In: **A Concise Review of Veterinary Virology**, Carter G.R., Wise D.J. and Flores E.F. (Eds.). International Veterinary Information Service, Ithaca NY (www.ivis.org), Last updated: 9-May-2006; A3411.0506

# Herpesviridae

**G.R. Carter**[1], **D.J. Wise**[2] and **E. F. Flores**[3]

[1]Professor Emeritus of the Department of Medical Sciences and Pathobiology, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Tech, Blacksburg, Virginia, USA. [2]Department of Biology, Concord University, Athens, West Virginia, USA. [3]Department of Veterinary Preventive Medicine, Federal University of Santa Maria, Santa Maria, RS Brazil.

Table of Contents

**Viral Characteristics**
**Classification**
***Simplexvirus*:**
Bovine Ulcerative Mammillitis
Pseudolumpy-skin Disease
***Varicellovirus*:**
Infectious Bovine Rhinotracheitis/Vulvovaginitis
Bovine Herpesvirus 5 Infection
Pseudorabies
Canine Herpesvirus Infection
Equine Herpesvirus Abortion
Equine Coital Exanthema
Equine Rhinopneumonitis
Feline Viral Rhinotracheitis
***Marek's Disease-like Viruses*:**
Marek's Disease
***Infectious Laryngotracheitis-like Viruses*:**
Infectious Laryngotracheitis
***Rhadinovirus*:**
Malignant Catarrhal Fever
**Unassigned Genera:**
Inclusion Body Rhinitis
Duck Viral Enteritis
**Glossary**

This is a large, diverse family of DNA viruses that infect humans and a wide variety of animal hosts. They are large in size and are noted for their ability to cause latent infections. They are divergent with regard to genome sequence and proteins, biological properties, but are similar in overall virion structure and genome organization.

## Viral Characteristics

- They are enveloped, double stranded DNA viruses (100 - 200nm in diameter) with an icosahedral capsid.
- The virions consist of four structural units: 1) the core of DNA around that is wrapped a protein fibrilar spool; 2) a capsid composed of 12 pentameric and 150 hexameric capsomeres; 3) an amorphous protein layer between the capsid and the envelope; and 4) the envelope.
- The envelope has projections (spikes) evenly distributed over its surface (see Fig. 11-1).
- The dsDNA is used as a template for the production of progeny genomes and mRNAs,
- Following fusion of the viral envelope with the cell membrane, the nucleocapsid migrates to the cell nucleus, where replication takes place.
- Viral transcription is divided into immediate early, early, and late transcription. The structural proteins and the genome (DNA or RNA) are assembled into icosahedral or helical virions, then released.
- Certain host cells can prevent the transcription of genes and thus the viral genome persists, does not replicate, and the host cell doesn't die. This constitutes a form of viral latency.
- All herpesviruses thus far examined have the capacity for latency in host cells.
- There is no common antigen for all members.

Figure 11-1. Herpesviridae (100 - 200 nm). Between the capsid and the envelope there is a protein-filled region known as the tegument. - To view this image in full size go to the IVIS website at www.ivis.org . -

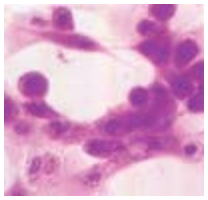

Figure 11-2. Equine "slow herpesvirus" intranuclear inclusions. *Courtesy of A. Wayne Roberts.* - To view this image in full size go to the IVIS website at www.ivis.org . -

## Herpesvirus Infections: General

All herpesviruses are thought to be capable of establishing latent infections. The classic example is human herpesvirus 1 (HSV-1) which infects of the dorsal root ganglia. The virus is latent between episodes of "cold sores". During latency only a small region of the viral genome is expressed, athough no protein has been unequivocally identified as a product of this transcription. The mechanism of reactivation of infection is not understood.

Some virus species infecting eukaryotic hosts are cell-associated and a small number are oncogenic. Many infections are silent or mild in natural hosts but serious in other hosts. For example, pseudorabies virus is a broad host range herpesvirus that causes fatal encephalitis in a wide variety of animal species but not in its natural host, the adult pig.

Herpesviruses are widespread and are frequently recovered in the diagnostic laboratory as they can be readily cultivated in cell cultures; some produce pocks on the chorioallantoic membrane. Only those herpesviruses causing significant animal diseases are discussed below.

A general rule is that every animal species harbors at least one herpesvirus.

## Classification

The family Herpesviridae is divided into three subfamilies, Alphaherpesvirinae, Betaherpesvirinae, and Gammaherpesvirinae.

Alphaherpesvirinae have a relatively short replication cycle (< 24 h), a variable host range, and usually cause rapid destruction of cultured cells. Viruses belonging to this subfamily establish latent infections in neural cells. Most herpesviruses of veterinary importance are found in the genus *Varicellovirus.*

Betaherpesvirinae contains the genera *Cytomegalovirus*, *Muromegalovirus*, and *Roseolovirus* of little veterinary significance. Unlike the Alphaherpesvirinae, this group of viruses has a relatively slow replication cycle (>24 h), a narrow host range, and causes a slow destruction of cultured cells. Infected cells are often greatly enlarged and may contain cytoplasmic as well as nuclear inclusions. These viruses establish latent infections in lymphoreticular and secretory gland cells.

Gammaherpesvirinae contains the genera *Lymphocryptovirus* (marine and fresh water fish) and *Rhadinovirus* (disease in marmosets and monkeys).

Alphaherpesvirinae (Subfamily)

***Simplexvirus***:

- Bovine herpesvirus 2:
  - Bovine ulcerative mammillitis, pseudolumpy-skin disease
- Cercopithecine herpes 1 (B virus of monkeys):
  - Infects Asian macaque monkeys naturally; has caused rare fatal encephalitis in monkey handlers.

***Varicellovirus***:

- Bovine herpesvirus 1:
  - Infectious bovine rhinotracheitis, pustular vulvovaginitis / balanoposthitis
- Bovine herpesvirus 5:
  - Causes meningo-encephalitis in cattle, particularly in South America
- Porcine herpesvirus 1:
  - Pseudorabies or Aujesky ’s disease
- Canine herpesvirus 1:
  - Canine herpesvirus infection
- Equine herpesvirus 1:
  - Equine herpesvirus abortion
- Equine herpesvirus 3:
  - Equine coital exanthema
- Equine herpesvirus 4:
  - Equine rhinopeumonitis
- Feline herpesvirus 1:
  - Feline viral rhinotracheitis

**Marek's disease-like viruses**:
Gallid herpesvirus 2:
Marek's disease
**Infectious laryngo-tracheitis-like viruses**:
Gallid herpesvirus 1:
Infectious laryngotracheitis
Betaherpesvirinae (Subfamily)
No viruses of significance in domestic and farm animals.
Gammaherpesvirinae (Subfamily)
***Rhadinovirus***
Alcelaphine herpesvirus 1:
Malignant catarrhal fever in cattle, deer and other ruminants in Africa; natural host is the wildebeest.
**Ovine herpesvirus 2**
Malignant catarrhal fever in cattle and some wild ruminants; sheep are natural host; occurs worldwide.
**Unassigned Genera**
Porcine herpesvirus 2:
Inclusion body rhinitis
Anatid herpesvirus 1:
Duck viral enteritis

***Simplexvirus***
**Bovine Ulcerative Mammillitis**
(Bovine herpes mammillitis, pseudolumpy skin disease, Allerton virus)

Cause
Bovine herpesvirus 2.

Occurrence
It occurs sporadically, mainly in dairy cattle, worldwide.

Transmission
By milkers, contaminated milking machines and mechanically by biting insects.

Pathogenesis
After inoculation into the skin or subcutaneous tissue the virus replicates locally without systemic spread.

Clinical & Pathologic Features
Bovine ulcerative mammillitis primarily affects dairy cattle causing a marked loss of milk production. It is characterized by edema of teats followed by vesicle formation and subsequent erosion of the teat and udder epithelium. Vesicles usually rupture within 24 hours and yield a serous exudate. Secondary bacterial infection may occur if no special care is taken. Scabs begin to form at four days, and healing occurs under the scab with recovery usually in 3 - 4 weeks. Milking may prevent scab formation and consequently delay healing.
Face and muzzle lesions may occur in nursing calves.
The Allerton strain of BHV-2 was originally isolated in Africa from cattle with generalized skin infections. This form of the disease, referred to as pseudolumpy-skin disease, occurs in tropical and subtropical regions.

Diagnosis
- Clinical specimens: Vesicular fluid, scabs, and scrapings of lesion.
- A rapid diagnosis of herpes mammillitis can be achieved by the electron microscopic demonstration of herpesvirus in distilled water lysates of lesion material.
- The virus can be isolated in cell cultures of bovine origin, but grows best at reduced temperature. Identification is accomplished by serum neutralization and fluorescent antibody tests. The virus produces large, characteristic syncytia in cultured cells.

Prevention
- Vaccines are not available.
- Control is best accomplished by sound milking practices. First-lactation cows should be milked first. Antiseptic teat-dipping and routine disinfection of the milking machine should be practiced. Any affected animal should be kept in isolation.

***Varicellovirus***

**Infectious Bovine Rhinotracheitis (IBR)**

(Infectious pustular vulvovaginitis / balanoposthitis)

Cause

Bovine herpesvirus 1.

Two subtypes of IBRV (BHV-1) virus have been defined based on monoclonal antibody binding/restriction enzyme analysis. They are designated:

BHV-1.1 (respiratory subtype)

BHV-1.2 (genital subtype).

Although BHV-1.1 is referred to as the respiratory subtype, it is also associated with abortion and very rarely with encephalitis. After the identification of BHV-5 as a major cause of meningoencephalitis in cattle, a question has been raised whether some events of encephalitis in the past attributed to BHV-1 were indeed caused by this virus or by BHV-5, since most diagnostic reagents are not capable of distinguishing between these viruses.

Subtype BHV-1.2 is further divided into BHV-1.2a and BHV-1.2b. The former-may cause abortion whereas the latter seems not to. Both have been associated with vulvovaginitis and balanoposthitis.

Occurrence

Infection by BHV-1 occurs in cattle worldwide, with the exception of some European countries that have eradicated the infection. Bovine herpesvirus 5 infection is discussed separately below.

Transmission

Infection occurs via the respiratory and genital routes. Spread is by direct and indirect contact (fomites) and aerosol droplets. The infection may be spread from infected bulls by coitus and artificial insemination. Frozen semen is an optimal condition for virus survival.

Pathogenesis

Replication takes place in the mucous membrane of the upper respiratory tract/genital mucosa and virus is shed in nasal/genital secretions. Semen may be contaminated during the ejaculation. Local nerve cell endings are infected and the virus is transported to trigeminal/sacral ganglia where it establishes a lifelong latent infection. Viremia is rarely detected, but it does occur, as infection of pregnant cows may lead to fetal infection and abortion. Once infected, the animals become lifelong carriers of the virus. The latent infection may be reactivated periodically, with or without clinical signs; the virus is transported back to the site of entry and is shed with potential transmission to other animals.

Clinical & Pathologic Features

IBR is an acute, contagious, widespread disease that is manifested in the following forms: rhinotracheitis, pustular vulvovaginitis / balanoposthitis and conjunctivitis. Neurological disease is attributed to another related virus, previously classified as a subtype of BHV-1, and now classified as BHV-5.

The respiratory form of the disease is most common. It has a sudden onset with high temperature. There is congestion and severe inflammation of the mucous membranes with serous ocular and nasal discharges. The morbidity is high in unvaccinated (nonimmune) herds but mortality is generally low. Recovery is usually uneventful in well-managed herds within about 14 days. Under stressful conditions (e.g., feedlots), secondary bacterial infection may lead to a severe tracheitis with diphtheritic membrane and bronchopneumonia.

The genital form, pustular vulvovaginitis and balanoposthitis, is characterized by inflammation of the genital mucosa and development of small pustules that coalesce and ulcerate. Infections may be mild or subclinical.

Abortion or stillbirths, which are infrequent, may occur 1 - 3 months postinfection.

The conjunctivitis form is common with occasional involvement of the cornea, and a panophthalmitis.

Bovine herpesvirus 5, initially identified Australia, is now considered the cause of fatal encephalitis in calves, a disease frequent in some South American countries.

Diagnosis

- Clinical specimens: Nasal and ocular swabs; vaginal and preputial swabs; trachea and lung; fetal liver, kidney, and lung; acute and convalescent sera. Specimens should be submitted for virus isolation in cell culture.
- A presumptive diagnosis is often made on the basis of clinical signs and lesions.
- A definitive diagnosis requires demonstration of viral infected cells by immunofluorescence, isolation, and identification of the virus, or the demonstration of a significant increase in IBR antibody levels between acute and convalescent serum samples.
- Immunofluorescence is the preferred method for the diagnosis of IBR abortions because the virus is often nonviable owing to advanced autolysis of fetal tissues.
- The virus is easily isolated from clinical specimens by the inoculation of cell cultures of bovine origin. The virus induces a well-recognized CPE in tissue culture.

- BHV-1 and BHV-5 cannot be differentiated serologically by routine tests, since they display an extensive serological cross-reactivity.

Prevention
- Modified live and killed vaccines often are available in combination with other bacterial and viral antigens. The modified live vaccines are of two types, one that is administered intramuscularly (IM) and one that is given intranasally (IN). The IN vaccine is recommended for pregnant cows since it is safe for the fetus.
- In eradication programs deletion mutant vaccines (marker vaccines) have been used to distinguish between vaccinal and natural antibodies using ELISA procedures.

**Bovine Herpesvirus 5 Infection ***

Cause

Bovine herpesvirus 5.

Apparently latent infections are reactivated by various stresses including those associated with transportation, weaning, and other management practices. In Brazil it is thought that some cases result from reactivation of latent BHV 5 infection by polioencephalomalacia.

Occurrence

The disease occurs rarely in Australia and some European countries. In South America, particularly in Brazil and Argentina, a number of outbreaks occur annually. Most outbreaks are in cattle seven months to three years of age; occurrence in younger cattle is infrequent. Although single cases in cattle up to six years of age have been reported they are uncommon. Up to 30% of animals in a herd may be affected. The disease occurs independently of classic IBR.

Transmission

This is probably similar to that described above for IBR viruses.

The most probable ingress of infection is thought to be via the nose and olfactory nerve. Thus most lesions involve the frontal cortex.

Clinical Features

The course is usually 4 - 7 days but may be as long as15 days. Clinical signs are mainly those of a meningoencephalitis. Blindness, head pressing and deep depression are particularly characteristic. The disease is almost always fatal.

Diagnosis
- Clinical specimens: Whole brain or portions from cerebrum, cerebellum and brain stem.
- The virus can be isolated from the brain and distinguished from IBR isolates as described under the diagnosis of IBR above.
- Diagnosis may be made on the basis of clinical features and characteristic histopathologic lesions in the brain. There is malacia of the cerebral cortex and encephalitis and meningitis involves mainly the cerebrum and to a lesser extent the brain stem and cerebellum. Inclusion bodies in astrocytes and neurons are frequently present.

Prevention

Although IBR vaccines containing bovine herpesvirus 1 are effective their use is not considered cost-effective in view of the usual infrequency of the disease.

**The help of Dr. Franklin Riet-Correa (Brazil) in preparing this note is gratefully acknowledged.*

**Pseudorabies (PR)**

(Aujeszky's disease)

Cause

Porcine herpesvirus 1 (also known as pseudorabies virus, PRV).

Occurrence

Hosts include swine, cattle, cats, dogs, horses, sheep, rats, mink, rodents, raccoons, skunks, opossum and other animals. Rabbits are particularly susceptible to experimental inoculation. Dogs and cats are also very susceptible to the infection and their death is often the first indication of the presence of the virus in some swine herds. Swine (domestic and wild) are the natural host and only known reservoir host.

The disease occurs worldwide and is widespread but often regional in distribution. Some European countries have eradicated the infection recently, while others are in the process of eradication. Canada is free of the disease as are most states of the USA.

Transmission
Direct contact between infected and susceptible swine appears to be the most important means of spread. Aerosol droplets and fomites also spread the virus. Infected animals may shed virus for up to a month in various secretions, milk and urine. Infection in species other than swine is via skin or mucous membranes and by ingestion.

Pathogenesis
The virus multiplies in the mucous membrane of the nasopharynx and in the tonsils. Spread is to the regional lymph nodes and to the CNS via axons of the cranial nerves. In virtually all infected animals that survive acute infection the virus establish latent infection in tonsils and trigeminal ganglia. In the acute disease a viremia follows introduction of the virus with rapid dissemination throughout the body.
Transplacental infection of the fetus is common. As for BHV -1, the latent infection is the major means for virus survival and transmission in nature, as it may be periodically reactivated.

Clinical & Pathologic Features
The severity of the disease in swine is inversely related to the animal's age. The morbidity in pigs up to one month of age is very high and the mortality may be nearly 100%.
Young pigs usually have high temperature and nervous signs such as incoordination of hind limbs, paddling movements and convulsions.
Older pigs, up to six months of age, are less susceptible and the mortality is usually less than 10%. They may show respiratory and nervous signs.
Adult hogs may have an inapparent infection or may develop anorexia and mild signs of respiratory infection.
Pregnant gilts and sows may experience reproductive failure, including abortions and stillbirths.
In cattle, sheep, dogs, cats and other subhuman mammals, the disease is highly fatal but not contagious. These animals are called dead-end hosts. There is an intense itching at the site of infection if infection is via the skin, followed by mania, encephalitis, paralysis, coma, and death.

Diagnosis
- Clinical specimens: brain, lungs, tonsil, spleen, kidney, liver, and serum. In animals other than pigs, a portion of the subcutaneous tissue is taken from the site of pruritis and spinal cord.
- Gross necropsy lesions consisting of small focal areas of necrosis are sometimes noted in the liver and spleen of aborted fetuses and baby pigs infected with PR. Microscopic examination of these tissues reveals the presence of intranuclear inclusions typical of herpesvirus. A nonsuppurative meningoencephalitis is the most common microscopic finding in pigs experiencing CNS signs.
- Fluorescent antibody tests on frozen sections of tissue are used for rapid diagnosis.
- Inoculation of infectious material subcutaneously into the rabbit produces an intense pruritus at the site followed by death, usually in 3 - 6 days. This inhumane procedure is no longer required.
- The virus can be propagated readily on the chorioallantoic membrane of chicken embryos, and in pig kidney and other cell cultures producing cytopathic changes as early as 16 hours postinoculation. The virus maybe identified by virus neutralization and fluorescent antibody tests.
- Serum neutralization, latex agglutination, and ELISA tests are used for the detection of antibody.

Prevention
- Modified live and inactivated vaccines are used as well as an intranasal vaccine used in sows and neonates. Vaccination of the complete herd may be advisable.
- Efforts should be made to keep herds free of PR by purchasing replacement stock only from certified free herds.
- Show animals and new additions should be isolated and serologically tested before introduction to the herd.
- Genetically engineered (gene-deletion) vaccines are used in areas where the disease is endemic. Deletion of the thymidine kinase gene renders the virus less able to replicate in neurons. The advantage of gene-deleted vaccines over other modified live or killed PR vaccines is that a special ELISA test can be used to differentiate vaccine induced antibody from antibody resulting from natural infection.
- Eradication can be achieved by repeating a test with removal of positive animals until all tests are negative.

**Equine Rhinopneumonitis**
(Equine herpesvirus 4 infection)

Cause
Equine herpesvirus 4 (EHV 4).

Occurrence
Equine rhinopneumonitis occurs frequently in horses throughout the world.

Transmission
Infection occurs by the respiratory route and spread occurs by direct or indirect contact, aerosol droplets, and fomites.

Clinical & Pathologic Features
EHV 4 causes a usually mild respiratory disease principally observed in young horses up to two years of age.
The incubation period is 2 - 10 days. Affected horses are febrile and display mild depression, nasal discharge and rhinitis.
In the absence of secondary bacterial infections, recovery is usually uneventful in 1 to 3 weeks.
On rare occasions, infection of pregnant mares may result in abortion.
Latent infection of trigeminal ganglia occurs with EHV-4. The epidemiological consequences of latent infection are the same as described for BHV-1 and PRV.

Diagnosis
- Clinical specimens: nasal swabs, whole blood, and acute and convalescent sera.
- Diagnosis of EHV 4 infection is confirmed by isolation of the virus in cell cultures of equine origin. The demonstration of a significant increase in specific antibody between acute and convalescent sera may also be used for diagnosis. EHV 4 is antigenically related to EHV 1 and conventional serologic tests do not differentiate between these two agents. Monoclonal antibodies are available to type isolates of the virus.
- A presumptive method to differentiate EHV 4 from EHV 1 is the inoculation of cell cultures of equine (equine dermal cell line) and rabbit (RK-13 cell line) origin. The virus of EHV 1 grows in both cell types, but EHV 4 only grows in equine cells. An ELISA procedure has been described to distinguish EHV 4 from EHV 1.

Prevention
- Modified live and killed virus vaccines are available for prophylaxis. Some vaccines contain both EHV-4 ands well as EHV-1. These vaccines are usually given at 3 - 4 months of age, with subsequent boosters at frequent intervals, especially while horses are young and most susceptible.
- Risk of infection can be minimized by sound management practices.
- Newly purchased horses and horses returning from shows and racetracks should be quarantined for several weeks.

**Equine Herpesvirus Abortion**
(Equine herpesvirus 1 infection, equine viral abortion)

Cause
Equine herpesvirus 1 (EHV-1).

Occurrence
Equine herpesvirus abortion (EHA) occurs frequently in horses worldwide.

Transmission
Spread is by direct and indirect contact and droplet infection.

Pathogenesis
Local infection may lead to a viremia with infection of the placenta, fetus and infrequently the CNS. Many horses are latently infected with EHV-1 and EHV-4. Reactivation may occur after various stresses and corticosteroid administration. Acute infection is followed by latent infection in regional nerve ganglia.

Clinical & Pathologic Features
Although EHV 1 may cause mild respiratory tract infections in horses, most herpesviral-associated respiratory disease is caused by EHV 4.
The virus of EHV 1 is principally associated with abortion and occasionally with neurologic disease. Most EHV 1 abortions occur after seven months of gestation and about 2 - 4 weeks following exposure of the pregnant mare.
Aborted fetuses often contain characteristic gross necropsy lesions of edematous lungs and small tan areas of focal necrosis most readily observed in the liver, lungs, and spleen. The virus has a predilection for vascular epithelium resulting in vasculitis and thrombosis.
Some infected foals are born live but usually exhibit loss of muscle tone, weakness, and the inability to stand. Affected foals generally die within a matter of days.
Central nervous system dysfunction is a relatively rare complication of EHV 1 infection. Affected horses may display clinical signs characterized by mild to severe ataxia. Recovery is usually uneventful, but some affected horses may remain permanently impaired.

Diagnosis

- Clinical specimens: Fetal liver, lung, spleen, and thymus. Nasal swabs, whole blood, cerebrospinal fluid, acute and convalescent sera, brain, and spinal cord from horses with central nervous system disease.
- A presumptive diagnosis of EHV 1 abortion is often made on the basis of gross lesions observed at necropsy. The finding of intranuclear inclusions in fetal tissues by histopathologic examination is supportive.
- Confirmation is most easily and rapidly obtained by the demonstration of viral antigens in infected cells by immunofluorescence examination of cryostat sections of affected tissue.
- The virus can be propagated in a variety of cell cultures, including those derived from the horse and rabbit (RK-13 cell line). The ability to propagate EHV 1 in cell cultures of nonequine origin provides a means to differentiate EHV 1 from EHV 4; the latter only grows in equine cells. An ELISA procedure has also been described for the differentiation of the two viruses.
- Diagnosis of EHV 1 associated central nervous system disease is more difficult. The virus may be isolated from nasal swabs and blood from acutely affected horses, but the virus is difficult to isolate from central nervous system tissue. Infection may be assumed if a significant increase in specific antibody can be demonstrated between acute and convalescent sera. The histopathologic finding of vasculitis in central nervous system tissue is suggestive.

Figure 11-3. Equine herpesvirus-1 immunofluorescence in frozen section of equine fetal liver. - To view this image in full size go to the IVIS website at www.ivis.org . -

Prevention

- Modified live and killed virus vaccines are available, but only the inactivated product is labeled as a prophylaxis for abortion. It is usually given at 5, 7 and 9 months of pregnancy. Other horses on the premises should also be vaccinated.
- Pregnant mares should be separated from other horses, and any mares that abort or develop respiratory disease should be isolated. The use of foot-baths and clean coveralls by attendants is advised.

**Equine Coital Exanthema**
(Equine herpesvirus 3 infection)

Cause
Equine herpesvirus 3.

Occurrence
Equine coital exanthema (ECE) has been reported in horse breeding populations worldwide.

Transmission
The virus is spread by coitus and possibly by flies feeding on infectious vaginal discharge.

Clinical & Pathologic Features
The disease is generally benign and clinically similar to infectious pustular vulvovaginitis / balanoposthitis (IPVB) of cattle.
Secondary bacterial infections are common, but without complications the disease runs its course in less than two weeks.
Animals recovering from ECE may be become lifelong carriers.
Pustular vesicles and ulcers like those of IPVB are seen on the mucosa of the vulva, vagina, penis and prepuce.
Many infections are subclinical or mild and may not be detected. There may be no fever or loss of appetite.Ulcers heal in about 2 - 3 weeks and may leave characteristic white spots of unpigmented skin that persist for life.
The virus can persist in clinically recovered horses in a latent state for long periods - probably for the lifetime - and flare-ups may occur with consequent shedding and transmission.

Diagnosis

- Clinical specimens: Scraping from the affected mucosa of the vulva and penis. Acute and convalescent sera.
- The disease is usually diagnosed clinically. Confirmation is by electron microscopy of clinical material, isolation of the virus or the demonstration of a significant increase in specific antibody between acute and convalescent sera (virus neutralization test).
- The virus can be propagated in cell cultures of equine origin.

Prevention
- Vaccines are not available.
- Affected horses are should be isolated.
- Ulcers will heal without treatment. Mild antiseptic lotions and ointments may be useful to prevent secondary infection. Mating should be discontinued until ulcers are completely healed.

**Canine Herpesvirus Infection**
Cause
Canine herpesvirus 1.

Occurrence
The disease is common, occurring in wild *Canidae* as well as domestic dogs.

Transmission
Infection of puppies takes place by contact with infectious oral, nasal or vaginal secretions during or shortly after parturition. Infections are also thought to be acquired *in utero*.

Pathogenesis
The virus replicates in the nasal mucosa, tonsils and pharynx. Following viremia in neonates with subnormal temperature there is multiplication of the virus in visceral organs. Latency occurs mainly in trigeminal ganglia.

Clinical & Pathologic Features
Canine herpesvirus 1 produces a brief but severe illness of puppies characterized by a viremia with an 80% mortality in puppies under one week of age. The severity of the illness in these young puppies is related to their inability to adequately regulate body temperature or to mount a febrile response to infection. Once these functions develop (2 - 3 weeks of age), puppies become resistant to generalized infections because the virus does not grow well above 36 °C.
The principal lesions noted in fatal infections are disseminated necrosis and hemorrhage involving the kidney, liver, and lungs. Intranuclear inclusion bodies are observed in the alveolar and interstitial cells of the lung and in cells adjacent to the areas of necrosis in the liver and kidney.
The virus has also been associated with mild vesicular vaginitis and tracheobronchitis. *In utero* infections may result in abortion, stillbirths and infertility.

Diagnosis
- Clinical specimens: Lung, kidney.
- Petechial hemorrhages on the surface of the kidneys and pulmonary edema are characteristic.
- The finding of typical inclusion bodies is diagnostically significant.
- A rapid diagnosis can be achieved by the fluorescent antibody staining of cryostat sections of affected tissues.
- The virus can be easily propagated in cell cultures of canine origin (primary or MDCK cells) and produces noticeable CPE.

Prevention
- Vaccination is not practiced.
- Prevention is best accomplished by reducing stress and minimizing contact between pregnant bitches and other dogs.
- Newborn puppies should be maintained in a warm environment.

**Feline Viral Rhinotracheitis**
(Feline rhinotracheitis, feline coryza, feline influenza)

Cause
Feline herpesvirus 1.

Occurrence
Feline viral rhinotracheitis (FVR) is a frequently occurring, endemic, worldwide, contagious disease of cats.
This virus causes about one-half of all respiratory disease in cats, and after acute infection cats become latent carriers. In these animals, various stresses may trigger the excretion of the virus.

Transmission
The virus is transmitted by direct or indirect contact and the mode of infection is considered to be inhalation.

Pathogenesis
Replication takes place initially in the oropharynx and conjunctivae followed by infection of the mucous membrane of upper respiratory tract. Ordinarily there is no viremia.

Clinical & Pathologic Features
Feline rhinotracheitis virus affects cats most often between 3 - 18 months of age.
The incubation period is usually 2 - 5 days. Clinical signs include fever, anorexia, depression, violent sneezing, conjunctivitis, lacrimation and nasal discharge. Frontal sinusitis and empyema may occur as sequelae.
The virus may cause a serious generalized infection in young kittens similar to that seen in young pups infected with canine herpesvirus 1.
Abortion (usually the sixth week of gestation), ulcerative keratitis, and bronchopneumonia often occur.
Common lesions are focal necrosis with occasional ulceration involving nasal passages and turbinates.
Intranuclear inclusions are seen in epithelial cells of nasal septum, tonsil, epiglottis, tradlea, and nictitating membrane.
Cats that recover from the infection should be considered potential carriers.
A milder FVR may be seen in vaccinated animals.

Diagnosis
- Clinical specimens: Conjunctival scrapings and swabs, nasal swabs, lung and trachea from necropsied cats.
- Most frequently diagnosed by clinical signs. Can be easily confused with feline calicivirus infection.
- The finding of intranuclear inclusions in epithelial cells of affected mucous membranes is diagnostically significant.
- A rapid definitive diagnosis can be obtained by the demonstration of viral infected cells in conjunctival scrapings or in frozen sections of tissue by immunofluorescence.
- The virus can be cultivated in cell cultures of feline origin, in which it produces cytopathic changes including intranuclear inclusions.
- Demonstration of a rising antibody titer in paired serum samples with serum neutralization can be used for diagnosis.

Figure 11-4. Feline viral rhinotraceitis immunofluorescence in feline conjunctival scraping. *Courtesy of A. Wayne Roberts.* - To view this image in full size go to the IVIS website at www.ivis.org . -

Treatment
- Symptomatic and supportive.
- Antibiotics may be indicated for secondary bacterial infection.

Prevention
- Conventional attenuated and killed virus vaccines are available as well as intranasal vaccines. Immunity is of short duration and several doses of vaccine are advised for young animals.
- Killed virus vaccines are used for pregnant queens.

## Marek's Disease-like Viruses

### Marek's Disease (MD)

(Neural lymphomatosis, fowl paralysis)

Cause
Gallid herpesvirus 2. There are three serotypes of the virus; types 1 and 2 occur in chickens and type 3 occurs in turkeys. Type 1 virus is oncogenic; types 2 and 3 are not.

Occurrence
Marek's disease is common, worldwide, highly contagious disease affecting domestic fowl, turkeys and quail. It occurs most often in chickens 8 - 20 weeks of age.

Transmission
Susceptible birds are infected via the respiratory tract through contact with viral contaminated airborne dust particles. Virus replication and release occurs in the epithelial cells of feather follicles and copious amounts of infectious virus are shed in dust and dander.

Pathogenesis
Initial infection of the respiratory tract occurs via inhalation of infectious dust. Three to five days postinfection B lymphocytes of the bursa of Fabricius, spleen and thymus become infected. The virus subsequently infects T lymphocytes of mostly the $CD4^+$ phenotype; infection becomes latent and the virus spreads throughout the host by a cell-associated viremia.
There is a secondary cytolytic infection of the feather follicle epithelium from which cell-free virus is produced and shed in

feather dander and debris.
Latently infected T lymphocytes are transformed leading to lesions of lymphomatosis in visceral organs. The main target cells for transformation are $CD4^+$ T cells and probably $CD8^+$ T cells.
Genomic regions with the potential for transformation have been identified.

Clinical & Pathologic Features
The most common clinical sign associated with "classical" Marek's disease is motor paralysis resulting from the effect of virus replication on peripheral nerves. Depending on the nerves affected, there may be signs of progressive paralysis in the neck, wings, or legs.
Characteristic necropsy lesions noted with "classical" Marek's disease are enlarged peripheral and autonomic nerves that appear yellow and translucent. Visceral tumors may or may not be present.
In the acute form of the disease, visceral tumors are common, often involving multiple organs, and birds may die without obvious signs of paralysis. The most common organs affected are gonads, kidney, liver, lung, muscle, and skin. Gross nerve lesions may not be noted.
Microscopically an infiltration of mononuclear cells is seen in affected tissues. Occasionally the eye may be affected, resulting in blindness. This form of the disease is referred to as gray-eye or ocular lymphomatosis.

Diagnosis
- Clinical specimens: Whole birds in extremis.
- Diagnosis is usually based on clinical signs and necropsy examinations. Marek's disease is suspected if signs of paralysis or paresis are noted and if peripheral nerves are enlarged.
  If only visceral tumors are noted, the disease must be differentiated from lymphoid leukosis by microscopic examination of tissues. With Marek's disease, there is usually perivascular cuffing in the white matter of the cerebellum and an infiltration of mononuclear cells in peripheral nerves. These lesions are absent in lymphoid leukosis.
  Also the cytologic appearance of the lymphoid cells is different. In Marek's disease, there is a mixture of mature and immature pleomorphic cells, whereas with lymphoid leukosis the cells are uniformly "blast" cells.
  Differential features of Marek's disease and lymphoid leukosis are summarized in Fig. 11-2.
- Viral and serologic procedures are usually not performed because the virus is present in most chicken flocks.
- The three virus types can be propagated in chicken embryo kidney cells and in duck embryo fibroblasts.

Figure 11-5. Differential features of Marek's Disease (MD) and Lymphoid Leukosis (LL). - To view this image in full size go to the IVIS website at www.ivis.org . -

Prevention
- Marek's disease is effectively prevented by vaccination of day-old chicks using serotype 3 Marek's disease virus (turkey herpesvirus). Chicks should be reared in a clean environment for 10 - 14 days until immunity is well established.
- *In ovo* vaccination is widely practiced; it is safe and effective. Embryonated eggs are inoculated with an automatic device at 18 days of incubation.
- All three serotypes are used individually and in combination, bivalent and polyvalent, in commercial vaccines. Recombinant vaccines have shown promise experimentally.
- Vaccine failures have been attributed to the emergence of unusually more virulent viruses.

## Infectious laryngo-tracheitis-like viruses

### Infectious Laryngotracheitis

Cause
Gallid herpesvirus 1.

Occurrence
Infectious laryngotracheitis (ILT) is a common, worldwide disease of chickens and pheasants.

Transmission
By direct and indirect contact and by droplet infection.

Pathogenesis
After initial infection, the virus replicates in the epithelium of the upper respiratory tact. The virus travels along sensory nerves to become latent in trigeminal ganglia.

Clinical & Pathologic Features
The virus causes a mild to severe respiratory disease in young and older birds, usually in the fall and winter months in Europe and North America.
Infection involves principally the larynx and trachea, resulting in coughing, gasping, and dyspnea. Infected birds may cough up blood-stained mucus.
Morbidity is high but mortality does not usually exceed 15%.
There is marked congestion and hyperemia of the larynx and trachea. In the advanced disease considerable caseous exudate present in the larynx and trachea; caseous cores and diphtheritic membranes may also be present.
Intranuclear inclusion bodies are seen in the epithelial cells of the trachea. The tracheal lesions are similar to those seen in the diphtheric form of fowlpox.
Infection with less virulent strains of ILT virus may only result in mild sinusitis and conjunctivitis.

Diagnosis
- Clinical specimens: Trachea and lung.
- A strongly presumptive diagnosis is made on the basis of clinical signs in severe outbreaks.
- The finding of typical herpesvirus intranuclear inclusions and characteristic gross lesions are diagnostically significant.
- Electron microscopic examination of distilled water lysates of tracheal scrapings, and fluorescent antibody examination are used for rapid diagnosis.
- The virus grows readily on the chorioallantoic membrane of embryonated chicken eggs. The membrane becomes thickened and white plaques are noted.

Prevention
- Prevention is best accomplished by maintaining closed flocks.
- Modified live vaccines administered in drinking water or by aerosol sprays are widely used to control the disease in layer flocks in areas where the virus is endemic. However, vaccination doesn't prevent the establishment and reactivation of latent infections.
- Birds that recover from the disease may remain latently infected.

## Rhadinovirus
### Malignant Catarrhal Fever (MCF)
(Snotsiekte - Africa)

Cause
Alcelaphine herpesvirus 1 causes malignant catarrhal fever (MCF) in Africa. Ovine herpesvirus 2 causes MCF in cattle in regions other than Africa.

Occurrence
Malignant catarrhal fever is a wide spread, infrequent, usually sporadic, often fatal disease.
It is caused by:
- Alcephine herpesvirus 1 causes the disease in Africa. Latent infections are present in the wildebeest and other wild ruminants; it spreads from these to cattle.
- Ovine herpesvirus 2 causes the disease in sheep (natural host; subclinical infection) and goats worldwide; the disease is transmitted from sheep to cattle.
  The non-African form (Europe, North and South America and other regions) of MCF may be transmitted to cattle and deer from sheep that shed virus during lambing. This form is sometimes referred to as sheep associated MCF.
  The incidence is not high. Except for feedlots, there are usually only one or two cases in a herd at one time.

Transmission
As mentioned above the non-African MCF is considered to be transmitted to cattle and deer from sheep that shed virus during lambing. Infection probably takes place via the respiratory route.

Pathogenesis
This is little understood. There is a cell-associated viremia and a dearth of virus in lesions. The latter are thought to have an immunological basis. Although latency probably occurs there is no evidence of recrudescence of infection.

Clinical & Pathologic Features
Most affected cattle may have the following signs: fever, depression, diarrhea, anorexia, rhinitis with nasal discharge that becomes mucopurulent and encrusted. The skin of the muzzle becomes eroded, and there is stomatitis, pharyngitis, laryngitis, and parotitis with salivation. After a short febrile period; most cattle with the severe disease die within 10 days. In addition to the lesions referred to the above, there may be edema of the meninges, perivascular cuffing in other areas of the brain, enteritis, general lymphoid hyperplasia, and corneal opacity. Gray foci may be seen in the kidneys and liver. The

anterior cervical and retropharyngeal lymph nodes may be hemorrhagic and edematous. Vasculitis is widespread.

Diagnosis
- Clinical specimens: Fresh leukocytes (buffy coat), fresh thyroid and adrenal tissue, serum.
- Diagnosis is usually based on clinical signs and pathologic changes. The usual sporadic nature of the disease helps distinguish MCF from bovine virus diarrhea and rinderpest. The history of sheep associated with cattle supports a diagnosis.
- Laboratory confirmation of MCF is difficult. Serologic tests, virus isolation, and molecular techniques (polymerase chain reaction) are used, but these procedures are not available in most diagnostic laboratories.
- The virus of the wildebeest-associated MCF has been isolated but is not ovine *herpesvirus* 2.

Prevention
- Vaccines are not available. The infrequency of the disease does not warrant use of a vaccine.
- Cattle should be kept separate from sheep.
- A PCR assay has been used to detect infection in sheep.

## Unassigned Genus

### Inclusion Body Rhinitis

The cause is suid herpesvirus 2, which occurs widely in swine but clinical disease is infrequent.
The virus is shed in nasal secretions and transmission is by direct and indirect contact and by aerosol droplets.
The disease is most severe in pigs up to two weeks of age.
Clinical signs include copious nasal discharge, sneezing, rhinitis and conjunctivitis with usual full recovery.
Inclusion body rhinitis may be present with the more serious disease atrophic rhinitis.

Diagnosis
- Clinical specimens: Nasal swabs or scrapings and lung tissue.
- The disease is usually diagnosed histologically by demonstrating large basophilic intranuclear inclusions in sections of or scrapings from the nasal mucosa. The inclusion bodies can also be demonstrated in exfoliated epithelial cells obtained with nasal swabs.
- Electron microscopy is useful for demonstrating the virus in negative stained distilled water lysates of nasal mucosa.
- The virus can be propagated in primary cell cultures of pig lung producing cytopathic changes, including large intranuclear inclusions within 11 - 18 days postinoculation.

Prevention
- Vaccines are not available.
- The disease is infrequent in well managed herds.

### Duck Viral Enteritis

(Duck plague)

Cause
Anatid herpesvirus 1.

Occurrence
Outbreaks in commercial geese and ducks can usually be traced to wild waterfowl. The disease, which has been responsible for great losses, has been reported from North America, Europe and Asia.

Transmission
This is by direct and indirect contact. Water contaminated with feces is the main source of infection.

Clinical & Pathologic Features
Signs of this acute infection includes oculonasal discharge, photophobia, depression, inappetence, thirst, and watery, blood-stained diarrhea. The mortality rate may be as high as 90%.
Recovered birds may shed virus for years.

Diagnosis
- Clinical specimens: Whole ducks *in extremis* or liver and mesenteric lymph nodes.
- A presumptive diagnosis is made on the basis of clinical signs and high death losses. Lesions noted at necropsy are supportive. Characteristic hemorrhages are seen in many organs, including the heart, liver, and intestine. Small white areas of focal necrosis may also be noted in the liver. The finding of intranuclear inclusions is highly suggestive.
- The fluorescent antibody test on frozen sections of affected tissues is used for rapid diagnosis.
- The virus can be propagated on the chorioallantoic membrane of duck embryonated eggs, which die approximately four days after inoculation. One-day-old ducklings are susceptible to experimental infection.

Prevention

- Modified live and killed virus vaccine are effective in prevention.
- Strict avoidance of contact with wild waterfowl.

**Glossary**

Exocystosis: A process by which a variety of substances are released from the cell within vesicles by transport to and fusion with the plasma membrane, resulting in the release of the vesicle contents from the cell.
Panophthalmitis: Inflammation involving all the tissues of the eyeball.