynein-mediated transport of partially disassembled virus capsid to microtubule organization center (MTOC) near the nucleus (Bremner et al. 2009). Next, the interaction of adenovirus hexon with cytoplasmic nucleoporin Nup214 located in fibrils on nuclear pore complex (NPC) associates disassembled virus capsid with NPC (Cassany et al. 2015). Interaction of protein IX with kinesin-1 bound to Nup358 induces further disruption of viral capsid (Strunze et al. 2011). Finally, viral DNA complex is transported to nucleus using cellular transport factors including transportin, importins, and histone H1.

Adenovirus genome in the nucleus is transcribed by host RNA polymerase II (Reviewed in Russel et al. 2009). The transcription of adenovirus genome is regulated temporally and can be divided into early (E) region before initiation of DNA replication, delayed early/intermediate (I) region during initiation of DNA replication and late (L) region after initiation of DNA replication. The proteins encoded by early (E) regions E1, E3, and E4 are nonstructural proteins and are involved in initiating viral gene transcription and cell cycle regulation (E1), evasion of host defense (E3) and viral gene transcription regulation and nuclear export (E4). The proteins encoded by early region E2 are structural and nonstructural proteins, which are involved in DNA replication. The proteins encoded by delayed early region/intermediate region are structural proteins (IX and IVa2) and are involved in virion stability, DNA packaging and activation of major late promoter.

The ITRs of adenovirus genome contain origin (ORI) of DNA replication sequences. Interestingly, a protein acts as a primer for the initiation of adenovirus DNA replication (reviewed in de Jong et al. 2003). The initiation of DNA replication occurs by covalent binding of hydroxyl group of serine (amino acid 580) of newly synthesized terminal protein (TP) to dCMP nucleotide residue on nascent DNA strand using Ser-dCMP phosphodiester bond. After initiation of adenovirus genome replication, chain elongation occurs by strand displacement mechanism in

the presence of viral (DBP, DNA polymerase) and cellular protein (nuclear factor II). The displaced strand can duplicate by formation of panhandle structure.

After adenovirus DNA replication, the L region is transcribed as one major transcript using major late promoter (MLP). This major transcript is processed in several overlapping transcripts using alternate splicing and usage of poly(A) signals addition sites. The L region encodes structural proteins (hexon, penton, fiber, IIIa, VI, VIII, IX, V, VII, Mu, TP, IVa2), protease and nonstructural proteins (100K, 32K,22K,52K). In addition, some adenovirus genomes carry virus-associated RNA genes transcribed by RNA polymerase III.

The transport of newly synthesized proteins to nucleus leads to the formation of empty capsids. Next, adenovirus DNA is packaged into empty capsid using cis-acting DNA sequences at the left end of the genome, viral proteins, and cellular proteins. Some reports suggest that capsid formation and DNA packaging occur simultaneously (Condezo and San Martín 2017). Final step in the production of infectious adenovirus virion involves the proteolytic cleavage of structural proteins pIIIa, pTP, pVI, pVII, pμ, and pVIII (reviewed in Russel 2009) by adenovirus cysteine protease. Although adenovirus E2 encoded 11.6K protein has been proposed to be involved in the lysis of infected cells (Tollefson et al. 1996), the virus usually remains in the infected cells till released by cell lysis.

1.2 Animal Adenoviruses

1.2.1 Bat Adenovirus

Bats are recognized as potential reservoir hosts of emerging and re-emerging diseases of humans and animals. They are also suggested to play an important role in the evolution of adenoviruses. The first bat adenovirus (BtAdV) strain FBV1\ BtAdV-1was isolated in 2008 from a fruit bat Ryukyu flying fox (*Pteropus dasymallus*) in Japan. The second BtAdV-designated as BtAdV-2 strain PPV1 was isolated from *Pteropus pipistrellus* in 2009. Subsequently, BtAdVs have been isolated from *Myotis chinensis* (BtAdV-3 strain TJM), *Rousettus leschenaultii* (BtAdV-4), *Eidolon helvum* (BtAdV-5), *Rhinolophus sinicus* (BtAdV WIV9–11), *Corynorhinus rafinesquii* (BtAdV 250-A), *Miniopterus schreibersii* (WIV12–13*), R. leschenaultii* (WIV17–18*)*, and *Eidolon helvum* (EhAdV 06–106) (summarized in Ogawa et al. 2017).

Based on analysis of complete genomic sequences, the BtAdV TJM and PPV1 strains, two species, namely, *Bat mastadenovirus-A* and *Bat mastadenovirus-B*, were established. Recently, analysis of additional novel BtAdVs genomes has led to the proposal of six more species: BtAdV C (WIV9–11), BtAdV D (250A), BtAdV E (WIV12), BtAdV F (WIV13), BtAdV G (WIV17–18), and BtAdV H (EhAdV 06–106). These species have been included into three groups, namely, Group 1 (*Bat mastadenovirus* A, B, and D), Group 2 (*Bat mastadenovirus* C), and Group 3 (*Bat mastadenovirus* E, F, G, and H) (summarized in Ogawa et al. 2017).

Since some BtAdVs are genetically closely related to *Canine mastadenovirus-A*, it was suggested that canine adenoviruses might have emerged from interspecies jumping of bat adenoviruses. However, analysis of novel BtAdVs WIV9–11 indicated that not all BtAdVs are closely related to *Canine mastadenovirus-A*. The epidemiology, pathogenesis, and molecular biology of BtAdVs are currently not well known.

1.2.2 Bovine Adenovirus

The bovine adenovirus (BAdV) was first isolated in 1959 from fecal samples of cow in the United States (Klein et al. 1959). Subsequently, BAdVs have been isolated from both healthy calves and those suffering from diarrhea and pneumoenteritis. Although shedding of BAdV by apparently healthy cattle and seroconversion with no apparent disease is widely reported, BAdV infection is also associated with several disease syndromes including respiratory disease in calves, digestive tract disease including enterocolitis, keratoconjunctivitis, and weak calf syndrome (Vaatstra et al. 2016). At present, based on viral neutralization tests, 10 serotypes of BAdV have been recognized, which are grouped into two genera: *Mastadenovirus* serotypes 1, 2, 3, 9, and 10 and *Atadenovirus* serotypes 4, 5, 6, 7, and 8 (ICTV 2016).

1.2.2.1 Epidemiology and Clinical Signs

Bovine adenovirus is a ubiquitous virus with a worldwide distribution in cattle population (Ursu et al. 2004). Various serological studies have reported the presence of antibodies to one or more BAdV serotypes in 25–87% of cattle sera tested. Virus transmission can occur directly by animal to animal contact or indirectly by contact with infectious virus excreted through saliva, feces, or nasal excretions via the conjunctival, oral, or nasopharyngeal route. BAdVs have also been implicated in cases of enzootic pneumonia in calves. A number of BAdV serotypes have also been associated with infectious keratoconjunctivitis. Repeated isolation of BAdV from bovine fetuses suggests that transplacental infection can occur (Bartha and Mate 1983).

BAdV's serotypes 3, 4, and 5 have been implicated in diseases of both upper and lower respiratory tract. Although isolation of BAdV-3 from outbreaks of acute respiratory disease showing symptoms of ocular and nasal discharge, pyrexia, pneumonia, and diarrhea in cattle has been frequently reported, the experimental infection of calves with BAdV-3 results in either no disease or disease with mild clinical signs (Akca et al. 2004). Repeated isolation of a number of BAdV serotypes including BAdV-4 and BAdV-8 from natural cases of pneumoenteritis with high mortality in calves has been reported. Calves 2 weeks to 4 months old are more susceptible to pneumoenteritis. Disease progresses from signs of upper respiratory tract infection followed by excessive salivation and diarrhea. Although calves usually recover with loss of condition, disease can be fatal in some of the calves that develop severe respiratory signs. Disease can be reproduced experimentally by using BAdV-4, but

symptoms are usually mild. In contrast, BAdV-8 could not produce the clinical signs in experimentally infected calves (Mohanty 1971).

BAdVs have been associated with abortion and weak calf syndrome. The affected calves are weak and listless at birth with pyrexia and polyarthritis. Occasionally, calves also have diarrhea. BAdV serotypes 5 and 7 have been isolated from the diseased calves. Moreover, experimental inoculation of calves with BAdV-5 resulted in a self-limiting, mild form of the disease with symptoms of pyrexia and diarrhea (Bartha and Mate 1983).

BAdV-10 has been associated with cases of fatal hemorrhagic colitis. The disease occurs in young calves and is characterized by signs of severe depression, recumbency, and severe hemorrhagic diarrhea resulting in death (Vaatstra et al. 2016).

1.2.2.2 Pathology

Adenovirus first infects lymphoid tissues of the oropharynx or epithelial cells of the respiratory tract. In case of alimentary tract infection, virus spreads to the intestinal epithelium, while, in case of respiratory tract infection, it spreads through the bloodstream to infect lungs and produce pneumonia. In cases of keratoconjunctivitis, virus infects conjunctival epithelium.

1.2.2.3 Diagnosis

Diagnosis of BAdV infections is difficult as clinical signs produced are indistinguishable from that produced by other bovine viruses. Moreover, since BAdV can also be isolated from healthy animal, virus isolation alone cannot lead to a definitive diagnosis. A definitive diagnosis thus requires virus isolation, identification of serotype, and seroconversion (Kahrs 1981). Diagnosis of BAdV can thus be done by combination of virus isolation, electron microscopy, PCR, and other tests like agar-gel immunodiffusion, ELISA, hemagglutination inhibition, complement fixation, and immunohistochemistry.

1.2.2.4 Prevention and Control

No specific treatment is available. Affected cattle should be treated according to symptoms. Antibiotics should be given to prevent secondary bacterial infection. The BAdV infection can be controlled by following good management practices. No vaccine is available in North America.

1.2.3 Canine Adenovirus

Canine adenovirus (CAdV) belongs to the genus *Mastadenovirus*. Based on virulence, genetic, and antigenic characteristics, CAdVs are classified into two groups: CAdV-1 and CAdV-2. Both viruses are grouped into the same species of *Canine mastadenovirus-A* (ICTV 2016). CAdV-1 was first recognized as the cause of infectious canine hepatitis (ICH) in 1947, which is characterized by acute necrohemorrhagic hepatitis formerly known as epizootic encephalitis of foxes. CAdV-2 was

first detected in 1962 and causes mild upper respiratory disease called infectious tracheobronchitis (ITB). CAdV-2 was also isolated in dogs that died from pneumonia and enteritis. Although CAdV-1 and CAdV-2 differ in their molecular characteristics, they show two-way cross protection.

1.2.3.1 Epidemiology and Clinical Signs

CAdVs are distributed worldwide in domestic and wild mammals in the family of Canidae, Ursidae, and Mustelidae. Red foxes, grey foxes, coyotes, wolves, and dogs are highly susceptible to infection. Serological surveys detected high prevalence of CAdV-specific antibodies in domestic dogs. CAdV-1, cause of ICH, is prevalent in wild canids as a subclinical infection and sporadic transmission can occur to unvaccinated susceptible domestic dogs. Virus transmission can occur directly by animal to animal contact or indirectly by contact with infectious virus excreted through urine; saliva; conjunctival, oral, and nasopharyngeal route; or feces (Willis 2000). Ectoparasites can act as mechanical vectors.

ICH occurs in young dogs less than 1 year of age. ICH has three forms: per-acute, acute, and mild. In per-acute disease, dogs die in 24–48 h without apparent clinical signs. The most common form of the disease is the acute form which causes high morbidity rate (10–30%). The incubation period of CAdV-1 is 4–7 days after ingestion of a material contaminated with virus or 6–9 days after direct contact with an infected animal. Acute form of the disease is characterized by acute or chronic hepatitis and interstitial nephritis. Common clinical signs are fever (>40°c), anorexia, blood in feces, vomiting, and diarrhea. Abdominal pain, conjunctivitis, photophobia, and bronchopneumonia are also common manifestations of CAdV-1 infection. Bilateral corneal opacity (blue eye) and uveitis develop in 25% of convalescent dogs but eventually disappears. In rare cases, infected dogs may develop encephalitis and show neurological signs. Virus persists in the kidney of recovered dogs, and virus is excreted in the urine for 6–9 months post infection. Mild form of ICH occurs in vaccinated animals that only developed partial immunity.

CAdV-2 is associated with canine respiratory disease complex or kennel cough syndrome. It causes mild respiratory disease with clinical signs that include tonsillitis, pharyngitis, tracheitis, and bronchitis (reviewed in Decaro et al. 2007).

1.2.3.2 Pathology

After infection of susceptible hosts, virus initially replicates in the tonsils and spreads to regional lymph nodes and other organs through the circulatory system. CAdV-1 has a tropism for vascular endothelial cells and hepatocytes, whereas CAdV-2 preferentially infects epithelial cells in the respiratory tract. During complications with secondary bacterial infections, CAdV-2 can also infect bronchial and alveolar epithelial cells. The disease is more severe in dogs less than 1 year of age, but unvaccinated dogs of all ages are susceptible. Virus replication takes place in the nucleus and forms characteristic large basophilic intranuclear inclusion bodies in hepatocytes. The inclusion bodies can also be observed in endothelial and epithelial cells of other virus-infected organs, mostly spleen and kidney (reviewed in Decaro et al. 2007). Chromatin condensation and margination occurs in infected

cells. Viruses are released by lysis of infected epithelial and endothelial cells causing tissue necrosis and disseminated intravascular coagulation.

Infected dogs with CAdV-1 show marked leucopenia, protein urea, and increased levels of liver enzymes. Due to impaired synthesis of clotting factors in the liver, clotting time of the blood is markedly reduced. Hence, bleeding in the oral cavity, ecchymotic hemorrhage in serosal surfaces, and lymph nodes are observed. Because of endothelial cell damage, multifocal vasculitis and hemorrhage and disseminated intravascular coagulation can occur. In addition, edema of the gall bladder can result in severe abdominal pain. Bilateral corneal opacity, uveitis, and interstitial nephritis occur as a result of deposition of circulating virus-antibody complexes.

1.2.3.3 Diagnosis

Diagnosis of CAdV infections is performed by virus isolation, electron microscopy, PCR, and serological test that include complement fixation test, hemagglutination inhibition test, and enzyme-linked immunosorbent assay (ELISA). The disease can also be diagnosed by histopathology and immunohistochemistry of infected tissue samples. CAdV-1 and CAdV-2 have 75% genetic sequence identity and can be differentiated by restriction enzyme analysis and DNA hybridization.

1.2.3.4 Prevention and Control

Maternal antibody is an important component of immunity that protects neonates from ICH and ITB. Modified live and killed vaccines are commercially available. CAdV-1-modified live vaccines are very effective; however, they produce corneal opacity and interstitial nephritis. Since CAdV-2 does not cause ocular or renal damage and antibodies induced against the virus cross-neutralize CAdV-1, current vaccines against ICH and ITB are mostly based on modified live CAdV-2. Lifelong immunity is conferred by live modified vaccine. Because of interference by maternal antibodies, 3 doses of vaccine in 4–5 weeks interval are recommended for puppies less than 16 weeks of age. Although CAdV-associated diseases are largely controlled by vaccination, in the recent past ICH outbreaks have been reported in different countries including Italy, Switzerland, and the United States.

1.2.4 Cervine Adenovirus

Cervine adenovirus (*Odocoileus adenovirus-1*) was first identified in 1993 as the cause of an epizootic of severe adenovirus hemorrhagic disease (AHD) that resulted in high mortality in mule deer in California, USA (Woods et al. 1996). Subsequently, *Odocoileus adenovirus-1* (OdAdV-1) has been isolated from white-tailed deer and black-tailed deer in the United States and a moose in Canada. OdAdV-1 has been tentatively placed in genus *Atadenovirus* (Boyce et al. 2000; Shilton et al. 2002).

1.2.4.1 Epidemiology and Clinical Signs

OdAdV-1 has been isolated from deer from various parts of North America. Virus transmission is directly by animal to animal contact or indirectly by contact with

infectious virus excreted through saliva, feces, or urine. Transmission through airborne routes, contaminated water, and contaminated equipment may also occur.

The AHD occurs in two forms: acute systemic form and chronic localized form. Animals suffering from acute form of disease show signs of weakness, difficulty in breathing, foaming or drooling from the mouth, and diarrhea that is often bloody. Progression of disease is rapid, and an infected animal can die within 3–5 days. Animals suffering from chronic infection show signs of extensive deep ulceration and necrosis in the mouth and throat and abscesses in oral cavity. Animals with localized lesions have difficulty in eating, which leads to weight loss and death. Rate of infection and mortality is higher in fawns compared to adults (Woods et al. 1996).

1.2.4.2 Pathology

The disease is characterized by pulmonary edema and erosions and hemorrhagic lesions and abscesses in the upper alimentary tract. Systemic vasculitis with endothelial intranuclear inclusions can be observed on histopathological examination (Boyce et al. 2000).

1.2.4.3 Diagnosis

OdAdV-1 infection can be diagnosed by virus isolation, detection of virions by electron microscopy, detection of virus antigen in tissues by immunofluorescence, and by virus- specific PCR assay.

1.2.4.4 Prevention and Control

No specific treatment or vaccine is available. Transmission of virus could be prevented by following standard biosecurity practices. Carcasses of animals should be disposed properly. Individuals handling animals should take adequate precautions to prevent spread of disease.

1.2.5 Equine Adenovirus

Equine adenovirus (EAdV) is widely distributed in horses and causes in apparent or subclinical infection in conventional foals. Two different serotypes designated as EAdV-1 and EAdV-2 have been isolated from horses. EAdV-1 is mainly isolated from the respiratory system of sick foals (Studdert and Blackney 1982). Pneumonia associated with EAdV infection has been reported in apparently immunocompetent foals, but virus has also been isolated from the respiratory tract of healthy foals. EAdV-2 is associated with clinical gastrointestinal tract infections of foals and subclinical gastroenteritis infection of horses.

1.2.5.1 Epidemiology and Clinical Signs

EAdV was first reported in the United States in 1969. Later, the virus was isolated and characterized from the pneumonic lung of an Arabian foal in California. EAdV-1 has been isolated from clinically healthy foals and foals with respiratory disease,

whereas EAdV-2 has been isolated from lymph node and feces of foals with respiratory disease and diarrhea (Studdert and Blackney 1982). Serological surveys have detected EAdV-specific antibodies in healthy horses. The mode of virus transmission is poorly characterized. However, foals potentially get infected from mares at birth via oral or nasopharyngeal route. Suckling Arabian foals with an autosomal recessive genetic disorder of severe combined immunodeficiency with a total lack of B and T cells are the most susceptible (Thompson et al. 1976). In these foals, EAdV-1 causes serious and often fatal respiratory infections. Adenoviral pneumonia in suckling Arabian foals is progressive and intractable. It is characterized by clear bilateral nasal discharge which later turns into yellow and slimy. Partial occlusion of the nostril makes suckling difficult and the foals gradually lose weight. A dry cough with extreme respiratory distress can be observed. The foals become dull and depressed. Secondary bacterial complications are common (Thompson et al. 1976). There have only been few reports of adenovirus pneumonia in non-Arabian foals. Experimentally infected thoroughbred yearlings showed watery nasal discharge starting between 4 and 12 days post infection with no significant changes in normal blood values, heart rate, and respiratory rate.

1.2.5.2 Pathology

Experimental infection of horses with EAdV causes pneumonia in horses regardless of breed. However, more severe lesions are observed in Arabian foals with combined immunodeficiency syndrome with extensive pneumonia of both lungs. Consolidated and firm lung especially the anterior ventral areas can be observed. The affected areas of the lung become depressed as compared to the unaffected parts of the lungs. The spleen can be very small and lymphoid follicles may not be present. On histopathology, distinctive lesions in the respiratory tract with focal areas of necrosis and large intranuclear inclusion bodies in the bronchial and bronchiolar epithelial cells are found. Purulent exudates with large number of leukocytes and hyperplastic bronchiolar epithelium can be observed (Webb et al. 1981).

1.2.5.3 Diagnosis

Diagnosis of EAdV infection is based on serological assays like complement fixation, agar gel diffusion, hemagglutination inhibition, and serum neutralization assays. Virus neutralization test is used as a gold standard to distinguish between EAdV-1 and EAdV-2 infection in horses. Isolation of virus and detection of virions by electron microscopy can also be performed. The use of PCR for the detection of EAdVs has also been reported. However, PCR and virus isolation do not necessarily suggest occurrence of clinical disease. Pulmonary histopathology is useful for postmortem diagnosis.

1.2.5.4 Prevention and Control

Although prevalence of equine adenoviral infection is widespread, infections are mild and self-limiting. Therefore, prevention and control measures are not economically feasible.

1.2.6 Murine Adenovirus

Murine adenovirus-1 (MAdV-1) (FL-1 strain) was first isolated in 1960 by Hartley and Rowe as a contaminant of Friend leukemia (FL) virus. Later, MAdV-2 (K87 strain) was isolated from the feces of clinically normal mice. In 2009, a novel murine adenovirus designated as MAdV-3 was isolated from a striped field mouse (*Apodemus agrarius*). MAdV-1, MAdV-2, and MAdV-3 are renamed as murine mastadenovirus A, B, and C, respectively, by the International Committee on Taxonomy of Viruses [ICTV] (ICTV 2016).

1.2.6.1 Epidemiology and Clinical Signs

Serological survey in the United Kingdom demonstrated that MAdV infections are common in wild house mouse populations with higher prevalence of MAdV-1 as compared to MAdV-2. Although mouse is the principal host of MAdV, rats can be infected. Naturally occurring disease due to MAdV infection has not been reported in immunocompetent adult mice. However, acute and persistent infections of MAdV-1with different disease conditions and associated clinical signs have been reported in experimentally infected immunocompetent or immunocompromised mice with MAdV-1 (Spindler et al. 2001). MAdV-2 is entrotropic and localizes in the intestine. The virus is shed for up to 3 weeks in the feces of immunocompetent mice and up to 6 months in athymic mice. Nevertheless, it is not known if it causes any disease conditions. MAdV-3 is known to be cardiotropic, but the virus is not well characterized.

MAdV-1 is transmitted by direct contact with virus-infected feces, urine, or nasal secretions. Clinical signs have never been observed in natural infections. Depending on age, immune status, strain of mouse, and virus dose, MAdV-1 can cause a fatal disease during experimental infections. Intraperitoneal infection of C57BL/6 mice with MAdV-1 produces encephalomyelitis as a result of endothelial cell activation and vasculitis. Although BALB/c mice are resistant to MAdV-1 infection, fatal generalized non-neurologic disease with focal hemorrhagic enteritis can be observed in BALB/c mice with severe combined immunodeficiency syndrome (SCID). Experimentally infected susceptible suckling mice show ruffled coat, lethargy, decreased food consumption, runting, and hunched posture usually resulting in death of mice in 3–10 days post infection. Neurological signs ranging from ataxia to flaccid paralysis can be observed in intraperitoneally infected adult immunocompetent CD-1 and NIHS mice with MAdV-1. Virus persists in adult immunocompetent mice with prolonged virus shedding in the urine for up to 2 years. Since it is not possible to study human adenoviruses pathogenesis in its natural host, MAdV-1 has been used as a model to understand the adenovirus virus host interactions and adenovirus pathogenesis in a natural host (mice) (Weinberg et al. 2007).

1.2.6.2 Pathology

MAdV-1 distributes widely in different tissues and organs post experimental infection. The major sites of MAdV-1 replication are the vascular endothelium and lymphoid tissues. Depending on the strain of mice, mononuclear phagocytes can be

systemically infected. Infected SCID BALB/c mice develop hemorrhagic enteritis after 17–19 day post infection. B cell or Bruton's tyrosine kinase (Btk) negative mice are highly susceptible to MAdV-1-induced disease. On postmortem examination of neonates infected with MAdV-1, necrosis of several tissues including the kidney, spleen, liver, pancreas, intestines, liver, and adrenal glands is observed. In histopathology, degenerative vascular changes, with infiltration of inflammatory cells, are observed in SJL/J mouse strains. Characteristic adenovirus intranuclear inclusion bodies are commonly seen in endothelial cells of the brain and epithelial cells of other infected tissues. Foci of necrosis with hemorrhage can also be observed in affected tissue. Cytotoxic CD8 + T cells are involved in immunopathology induced by MAdV-1. Survival of experimentally infected mice is dependent on both B and T lymphocytes. Antibodies play a great role in preventing the occurrence of generalized disease (Molloy et al. 2017).

1.2.6.3 Diagnosis

Complement fixation test, virus neutralization assay, indirect immunofluorescence (IF) test, and virus isolation and detection of virions by electron microscopy are used for diagnosis. Since MAdV-2 antiserum cross reacts with MAdV-1, but not vice versa, MAdV-2 antigens are commonly used for serological tests.

1.2.6.4 Prevention and Control

Most mouse colonies are currently free of MAdV infection. Biosecurity measures can be applied to prevent intrusion of wild mice to mouse colonies.

1.2.7 Ovine Adenovirus

Ovine adenovirus (OAdV) has worldwide prevalence as it has been isolated from different countries (Lehmkuhl et al. 1993). OAdVs are frequently isolated from lambs and are mainly associated with mild or inapparent infection of the respiratory and intestinal tract. Similar to BAdV, OAdVs are also grouped into two genera: *Mastadenovirus* and *Atadenovirus*. OAdV 1–5 and goat adenovirus-2 (GAdV-2) belong to *Mastadenovirus*, while OAdV-7 and goat adenovirus-1 are members of *Atadenovirus* (ICTV 2016).

1.2.7.1 Epidemiology and Clinical Signs

High prevalence of OAdV-specific antibodies has been detected in healthy sheep. Virus transmission can occur directly by animal to animal contact or indirectly by contact with infectious virus excreted through feces or nasal excretions. OAdVs have been isolated from apparently normal sheep as well as from sheep showing signs of respiratory tract infection and from sheep with intestinal tract infection.

OAdVs have been associated with pneumoenteritis in lambs. Disease starts with mild fever and diarrhea followed by signs of respiratory tract infection. Infected lambs show signs of sneezing, coughing, and nasal discharge. Frequently, there is

secondary bacterial infection which is characterized by signs of high fever and forced respiration (Belak et al. 1976).

Experimental infection of lambs with OAdV-4 or OAdV-5 failed to produce any clinical disease, but virus could be recovered from nasal and rectal swabs. However, experimental inoculation of 3 weeks old colostrum deprived lambs with OAdV-1 by intranasal and intratracheal route resulted in the production of clinical signs of respiratory and intestinal tract infection. Similarly, intranasal and intratracheal experimental infection of lambs with OAdV-6 showed signs of upper and lower respiratory tract infection.

1.2.7.2 Prevention and Control

No specific treatment or vaccine is available. Transmission of virus could be prevented by following standard biosecurity practices.

1.2.8 Porcine Adenovirus

Porcine adenovirus (PAdV) was first isolated in the 1960s from the rectal swab of a pig suffering from diarrhea (Haig et al. 1964). A few years later, another isolation of PAdV was reported from the brain of a pig suffering from encephalitis (Kasza 1966). In following years, PAdV isolation has been reported from samples from healthy pigs as well as from pigs suffering from respiratory disease, enteritis, encephalitis, nephritis, and reproductive disorders. Porcine adenovirus (PAdV) belongs to the genus *Mastadenovirus*. Based on serum neutralization tests, five serotypes of PAdV have been identified. These five serotypes are further grouped into three species: PAdV-A (serotypes 1, 2, and 3), PAdV-B (serotype 4), and PAdV-C (serotype 5). Recently, isolation of novel PAdVs, PAdV-WI and PAdV-SVN1, has led to the proposal of a new *Mastadenovirus* species.

1.2.8.1 Epidemiology and Clinical Signs

PAdVs are distributed worldwide in swine population. Serologic studies have detected PAdV- specific antibodies in 50–90% of heathy pigs. PAdV-4 appears to be most widely distributed and is the most frequently isolated serotype. PAdVs are host specific and can only infect pigs. There has been no report of transmission of PAdV from pigs to other species of animals or humans. Since PAdV has been reported to be shed in feces, the virus transmission can occur by ingestion of contaminated material (fecal-oral route) or through inhalation (fecal-nasal route) (Benfield and Richard 2012). Although PAdV is considered a low-grade pathogen in pigs, it has been associated with enteritis, respiratory disease, encephalitis, and abortion.

PAdV-1, PAdV-3, and PAdV-4 have been isolated from pigs showing signs of gastrointestinal disease. One to four weeks of piglets are most susceptible. Infected animals show signs of depression, emaciation, and dehydration. The most consistent clinical sign observed is intermittent yellow watery diarrhea. Experimental inoculation of piglets with serotype 1, 2, 3, or 4 produces no symptoms or

occasionally mild diarrhea (Coussement et al. 1981; Shadduck et al. 1967; Sharpe and Jessett 1967). Death following experimental infection has never been reported.

PAdV-5 can be isolated from brain of pigs and from nasal secretions of pigs showing signs of respiratory disease. Interstitial pneumonia following experimental infection with PAdV-4 has also been reported. Isolation of PAdV-4 from the brain of pig suffering from encephalitis has been reported. Moreover, encephalitis can be reproduced by experimental intracerebral inoculation of less than 2 days old with PAdV-4 (Shadduck et al. 1967). Isolation of PAdV from aborted fetuses suggests that PAdV might contribute to reproductive failures mainly leading to abortion (Dee 1995).

1.2.8.2 Diagnosis

The PAdV infection can be diagnosed by virus isolation, detection of virus by electron microscopy, and serological tests like complement fixation, virus neutralization, and indirect immunofluorescence assay. An increase in anti-PAdV antibody titer and presence of clinical disease point to the role of PAdV in causing the disease (Benfield and Richard 2012).

1.2.8.3 Prevention and Control

There is no specific treatment or vaccine available. Transmission of virus could be prevented by following standard biosecurity practices.

1.2.9 Simian Adenovirus

The simian adenovirus (currently known as SAdV-21) was first isolated from feces of a chimpanzee suffering from respiratory disease (Rowe et al. 1956). At present, more than 50 serotypes of SAdV have been identified. Based on genomic properties, host origin, hemagglutinin properties, and a number of fiber genes, several identified simian adenovirus serotypes have been proposed to be grouped into seven species (*Simian mastadenovirus-A–G*) (Podgorski et al. 2016). The nonhuman primate adenoviruses which are genetically very similar to human adenoviruses are grouped under corresponding human adenovirus species or under officially accepted species for nonhuman primate adenoviruses designated as *Simian mastadenovirus-A*.

1.2.9.1 Epidemiology and Clinical Signs

Infections of nonhuman primates with simian adenoviruses are predominantly subclinical. Healthy chimpanzees, bonobos, gorillas, orangutans, and New World monkeys frequently shed significant amount of infectious adenovirus in their feces suggesting that persistent/latent infections could be established in nonhuman primates, without any clinical disease. So far, epidemiological studies are focused on isolation of adenoviruses from feces of asymptomatic captive nonhuman primates.

Though simian adenoviruses are associated with hepatitis, conjunctivitis, gastroenteritis, and respiratory disease problems in captive primates, their clinical

relevance in wild primates is unknown. Simian adenoviruses have been isolated from fecal samples of Western lowland gorillas (*Gorilla gorilla gorilla*) with prolonged diarrhea and self-limiting respiratory disease. Species D and E like adenoviruses have also been isolated from the stool of chimpanzees with acute upper respiratory signs in Western Tanzania. Interestingly, certain simian adenoviruses have the ability to cause neoplasia in hamsters.

Although most adenoviruses exhibit very narrow host specificity, there are reports of zoonotic transmission of simian adenoviruses from nonhuman primates to humans and between different primate species. Thus, virus host switching between different primate species might have contributed in the evolution of human and nonhuman primate adenoviruses. In a California research facility, an adenovirus outbreak characterized by fulminant pneumonia and hepatitis occurred in captive monkeys (*Callicebus cupreus*) with potential transmission to humans. The infection was assumed to be due to host switching from co-housed reservoir macaques. Serological surveys in Brazil and sub-Saharan Africa suggested infection of humans with New and Old World monkey adenoviruses. In addition, an adenovirus-associated acute respiratory disease outbreak occurred in a baboon colony in Texas, USA, which crossed over and infected staff personnel. Intra- and interspecies recombination between simian adenoviruses is also a common phenomenon.

1.2.9.2 Diagnosis

Simian adenoviruses can be diagnosed by virus isolation and detection of virus by electron microscopy, virus neutralization test, hemagglutination test, and PCR assay.

1.2.9.3 Treatment

There is no specific treatment or vaccine available.

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References

Akca Y, Burgu I, Gur S, Dagalp SB (2004) Investigation of the occurrence of some viral infections in buffaloes in Turkey. Rev Med Vet 155:268–271

Bartha A, Mate S (1983) Transplacental transmission of bovine adenoviruses. Comp Immunol Microbiol Infect Dis 6:189–192

Belak S, Palfi V, Palya V (1976) Adenovirus infection in lambs. I. Epizootiology of the disease. Zentralbl Veterinarmed B 23:320–330

Benfield DAH, Richard A (2012) Porcine adenoviruses. In: Zimmerman JJ, Karriker LA, Ramirez A, Schwartz KJ, Stevenson GW (eds) Diseases of swine. Wiley, Hoboken, pp 392–395

Boyce WM, Woods LW, Keel MK, MacLachlan NJ, Porter CO, Lehmkuhl HD (2000) An epizootic of adenovirus-induced hemorrhagic disease in captive black-tailed deer (*Odocoileus hemionus*). J Zoo Wildl Med 31:370–373

Bremner KH, Scherer J, Yi J, Vershinin M, Gross SP, Vallee RB (2009) Adenovirus transport via direct interaction of cytoplasmic dynein with the viral capsid hexon subunit. Cell Host Microbe 6(6):523–535

Cassany A, Ragues J, Guan T, Bégu D, Wodrich H, Kann M, Nemerow GR, Gerace L (2015) Nuclear import of adenovirus DNA involves direct interaction of hexon with an N-terminal domain of the nucleoporin Nup214. J Virol 89(3):1719–1730

Condezo GN, San Martín C (2017) Localization of adenovirus morphogenesis players, together with visualization of assembly intermediates and failed products, favor a model where assembly and packaging occur concurrently at the periphery of the replication center. PLoS Pathog 13(4):e1006320

Coussement W, Ducatelle R, Charlier G, Hoorens J (1981) Adenovirus enteritis in pigs. Am J Vet Res 42:1905–1911

Davison AJ, Benkő M, Harrach B (2003) Genetic content and evolution of adenoviruses. J Gen Virol 84:2895–2908

de Jong RN, van der Vliet PC, Brenkman AB (2003) Adenovirus DNA replication: protein priming, jumping back and the role of the DNA binding protein DBP. Curr Top Microbiol Immunol 272:187–211

Decaro N, Campolo M, Elia G, Buonavoglia D, Colaianni ML, Lorusso A, Mari V, Buonavoglia C (2007) Infectious canine hepatitis: an "old" disease re-emerging in Italy. Res Vet Sci 83(2):269–273

Dee SA (1995) Viral causes of porcine reproductive failure – part II. Compend Contin Educ Pract Vet 17:1159–1162, 1164–1170

Doszpoly A, Wellehan JF, Childress AL, Tarján ZL, Kovács ER, Harrach B, Benkő M (2013) Partial characterization of a new adenovirus lineage discovered in test udinoid turtles. Infect Genet Evol 17:106–112

Enders JF, Bell JA, Disgle JH, Francis T Jr, Hillemas MR, Huebner RJ, Payne AM (1956) "Adenoviruses": group name proposed for new respiratory-tract viruses. Science 124:119–120

Gorman JJ, Wallis TP, Whelan DA, Shaw J, Both GW (2005) LH3, a "homologue" of the mastadenoviral E1B 55-kDa protein is a structural protein of atadenoviruses. Virology 342:159–166

Grgić H, Yang DH, Nagy E (2011) Pathogenicity and complete genome sequence of a fowl adenovirus serotype 8 isolate. Virus Res 156:91–97

Haig DA, Clarke MC, Pereira MS (1964) Isolation of an adenovirus from a pig. J Comp Pathol 74:81–84

International Committee on Taxonomy of Viruses (ICTV) Virus Taxonomy: 2016 Release

Kahrs RF (1981) Adenoviruses. In: Kahrs RF (ed) Viral diseases of cattle. Iowa State University Press, Ames, pp 61–70

Kaján GL, Davison AJ, Palya V, Harrach B, Benko M (2012) Genome sequence of a waterfowl aviadenovirus, goose adenovirus 4. J Gen Virol 93(11):2457–2465

Kasza L (1966) Isolation of an adenovirus from the brain of a pig. Am J Vet Res 27:751–758

Klein M, Earley E, Zellat J (1959) Isolation from cattle of a virus related to human adenovirus. Proc Soc Exp Biol Med 102:1–4

Kovacs GM, LaPatra SE, D'Halluin JC, Benko M (2003) Phylogenetic analysis of the hexon and protease genes of a fish adenovirus isolated from white sturgeon (*Acipenser transmontanus*) supports the proposal for a new adenovirus genus. Virus Res 98(1):27–34

Lehmkuhl HD, Cutlip RC, Brogden KA (1993) Seroepidemiologic survey for adenovirus infection in lambs. Am J Vet Res 54:1277–1279

Meier O, Greber UF (2004) Adenovirus endocytosis. J Gene Med 6(Suppl. 1):S152–S163

Mohanty SB (1971) Comparative study of bovine adenoviruses. Am J Vet Res 32:1899–1905

Molloy CT, Andonian JS, Seltzer HM, Procario MC, Watson ME Jr, Weinberg JB (2017) Contributions of CD8 T cells to the pathogenesis of mouse adenovirus type 1 respiratory infection. Virology 507:64–74

Ogawa H, Kajihara M, Nao N, Shigeno A, Fujikura D, Hang'ombe BM, Mweene AS, Mutemwa A, Squarre D, Yamada M, Higashi H, Sawa H, Takada A (2017) Characterization of a novel bat adenovirus isolated from straw-colored fruit bat (Eidolon helvum). Viruses 4(9(12)):371

Podgorski II, Pantó L, Papp T, Harrach B, Benkö M (2016) Genome analysis of four Old World monkey adenoviruses supports the proposed species classification of primate adenoviruses and reveals signs of possible homologous recombination. J Gen Virol 97(7):1604–1614

Rowe WP, Hartley JW, Huebner RJ (1956) Additional serotypes of the APC virus group. Proc Soc Exp Biol Med 91:260–262

Russel WC (2009) Adenoviruses: update on structure and function. J Gen Virol 90(1):1–20

Shadduck JA, Koestner A, Kasza L (1967) The lesions of porcine adenoviral infection in germfree and pathogen-free pigs. Pathol Vet 4:537–552

Sharpe HB, Jessett DM (1967) Experimental infection of pigs with 2 strains of porcine adenovirus. J Comp Pathol 77:45–50

Shilton CM, Smith DA, Woods LW, Crawshaw GJ, Lehmkuhl HD (2002) Adenoviral infection in captive moose (*Alces alces*) in Canada. J Zoo Wildl Med 33:73–79

Spindler KR, Fang L, Moore ML, Hirsch GN, Brown CC, Kajon A (2001) SJL/J mice are highly susceptible to infection by mouse adenovirus type 1. J Virol 75:12039–12046

Strunze S, Engelke MF, Wang IH, Puntener D, Boucke K, Schleich S, Way M, Schoenenberger P, Burckhardt CJ, Greber UF (2011) Kinesin-1-mediated capsid disassembly and disruption of the nuclear pore complex promote virus infection. Cell Host Microbe 10(3):210–223

Studdert MJ, Blackney MH (1982) Isolation of an adenovirus antigenically distinct from equine adenovirus type 1 from diarrheic foal feces. Am J Vet Res 43:543–544

Thompson DB, Spradborow PB, Studdert M (1976) Isolation of an adenovirus from an Arab foal with a combined immunodeficiency disease. Aust Vet J 52:435–437

Tollefson AE, Scaria A, Hermiston TW, Ryerse JS, Wold LJ, Wold WS (1996) The adenovirus death protein (E3-11.6K) is required at very late stages of infection for efficient cell lysis and release of adenovirus from infected cells. J Virol 70(4):2296–2306

Ursu K, Harrach B, Matiz K, Benko M (2004) DNA sequencing and analysis of the right-hand part of the genome of the unique bovine adenovirus type 10. J Gen Virol 85:593–601

Vaatstra BL, Tisdall DJ, Blackwood M, Fairley RA (2016) Clinicopathological features of 11 suspected outbreaks of bovine adenovirus infection and development of a real-time quantitative PCR to detect bovine adenovirus type 10. N Z Vet J 64:308–313

Webb RF, Knight PR, Walker KH (1981) Involvement of adenovirus in pneumonia in a thoroughbred foal. Aust Vet J 57:142–143

Weinberg JB, Jensen DR, Gralinski LE, Lake AR, Stempfle GS, Spindler KR (2007) Contributions of E1A to mouse adenovirus type 1 pathogenesis following intranasal inoculation. Virology 357:54–67

Willis AM (2000) Canine viral infections. Vet Clin North Am Small Anim Pract 30:1119–1133

Woods LW, Swift PK, Barr BC, Horzinek MC, Nordhausen RW, Stillian MH, Patton JF, Oliver MN, Jones KR, MacLachlan NJ (1996) Systemic adenovirus infection associated with high mortality in mule deer (*Odocoileus hemionus*) in California. Vet Pathol 33:125–132