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VIRAL INFECTIONS

CHAPTER 16

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Neonatal and puppy-kitten mortality rates (animals dying before 1 year of age) are often used as clinical indicators of the general level of health in the community, including the level of vaccination that is used in the area (Table 16-1). Infectious diseases are a major threat to the health of neonatal animals and may contribute to the mortality rate. Neonatal puppies and kittens depend in large part on the presence of sufficient maternal immunity, which provides short-term, passive immunity to protect them against microbial pathogens in the neonates' environment. The severity of clinical symptoms (disease) in puppies and kittens that may result from infectious microorganisms depends on several key factors (Box 16-1). In addition to current maternal passive immunity, they include preexisting maternal infection status, maternal and neonatal nutrition, neonatal thermoregulation, concurrent neonatal infections and parasitism, and hereditary defects of the immune system.

Viral pathogens in particular can be life threatening for the neonate because for most infections, no specific antiviral therapy is available. Spread within a litter can be rapid as a result of the contagious nature of these pathogens. Adults with subclinical infections, including the dam, can be an important source of infection. Although some viruses, such as the feline retroviruses, are relatively labile outside the carrier host, others such as feline calicivirus and canine parvovirus are extremely hardy and can persist for months in contaminated environments. Transmission from dam to offspring can occur in utero or during birth of the neonate, whereas others are transmitted via nursing or grooming. The efficiency of the various modes of transmission varies with the agent involved.

Physical examination results will vary with the microbial pathogen involved. Fever may occur, but with peracute disease, animals may be hypothermic. Crying, restlessness, and anorexia may also be evident. Depending on the pathogen, evidence of specific organ involvement may be seen, such as nasal and ocular discharge with respiratory tract disease. Alternatively, multiorgan involvement may occur.

Diagnosis of viral infections of the neonate primarily involves direct detection of the virus, as serology in the neonate will not be useful. This can be done using three basic assays: antigen detection, nucleic acid detection, and viral cultivation. For antigen detection, cellular materials (mucosal swabs, fluid sediment, tissue impressions, and fixed tissues) on glass slides can be probed by fluorescent or immunoperoxidase-labeled specific antibody. Although rapid and inexpensive, these assays have relatively low sensitivity. For some pathogens, specific enzyme-linked immunosorbent assay (ELISA) tests are available. These include feline leukemia virus (FeLV) and parvoviral infections (canine parvovirus type 2 [CPV-2] and feline panleukopenia [FPL]). Sensitivity of these assays is regarded as high. Nucleic acid detection involves polymerase chain reaction (PCR) for amplification of the viral genetic material in biologic samples, including blood, mucosal swabs, feces, and fresh or fixed tissues. These assays are relatively fast and very sensitive. Viral cultivation, done on fresh samples, remains the gold standard but may take several (1 to 4) weeks. Serological analysis of the dam may provide information of previous infection or vaccination status but is often inconclusive.

In any investigation of reproductive disease, the veterinarian should consider the possibility of viral infections that are species specific (canine herpesvirus [CHV]), those that can be transmitted from one species to another (CPV-2), and those that are vector borne (West Nile virus). Such epidemiologic information is valuable both for establishing a diagnosis and for designing control strategies.

Control of neonatal viral infections involves screening for preexisting infections and vaccination (when available) of the dam, minimizing potential exposure during critical periods (Table 16-2) and ensuring adequate colostral intake by the neonates (see Chapter 14). The critical periods are

TABLE 16-1 Effects of population (herd) immunity* on neonatal puppy and kitten survival

Effects on	High survivability	Low survivability
Herd immunity	Increased	Decreased
Maternal immunity	Increased	Decreased
Colostral immunity	Increased	Decreased
Maternal/cohort shedding	Decreased	Increased
Survival of neonates	Increased	Decreased

*Defined as 85% or greater of the population that are immune. Immunity is attained by regular vaccination boosters and/or continual boosters from natural infections from subclinical carrier animals.

BOX 16-1 Factors influencing the severity of clinical symptoms in puppies and kittens

- Preexisting maternal infection status (including congenital infections like *Neospora caninum* and CHV)
- Current maternal immune status
- Degree of maternal passive immunity
- Maternal and neonatal nutrition
- Neonatal thermoregulation
- Concurrent neonatal infections and parasitism
- Hereditary defects of the neonate immune system

Modified from Root Kustritz MV: Neonatology. In Root Kustritz MV (ed): *Small animal theriogenology,* St. Louis, 2003, Elsevier, p. 283.

TABLE 16-2 Stages of the naive-susceptible dog/cat and potential outcomes of infection

Host(s) and outcomes	Preconception	Pregnancy	Periparturient	Postnatal
Canine	CDV, CPV-2, CHV, CAV	CPV-2, CHV, CPV-1	CHV	CPV-2, CAV, CCV
Feline	FPL, FHV, FCoV-FIP, FeLV	FHV, FeLV, FPL	FeLV, FIV	FHV, FeLV, FIV, FCV
Outcomes of infection	Immunity, decreased conception	Abortion, congenital infection, immunity	Stillbirth	Neonatal infection, neonatal disease, immunity

preconception, pregnancy, periparturient, and postnatal. The outcome of infection during these periods depends on previous individual animal immunity and viral challenge from the environment.

SPECIFIC VIRAL DISEASES OF PEDIATRIC CANINE PATIENTS

Canine Parvoviruses (CPV-2, CPV-1)

CPV-2

CPV-2 is endemic in most countries of the world. It is carried by a high percentage of dogs as a subclinical infection in the gastrointestinal (GI) tract and is shed intermittently in the feces. The virus can retain infectiousness outside the dog's GI tract for up to 12 months if environmental conditions are optimum (moist, cold). The newer variants of CPV-2 (CPV-2b, CPV-2c) have also acquired the cat as a host, and control efforts must take this into consideration. The virus can be inactivated by disinfectants with oxidizing activity, heat, and diluted bleach (1:30 parts with water).

Infection is spread and acquired by the fecal-oral route. During the first 2 days after ingestion, viral replication occurs in the oropharynx and local lymphoid organs. Viremia from 3 to 4 days postinfection spreads virus throughout the body. Viremia is usually terminated when virus-neutralizing antibodies (IgG) are generated, usually 6 to 9 days postinfection. Clinical symptoms are most severe in puppies and may occur up to age 12 months. Parvoviral enteritis may present acutely or peracutely with anorexia and depression followed by vomiting and profuse, usually hemorrhagic, diarrhea. Newer variants of CPV-2 may cause a mild nonhemorrhagic diarrhea. Pyrexia, depression, anorexia, and dehydration are commonly observed. Intestinal damage in the rapidly developing crypt cells permits bacterial colonization that may result in endotoxic shock characterized by hypothermia, disseminated intravascular coagulation, and jaundice. Mortality rate may be as high as 25% and is a consequence of dehydration, endotoxic shock, electrolyte imbalances, and secondary bacterial infections (see Chapter 15). Mild or subclinical infections are common, especially in dogs aged more than 6 months.

CPV-2 variants can be detected in antemortem samples by in-clinic antigen (Ag) ELISA or by electron microscopy of fecal/diarrheal material. Affected dogs can also be tested by serology, as CPV-specific IgM titers can be detected in serum. Although PCR is available, it may detect dogs that are carriers of CPV-2, and the clinical predictive value may not be as high as the previously mentioned assays. Postmortem detection of CPV-2 uses a combination of histopathology and immunohistochemistry (IHC) for CPV-2–specific antigens. The tissues of choice are the small intestine, mesenteric lymph nodes, and spleen fixed in buffered formalin.

Although there is no specific treatment for CPV-2, viral-bacterial enteritides generally consist of treating dehydration, sepsis, and acidosis/electrolyte imbalances. Intravenous balanced electrolyte solutions, systemic antibiotics (see Chapter 27), and antiemetic therapy may be indicated if vomiting is a significant component of the symptoms. Control measures include disinfection to reduce (dilute) the viral challenge load

TABLE 16-3 Most common viral agents associated with fading puppy and kitten syndromes

	Puppy			Kitten		
	Canine herpesvirus	Canine parvovirus-2	Canine parvovirus-1	Feline herpesvirus	Feline calicivirus	Feline panleukopenia
Nature of the virus	Very labile, temperature sensitive	Very resistant	Very resistant	Very labile	Very resistant	Very resistant
Most common source	Dam	Dam	Dam	Queen	Queen	Queen
Diagnosis	VI, PCR, histopathology (pup), serology (dam)	Histopathology, PCR (pup)	Histopathology (rule out CPV-2)	VI, PCR, histopathology (kitten)	VI, PCR	Histopathology, PCR (kitten)
Control	High levels of hygiene and close adherence to "6-week danger period," no vaccine available	High levels of hygiene, routine vaccination of adult dogs	High levels of hygiene, no vaccine available	High levels of hygiene and routine vaccination of adult cats	High levels of hygiene and routine vaccination of adult cats	High levels of hygiene and routine vaccination of adult cats

VI, Virus isolation.

and immunization with modified live CPV-2 vaccines of adult dogs in the population and the susceptible puppies (Table 16-3). The role of immunization is twofold: the first is protection of individual puppies, and the second is to hyperimmunize adults to minimize viral shedding.

CPV-1

Canine parvovirus type 1 (CPV-1) is also referred to as minute viruses of canines and was initially reported in military dogs with diarrhea. This virus is antigenically distinct from CPV-2 and is more closely related genetically to bovine parvovirus.

CPV-1 is usually a subclinical infection in dogs but may cause enteritis, pneumonitis, myocarditis, and lymphadenitis in puppies aged between 5 and 21 days. Most pups have mild symptoms, but those that worsen may be classified as having fading puppy syndrome. Affected pups may show diarrhea, vomiting, and dyspnea and constantly cry out. Systemic viral infections in naive dams may lead to failure to conceive, fetal death, or abortion.

Because of the similarities of CPV-1 clinical symptoms with CHV and CPV-2, a thorough diagnostic workup is recommended. More specific assays such as PCR or immunoelectron microscopy are required to diagnose CPV-1 presence in fecal matter. Histopathologic changes seen in the thymus, lymph nodes, small intestine, and myocardium are very similar to CPV-2, and without specific IHC or CPV-1–specific PCR, these lesions may be misdiagnosed.

Because there is no vaccine available for CPV-1 control, it is important to maintain a clean whelping environment and keep optimal temperatures for newborn pups.

Canine Distemper Virus

Canine distemper virus (CDV) is a multisystemic viral disease of dogs that affects puppies most commonly aged between 3 and 6 months. The virus can be carried by adult dogs in the respiratory tract and is commonly shed in aerosols. The virus is enveloped and highly susceptible to environmental and chemical inactivation. Although there is only one serotype of CDV, there are numerous strains that vary in their tissue tropism and pathogenicity. Although considered a disease of domestic dogs, many other canids are equally susceptible, as are mustelids (e.g., ferrets). Felines are reported to be infected, but clinical symptoms are rare except in exotic felines (e.g., lions, tigers).

The route of infection with CDV is usually by aerosols, saliva, or grooming. The virus spreads rapidly to the oropharyngeal lymphoid organs, where it then enters the first of two viremic phases. During the first phase, there is generalized immune suppression. There may be fever, anorexia, and mild respiratory symptoms during this phase (7 to 10 days postinfection). During the second viremic phase, the virus is more disseminated to the GI tract, central nervous system, and skin. Hemorrhagic diarrhea may occur 10 to 20 days postinfection. Mortality rate in dogs symptomatic with this form may be as high as 50%. In classic forms of distemper, conjunctivitis is observed first, followed by a dry cough. The cough becomes progressively wet and productive, concurrent with oculonasal discharge. The discharge becomes mucopurulent within several days. Affected dogs are usually pyretic (>104° F, 40° C), depressed, and anorectic. It is estimated that at least 50% of CDV infections are subclinical and that dogs may shed virus for up to 60 days postinfection.

CDV can cause abortion, stillbirth, and birth of weak puppies. Neonatal infection in puppies aged less than 1 week may result in cardiomyopathy and cardiac failure less than 3 weeks postinfection.

CDV presentation is usually classical enough that antemortem diagnostic assays are not conducted. If a definitive diagnosis is of value, then fluorescent antibody-specific CDV staining can be done on either conjunctival smears or whole blood smears. Nucleic acid detection can be done by PCR on whole blood and urine, which offers a good clinical predictive value for a dog with viremia; tissue may be tested postmortem. Serologic detection can identify CDV-specific IgM in serum or CDV-specific IgG in cerebrospinal fluid. Postmortem diagnosis of CDV-induced disease can be verified by histopathology and, if necessary, CDV-specific IHC on fixed tissues from brain, lung, spleen, urinary bladder, and skin.

There are no specific antiviral drugs to treat CDV-induced disease. Treatment is supportive with fluids, expectorants, antiemetics, and antibiotics. Puppies that develop neurologic disease have a poor prognosis. Control measures rely predominately on the use of a modified live virus (MLV) immunization program in dogs. This consists of a thorough vaccination series in puppies, a booster at 6 months, and another booster at age 1 year. Adult dogs in proximity to pregnant dogs and puppies should receive regular boosters to minimize CDV shedding in the environment.

Canine Adenoviruses

The canine adenoviruses (CAV) consist of two predominant serotypes, CAV type 1 and type 2 (CAV-1 and CAV-2). CAV-1 is predominately multisystemic and causes hepatocellular necrosis and vasculitis. The virus is moderately resistant in the environment but susceptible to heat (steam cleaning) and disinfection by quaternary ammonium compounds. Dogs may carry this virus subclinically despite high levels of neutralizing antibodies (immune carriers, see Chapter 14). The antigenically related CAV, CAV-2, is predominately associated with upper respiratory tract disease. It is shed for 8 to 9 days postinfection.

CAV-1 is considered to cause the more serious clinical symptoms in dogs when compared with CAV-2. CAV-1 infects by the oronasal route, where the virus replicates in the oropharyngeal lymph nodes. Viremia occurs wherein hepatocytes and reticuloendothelial cells in other organ systems are the sites of virus replication and subsequent lysis and necrosis. During the acute phase (7 to 9 days) of CAV-1 disease, the virus is excreted in the feces, urine, and oropharyngeal secretions. The occurrence of multisystemic symptoms carries a guarded prognosis. Infection during pregnancy by CAV-1 may result in the birth of dead puppies or weak puppies that die within a few days postwhelping. Carrier dams occur and may act as a source of infection for puppies or other pregnant dogs.

Infections by CAV-2 may result in bronchitis, bronchiolitis, and focal turbinate and tonsillar necrosis. The virus has been reported to be associated with kennel cough syndrome. The important feature of CAV-2 is its antigenic relatedness to CAV-1 and the use of this strain in vaccines, which provides protective immunity to CAV-1.

The diagnosis of CAV-1 is important to differentiate from the multisystemic CHV (see below). Antemortem diagnosis may be done by virus isolation from fecal samples and oral-pharyngeal swabs in viral transport media. Nucleic acid detection by PCR may be used to detect CAV in the same samples, but the clinical predictive value may be compromised because of the presence of known carrier dogs in the population. Postmortem diagnosis is considered to be the most reliable for CAV-1 disease. Hepatic lesions are pathognomonic and include mottling and fibrinous exudates attached to the liver capsule. The gall bladder may be edematous and hemorrhagic. Histopathology and CAV-specific IHC are confirmatory on the fixed liver tissue.

There is no specific antiviral therapy for CAV-1 disease. Symptomatic supportive therapy for acute liver failure is required for treatment. Immunization with CAV-2 MLV vaccine is an important control measure for CAV-1. This consists of a vaccination series in puppies, a booster at 6 months, and a second booster at age 1 year. Adult dogs in proximity to pregnant dogs and puppies should receive regular boosters to minimize viral shedding.

Canine Herpesvirus

CHV has been recognized as one of the most common and virulent viral infections of neonatal puppies. Recent reports have indicated that this virus may be carried subclinically by up to 70% of some canine populations. As with other herpesviral infections, in particular, feline herpesvirus (see this chapter), CHV can be exacerbated following periods of physiologic, hormonal, and nutritional stress. CHV has several components that are important in control because there is no vaccine available in the United States. The virus is shed predominately in oronasal secretions from carrier dogs to susceptible dogs. This knowledge has been the basis for establishing the 6-week danger period, which includes the 3 weeks before whelping and 3 weeks postwhelping (Figure 16-1).

The effects of CHV can best be described based on what sex is infected and when the dog is exposed. Dogs usually enter adulthood having been infected as puppies and have adequate levels of immunity to control disease. However, if females reach reproductive age and are naive, then they can experience fetal death and mummification early during pregnancy, as well as premature birth and neonatal disease during late pregnancy. Although the female will lose her litter, it is now generally considered that she is immune to subsequent CHV-induced disease.

The puppies whelped by a naive female are susceptible to CHV from other shedding dogs in the vicinity to the female and her litter. The puppies are infected via oronasal secretions from the recently infected female or another dog. The virus infects via the oropharyngeal lymph nodes and rapidly spreads systemically by viremia. Puppies infected at birth or postnatally up to age 3 weeks may develop a systemic disease

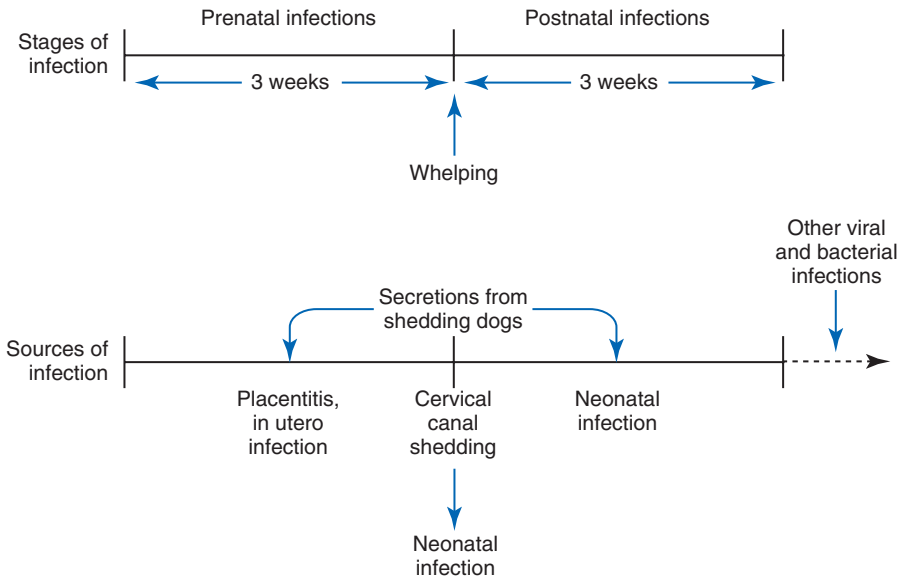

Figure 16-1 The 6-week danger period in relationship to whelping and the various sources of CHV for neonatal infections. (Redrawn from Diagnosis of canine herpetic infections. In *Kirk's current veterinary therapy X*, 1989, Elsevier.)

that is usually fatal. Resistance to systemic disease is age-related and is considered to be directly correlated to the thermoregulatory system of the puppy. The disease has an incubation period of 3 to 7 days. Clinical symptoms include anorexia, abdominal pain, and lethargy.

Male dogs that are infected with CHV can also carry the virus but are usually subclinical. Genital lesions associated with CHV may include hyperemia and lymphoid hyperplasia over the base of the penis. The male may also develop a serous oculonasal discharge, which appears to be one of the major modes of virus spread to susceptible females and her puppies.

CHV has been detected by virus isolation from swabs of vesicular lesions on the genitalia of affected females. These lesions frequently develop during proestrus, indicating that venereal spread may be an important mode of virus spread. Bitches that have fetal death or abort may be tested for CHV-specific neutralizing antibody on a serum sample. Puppies born with clinical symptoms or those developing symptoms during the first 3 weeks can be submitted for necropsy. The puppies will have characteristic petechial hemorrhages on the kidneys.

Swabs in viral transport media from lungs, liver, and kidney can be analyzed by viral isolation. Whole blood can be submitted for CHV-specific PCR. Histopathology can be conducted on the aforementioned tissues, and characteristic intranuclear inclusion bodies can be observed.

Male dogs with genital lesions and serous nasal discharge can be tested for CHV-specific antibodies in serum or by virus isolation using swabs collected in viral transport media.

CHV is regarded as naturally temperature sensitive and does not replicate at elevated body temperatures. Knowing this, as well as the susceptibility of the virus outside the dog's body, allows for a good control measure through sustained superoptimal environmental temperatures for puppies. Once puppies have been infected and demonstrate clinical symptoms, the prognosis is guarded to poor. In some cases, hyperimmune canine serum with CHV antibodies can be administered subcutaneously to assist with management of CHV in a litter if administered early during the course of infection. There is no commercially available vaccine in the United States. A vaccine marketed in Europe has demonstrated good efficacy when administered to the dam. This vaccine would have value in selected canine environments and should be considered for licensure in the United States.

CANINE CORONAVIRUS

Canine coronavirus (CCV) predates CPV-2 by several years as a cause of canine enteritis. The virus is a member of the broader coronavirus family with known pathogens in every mammalian species, including humans. The virus shares common antigens and remarkable similarities in pathogeneses with transmissible gastroenteritis of swine and feline enteric coronavirus (parent virus of feline infectious peritonitis). The virus occurs worldwide, with infection rates ranging from 45% to 100% in some high-density dog populations. CCV is considered to be a primary infection of the GI tract. However, a similar but antigenically distinct coronavirus has been recently reported as the cause of canine respiratory disease. Current studies have indicated that the virulence of enteric CCV has increased, which may be accounted for by the generation of recombinational mutants.

Coronaviral infections of dogs occur very early in the neonatal period and are primarily spread via the fecal-oral

route. Maternal antibodies protect the puppy up to about 4 to 5 weeks of age, at which time the puppy becomes susceptible to disease. The virus infects the enterocytes of the small intestine, resulting in epithelial loss and villus atrophy. Colonic epithelium and mesenteric lymph nodes may also become infected, which contributes to the shedding of the virus in the feces. The age range for greatest susceptibility to disease is 5 to 12 weeks of age. The virus is shed in the highest quantity for 16 days postinfection and then intermittently thereafter. The primary clinical symptom is a watery diarrhea that ranges from mild to moderately severe. The severity of the disease can be enhanced by concurrent viral (CPV-2) and bacterial (*Campylobacter* sp.) infections. Recovery usually occurs within 7 to 14 days.

The diagnosis of CCV enteritis has relied on electron microscopy and, to a lesser extent, on virus isolation. Because both techniques are regarded as marginally sensitive, there are a number of false-negative results. Serology has been useful in determining the prevalence of the viral infection in the dog population but has not been widely used to diagnose an acute infection. More recent reports have used CCV-specific IHC on fixed GI tissues from dogs with fatal enteritis. This technique has proven valuable in cases where CPV-2 has not been detected. Molecular detection of CCV by PCR has become an accepted method of viral diagnosis. However, because there is a reasonably high carrier rate with CCV, the clinical predictive value of PCR on fecal preparations or intestinal contents must be interpreted cautiously.

There is no specific treatment for CCV. Puppies with watery, nonhemorrhagic diarrhea can be treated as CPV-2 patients with rehydration and antibiotic therapy. Control of CCV-induced disease depends heavily on vaccination of the dam. This reduces the shedding of the virus and enhances colostral and lactogenic (passive antibodies in dam's milk) immunity. Ultimately, oral vaccines to stimulate mucosal immunity (IgA) will be needed to control the disease associated with this virus. This same type of vaccine will probably be important in controlling the newer CCV variants, which are associated with respiratory disease in 8- to 12-week-old puppies.

SPECIFIC VIRAL DISEASES OF PEDIATRIC FELINE PATIENTS

Feline Herpesvirus

Feline herpesvirus (FHV) is a common respiratory pathogen of cats. The virus is a spherical enveloped virus with a double-stranded (ds) DNA genome and is classified as a member of the Alphaherpesvirinae subfamily of the Herpesviridae family. The virus is highly contagious and is spread via direct and indirect contact. As with other alphaherpesviruses, after acute infection, the virus achieves latency in neural tissue; recrudescence with viral replication and shedding may occur during stressful episodes. The virus targets epithelia of the upper respiratory tract and conjunctiva. Although systemic spread of herpesviruses of other domestic animals occurs, this does not appear to be common with FHV.

Unlike herpesviruses of dogs, horses, swine, goats, and cattle, infection with FHV during gestation does not generally lead to viremia and abortion. Queens infected during gestation have aborted secondary to severe respiratory disease, but no placental lesions were found. Recrudescence of latent infections may occur during queening, leading to exposure of the kittens. Infected kittens may exhibit mild conjunctivitis and serous ocular and nasal discharge; those with insufficient passive immunity may develop severe clinical disease with lower respiratory tract involvement. Secondary bacterial infection may occur following infection, and mortality rates may be high. Affected kittens are inactive, anorectic, and exhibit profuse mucopurulent oculonasal discharge and respiratory distress. In kittens that have not yet opened their eyes, accumulation of purulent material behind the eyelids may occur, leading to noticeable distention.

Viral detection through virus isolation from clinical samples (mucosal swabs antemortem or respiratory tract tissues postmortem) remains the gold standard but may take 2 days to 2 weeks for results. Antigen detection may be done on cells collected from mucosal surfaces or tissue impressions using immunofluorescence. Alternatively, nucleic acid detection on mucosal swabs or tissues using PCR can be done. These latter two assays have a fast turnaround time and are relatively inexpensive. For antigen detection, sensitivity is low to moderate, whereas PCR is high in sensitivity but may detect subclinical or even latent infection.

Antiviral therapy is an option for FHV, although the safety of these regimens in neonatal kittens is not known. In vitro nucleotide analogs such as acyclovir and ganciclovir have shown efficacy. L-lysine is used to minimize recrudescent episodes and functions as an antagonist to arginine uptake, thus inhibiting FHV replication. Administration to infected queens may minimize shedding during the stress of parturition and lactation.

Supportive care is also required and includes fluid replacement, nutritional support, and antibiotics for secondary bacterial infection. Topical antiviral and antibiotic medications may be used for ocular involvement. Most kittens will fully recover unless immunocompromised or secondary bacterial pneumonia occurs. In cases of severe disease with turbinate destruction, chronic rhinosinusitis ("chronic snuffler") may occur.

Vaccination of adults will minimize virus exposure of kittens and enhance maternal immunity for passive transfer. Intranasal vaccines may be used in kittens as young as 3 to 4 weeks of age in populations with endemic infection. During an outbreak, the virus is easily killed with standard detergents. Adults are often subclinical shedders of FHV; thus, contact of adults other than the queen with the kittens should be avoided.

Feline Calicivirus

Feline calicivirus (FCV) is a common pathogen of cats affecting the respiratory tract. It is a small nonenveloped

virus with a single-stranded (ss) RNA genome classified in the *Vesivirus* genus of the Caliciviridae family. The virus is very resistant in the environment, and indirect transmission via fomites is a major mode of spread. Replication occurs in the upper respiratory tract epithelia and oral and conjunctival mucosa leading to conjunctivitis, oral ulcers, and typical signs of upper respiratory tract disease. Following recovery from acute infection, a carrier-mucosal infection persists, and viral shedding may continue from the oropharyngeal region for weeks to months. Unlike FHV, latency does not occur.

Less commonly, the virus may exhibit pneumotropism leading to severe interstitial pneumonia. Recently lethal outbreaks associated with systemic spread and multiorgan dysfunction have occurred. Clinical manifestations in these outbreaks have included high fever, depression, anorexia, edema (particularly of the head and limbs), and ulcerative dermatitis of the face, pinnae, and feet. Affected tissues included lungs, pancreas, and liver. Most outbreaks have originated in cats from shelters or rescue facilities, and vaccinated and unvaccinated cats have been affected with significant mortality rates reported.

FCV is rarely associated with abortion in the pregnant queen. It has been isolated from aborted fetuses, indicating transplacental transmission can occur. Viremia occurs in some FCV infections, and the recently characterized isolates from virulent systemic disease could lead to gestational termination, although it has not been described; however, severe signs will be evident in the queen, including edema, ulcerative dermatitis, and hepatic necrosis.

Neonatal kittens may be exposed from subclinically shedding contact animals or via indirect contact with contaminated fomites, including caretakers. Signs may be similar to those described for FHV and require specific diagnostics for differentiation. Primary viral pneumonia can occur with some strains and may have high mortality rates. Affected kittens will exhibit not only the typical signs of upper respiratory tract infection but also severe respiratory distress, and death can be peracute. Although it is likely that infection with strains associated with systemic disease can occur in kittens, specific outbreaks have not been described. In kittens that recover from FCV infection, polyarthritis may be seen associated with mononuclear cell infiltration of joints. Referred to as "limping kitten syndrome," signs are generally self-limiting.

Diagnosis of neonatal FCV infection is similar to that for FHV, involving virus isolation, antigen detection, or genetic detection using PCR on clinical samples.

Treatment for FCV infection is supportive as no specific antiviral therapies currently exist. Control, as for FHV, should emphasize vaccination of adults and, during outbreaks, intranasal vaccination of preweaning-aged kittens. As with FHV, kittens should be isolated from adults other than the queen, as they can be subclinical shedders. During an outbreak, because of the hardy nature of the virus, strict barrier nursing and rigorous disinfection with appropriate reagents (oxidizing agent as active ingredient) are required.

Feline Panleukopenia

Feline panleukopenia (FPL) is an important systemic parvoviral infection of cats associated with replication in and cytopathic effects on rapidly dividing cells, such as bone marrow, lymphoid cells, and intestinal epithelia. In addition, it may target the fetus in utero, and in late gestation and the neonatal period, infection can lead to congenital defects. This agent is one of the smallest animal viruses, barely 18 to 20 nm in diameter. It contains a small ssDNA genome and has a mutation rate similar to RNA viruses. It is extremely hardy in the environment and may persist for as long as 2 years. Following oronasal exposure, the virus spreads systemically via the lymphatic system and blood. Infections are acute, and long-term shedding is uncommon. With the advent of effective vaccines for FPL, reproductive losses resulting from FPL disease have been reduced. However, infections continue to occur among both pedigreed cats and cats from rescue facilities. In one study of 274 kitten deaths in the United Kingdom, 25% were caused by FPL infection.

Infection of the pregnant queen may lead to abortion, stillbirths, fading kittens, or congenital defects depending on the stage of gestation, with the latter resulting from in utero infection in late gestation. These congenital defects may include cerebellar hypoplasia, exhibited by intention tremors and ataxia; hydranencephaly, with abnormal behavior; or cardiomyopathy. Infection in the early neonatal period can lead to similar defects.

Postnatal infection may lead to necrosis of intestinal epithelia and hematopoietic progenitor cells, the classic panleukopenia syndrome, with vomiting, diarrhea, severe depression, and anorexia. Endotoxemia or sepsis may occur secondarily. Peracute deaths may occur in some kittens.

Diagnostics for FPL involve viral detection. Viral antigen can be detected in feces from kittens with diarrhea using commercially available ELISA. Electron microscopy can also be done on fecal samples. For detection in tissues postmortem, virus isolation or nucleic acid detection by PCR is required. Panleukopenia associated with typical signs is also considered diagnostic.

For disease resulting from congenital infections, no specific treatment exists. For cerebellar hypoplasia, the condition is not progressive, and as long as kittens can eat, their overall health will not be affected. More severe neurologic involvement is generally incompatible with a good quality of life. Cardiac damage from FPL infection is also not specifically treatable, and the resultant cardiomyopathy can be life threatening.

Treatment for postnatal infection is supportive, as no specific antiviral therapies exist for parvovirus. Replacement of fluid and electrolyte loss is critical. Transfusion may be required with severe anemia or hypoproteinemia. Treatment of gram-negative sepsis with broad-spectrum parenteral antibiotics will also be necessary. With aggressive treatment, survival is probable.

Control through vaccination of adults is effective. Queens with high levels of neutralizing antibodies will protect

kittens in utero, as well as in the neonatal period, through passive transfer. Modified live vaccines should not be used during pregnancy or in kittens aged less than 4 weeks. If an outbreak occurs, adequate disinfection will be critical because of the resistant nature of the virus. Disinfectants must incorporate an oxidizing agent as an active ingredient to be effective. Disinfection of soil is not practical, and objects with porous surfaces, such as carpeting, should be steam cleaned or removed from the environment.

Feline Coronavirus

Feline coronavirus (FCoV) is a common enteric pathogen of cats, and infection in some leads to the fatal disease feline infectious peritonitis (FIP). The virus is an enveloped virus with a helical capsid containing an ssRNA genome of approximately 20 kilobases, one of the largest RNA genomes of animal viruses. As with other RNA viruses, the mutation rate is high and may lead to an FIP-causing phenotype. Most infections target the intestinal epithelia, leading to malabsorption and maldigestion and manifesting as diarrhea. Infection follows oronasal exposure; the virus is shed in feces, and some adults may shed the virus subclinically for extended periods. In populations where infection is endemic, viral infection may be detectable as early as 4 weeks of age.

FCoV is uncommonly associated with reproductive problems in the pregnant queen or with fading kitten syndrome. Postnatal infection of kittens can manifest as enteritis with watery diarrhea. Less commonly, vomiting may be observed. The diarrhea is generally not hemorrhagic, and an associated panleukopenia is not observed, aiding differentiation from FPL infection. Individual kittens in a litter may develop FIP after weaning, but it is uncommon before weaning.

Virus detection via electron microscopy or PCR from diarrheic feces will aid diagnosis of FCoV enteritis. The former, because of its lower sensitivity relative to PCR, is preferable; the high sensitivity of PCR will allow detection of subclinical infections. If FCoV is suspected in cases of abortion or fading kittens, PCR detection on tissues postmortem is optimal for virus identification.

To develop a diagnosis of FIP, a combination of data and tests is required and includes history and clinical signs (multi-cat origin or purebred, fever, weight loss, anorexia), lymphopenia, elevated total protein (TP), decreased albumin: globulin (A:G) ratio, typical effusion (transudate high in TP), and ruling out other etiologies. Coronavirus-specific assays are available but cannot distinguish the enteric virus from that of FIPV. Virus detection assays include antigen detection (effusion sediment, tissue impressions) and genetic detection by PCR. Recently a quantitative PCR to detect viral mRNA in monocytes has been developed. This assay detects efficient viral replication in circulating monocytes, a characteristic of FIPV; however, a recent study has found detectable mRNA in the blood of cats without FIP. Thus, although this assay may provide additional diagnostic information, it is not specific for FIP. Confirmation can only be accomplished through histopathology and IHC.

Treatment of FCoV, both enteric and FIP, is largely supportive and includes fluid and nutritional support. For FIP, treatments using immunomodulation have been tried with minimal success. These include interferon, both feline and human recombinant products, and corticosteroids. The disease is progressive and ultimately fatal.

Infection with FCoV is common and, in the majority of cases, leads to little or no disease. A vaccine is available for FCoV but is not widely recommended. In catteries, early weaning with isolation of the kittens has been recommended as a preventive measure, but this is not feasible for most.

Feline Leukemia Virus

Although uncommon in most breeding catteries, FeLV still occurs in many cat populations. A gammaretrovirus in the Retroviridae family, it is an enveloped virus with a protein core and a diploid ssRNA genome. The capsid is made up of several small proteins, one of which, p27, is detected by commercially available diagnostic ELISAs. Another structural protein, the envelope glycoprotein p15e, has been found to be immunosuppressive through inhibition of a variety of immune functions. As part of its replication cycle, FeLV converts its RNA genome into dsDNA, which integrates into the host cell DNA. Unless virus is cleared early during infection, a persistent infection may occur, leading to neoplasia, bone marrow suppression, and immunosuppression. The majority of cats undergo a latent infection in which the virus remains integrated into host cell DNA.

The virus is transmitted by direct contact between cats, usually via saliva, as shedding in saliva is consistent in persistently infected cats. Therefore, mutual grooming is an important means of transmission. Because of the lability of FeLV, it does not persist in the environment; thus, indirect transmission is not an efficient mode of spread. It can be transmitted in utero to fetuses in pregnant queens and to kittens during parturition by maternal grooming or via milk. After infection, viremia occurs, and if not cleared by the cat's immune response, infection of hematopoietic cells in the bone marrow will occur. Infection that reaches this stage is less likely to be cleared. Resistance increases with age, and kittens are most susceptible to persistent infection.

Infection in utero most commonly leads to pregnancy failure. Pregnant queens that become infected may experience abortion, stillbirths, or fading kittens that die soon after birth. Perinatal infection may also lead to fading kittens, with poor nursing, hypothermia, inactivity, and crying. Rarely kittens infected in utero or during the perinatal period may survive beyond weaning. These kittens may suffer a panleukopenia-like syndrome or may die from septicemia or other infections secondary to FeLV-induced immunosuppression. Long-term survivors may develop any of the typical FeLV clinical syndromes. Infection that occurs in the pre- or perinatal period is likely to affect most or all of the litter; however, it is inappropriate to test only representative littermates.

Diagnosis of FeLV infection involves detection of viral antigen in the queen and her offspring. Initial screening is

done most commonly using commercially available ELISA kits. Testing should be done on serum, as saliva and tears may not contain detectable virus for weeks or longer after infection. Positive ELISA results should be confirmed using immunofluorescence on whole blood smears. Animals testing positive by both assays are unlikely to clear the virus. Cats with ELISA-positive results only may clear the virus, but this is unlikely in kittens aged less than 16 weeks as compared with adults. Serial testing in kittens born to infected queens may be necessary to confirm their infection status. Genetic detection by PCR is not routinely done, as antigenemia-negative cats are unlikely to be infected; however, at least one investigation has indicated that a small minority of infected cats may remain latently infected with nonreplicating virus capable of reactivation and detectable only by PCR.

Treatment of FeLV is primarily supportive, including maintenance of hydration and nutrition and broad-spectrum antibiotics. Treatment regimens using various immunomodulators have had little success in improving the health of affected cats. Treatment of affected kittens is unlikely to be successful.

Control involves vaccination and screening of cats to prevent introduction of infected animals into uninfected populations. Screening is done with the ELISA as described above. Vaccines available include a killed whole virus and a recombinant vector vaccine and have reported efficacy rates of 80% to 100%. If infection is identified in a population, disinfection after removal of infected animals is easy and effective using any detergent. The virus is extremely labile and will not persist in the environment or on fomites for longer than minutes to hours.

Feline Immunodeficiency Virus

Feline immunodeficiency virus (FIV) is also a member of the Retroviridae family with a structure similar to FeLV but is a lentivirus related to HIV. It is endemic in domestic cats and causes an immunosuppressive disease. The primary target cell is the T-helper lymphocytes, but the virus also infects cytotoxic T lymphocytes, B lymphocytes, and some epithelial, fibroblast, and neural cell lines. As with FeLV, the replication cycle involves conversion of the RNA genome into dsDNA and integration into host cell DNA. It is shed in saliva and is transmitted efficiently by penetrating bite wounds. Other body fluids are also infectious, and transmission to kittens may occur in utero or via vaginal fluids or milk. The former is not as significant as a mode of transmission as the latter unless the queen is suffering acute infection, has declining CD4+ lymphocyte levels, or is in an advanced disease state. Transmission via milk or grooming by the queen is more likely to result in transmission to the offspring. One study has indicated that the virus is concentrated in milk in early lactation.

Once infection occurs, followed by seroconversion, viral persistence is virtually ensured. The cat may remain asymptomatic for months to years, but viral replication continues at low levels. A progressive immune dysfunction occurs with declining T-helper lymphocyte and cytotoxic T-lymphocyte levels and impairment of cytokine production along with increasing viral levels. Kittens are among the most susceptible to the hematologic changes. Death occurs as a result of multiple disease syndromes, including degenerative, infectious, and neoplastic diseases.

Infection of the pregnant queen may lead to fetal resorption and arrest of fetal development with reduced litter size. Abortion, stillbirths, and fading kittens also may occur. The virus has a predilection for the thymus and leads to thymic atrophy in the kitten. Signs in the neonate are similar to signs in those that fade as a result of FeLV. Those that survive until weaning will ultimately progress to the immunodeficiency state.

Diagnosis of infection with FIV relies on detection of antibody. Screening is done using a commercially available ELISA and is confirmed with Western blot on serum. The diagnosis of infection in kittens can be compromised because of the presence of maternal antibodies. Queens may have antibodies as a result of infection or vaccination. These antibodies interfere with the results often well past the age of weaning, as antibodies from infection cannot be distinguished from maternal antibodies. Virus detection using PCR may be used, but because of the high level of genetic variation of FIV, false-negative results can often occur. Multiple testing may be required to confirm the infection status.

As with FeLV, treatment is largely supportive. Various immunomodulatory therapies have also been tried with FIV with variable success.

Control is also similar to FeLV and involves screening of cats to prevent introduction of infected cats to a household. Most are screened using the ELISA kit; seroconversion may take several weeks to months, thus testing of kittens of unknown history should be repeated during the first 6 months of life. Kittens testing antibody positive should be isolated until their true infection status can be definitively determined by PCR.

A killed vaccine containing two strains of FIV is available, but efficacy rates have been variable. Additionally, because the vaccine antibody response cannot be distinguished from that caused by infection, it is not widely recommended unless the animal is at high risk. If questions arise regarding true infection status versus vaccine-induced antibody, then the kitten can be tested by PCR on whole blood. Kittens born to vaccinated queens will test antibody positive with routine screening because of maternal antibody but should convert to negative status as the antibodies wane.

Disinfection to inactivate FIV is similar to FeLV—the virus is very labile, does not persist in the environment, and is easily inactivated by detergents.

INTERSPECIES VIRAL SPREAD BETWEEN DOGS AND CATS

Virus transmission within a species is considered to be the norm because viral-coded host cell receptors on the virus

surface restrict the host range of the virus. Although there are several mechanisms whereby a virus may persist in an animal population, interspecies spread or crossover has become of particular interest. This is because interspecies spread hampers control efforts in a population and may allow for emergence of new strains of multihost viruses. There are three particular types of dogs and cats that are susceptible to interspecies viral and bacterial spread. This susceptibility is directly correlated with the immune status of the host (see Chapter 14). The three types are pregnant animals, neonatal animals, and those animals that have genetic or acquired immunodeficiencies. The viruses that have been reported to cross over include canine distemper to cats, feline calicivirus to dogs, canine coronavirus to cats, and CPV-2 variants to cats. Another source of potential interspecies spread occurs from immunization of high-risk animals with contaminated vaccines. This occurred when a MLV canine vaccine that contained bluetongue virus was used in pregnant dogs. The vaccine was administered to booster maternal antibody but proved to be fatal for the puppies and a high percentage of the pregnant dogs. Nonpregnant dogs that received the contaminated vaccine did not develop clinical symptoms, and there was no evidence that further virus spread occurred.

FADING PUPPY AND KITTEN SYNDROMES

The use of the phrase, "the fading puppy and kitten syndromes" has continued in the pediatric literature. The syndromes are multifactorial in nature and are generally used to describe litters of puppies or kittens that fail to thrive (see Chapter 11). The syndromes can occur from birth up to 9 to 10 weeks of age. The affected neonates decline quickly, and the mortality rate can be high. There are at least three potential causes for these syndromes. They include environmental effects, genetic effects, and infectious microorganisms. The environmental effects include hypothermia or hyperthermia. Neonates that are too cold or too warm are unable to nurse and digest food correctly. Heart rates become erratic, and respiratory systems may collapse. Maternal factors that contribute to these syndromes are dams that are overweight and maternal neglect leading to inadequate colostral antibody intake.

Genetic effects that contribute to the syndromes are congenital deformities or deficiencies of the immune system and low birth weights for puppies and kittens.

Infectious causes of the syndromes have been delineated during the past decade and are summarized in Table 16-3. The most common infections for the puppy are CHV, CPV-2, and CPV-1. The dam is the primary source of infection to her puppies at birth or shortly thereafter. The occurrence of CPV-2–related neonatal deaths has decreased with the use of routine vaccination. Under high challenge environments and in populations of dogs not routinely vaccinated, it is possible to see early CDV and CAV-1 infections occurring with high mortality rates. Newer strains of enteric CCV appear to be more virulent and are associated with fatal enteritis in puppies as early as 5 weeks of age.

The most common infections for the kitten are FHV, FCV, and FPL. The queen is the primary source of infection to her kittens. The occurrence of these three viruses causing "fading kittens" has decreased with the routine use of vaccines in queens and adult cats in proximity to the kittens. Other feline viruses that may cause neonatal loss are FeLV and FIV. These two viruses can be readily tested for by the Ag ELISA (FeLV) and antibody ELISA (FIV) on all queens as part of their biosecurity screen.

EMERGING VIRUSES TO WATCH

A main theme throughout this chapter has been the awareness of the carrier status of the viruses in the adult population of dogs and cats. These asymptomatic carriers are usually the source of viral infections to puppies and kittens early in life. Other sources of viral infections are the environment where wildlife cohabitate and interspecies infections between animals in the same household or facility. As was mentioned in Chapter 14, the dam and queen are unusually susceptible to infections and to exacerbation of preexisting infections as a result of temporary immune suppression. The immunologically naive neonatal puppy and kitten are equally susceptible to infections. Several viral infections that have emerged during the past few years are more virulent strains of CCV causing enteritis and respiratory disease, more virulent calicivirus strains affecting both dogs and cats, and influenza strains being spread from horses to dogs (canine influenza) and from birds to cats (avian influenza). More virulent strains of CDV have been reported within some dog populations, as well as in large felids. The clinical recognition of unusual outbreaks of viral disease will most likely occur initially in pregnant animals and neonates and then proceed to susceptible animals before involving the general population of dogs and/or cats.

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