Introduction
During the first half of this century, canine distemper (CD) was the most common fatal disease in dogs worldwide. Inactivated canine distemper virus (CDV) vaccines which were available since the 1940's did not control the disease. A dramatic change was seen in the 1960's when modified live CDV vaccines became available. For some years thereafter it appeared that CD was under control. In recent years the incidence of distemper in dogs appears to have increased, which may be the result of insufficient vaccination and/or vaccination failures.

Etiology
Canine distemper virus is closely related to measles virus (MV), rinderpest virus (RPV), peste de petits ruminants virus (PPRV), the phocine (seal, PDV) and dolphin distemper virus. All are classified as morbilliviruses in the paramyxoviridae family. The virus is enveloped and contains a negative sense single stranded RNA and a RNA polymerase. The lipoprotein envelope is readily destroyed by lipid solvents which renders the virus non-infectious. It contains the H and F proteins which induce a neutralizing antibody response (Fig. 1).

Although small antigenic differences have been demonstrated by serology between different CDV strains, it is generally accepted that there is only one serotype. However, there are considerable differences in the pathogenicity of different virus isolates. CDV strains with different biological properties may have the same response patterns by monoclonal antibody analysis. Only slight differences have been shown in RNA sequence patterns.

Virulent CDV replicates readily in activated canine lymphocytes and in canine macrophages in vitro but only after adaptation in monolayers of epithelial cells or fibroblasts. In contrast, attenuated vaccine virus replicates in lymphocytes/macrophages as well as in epithelial and fibroblastic cells in vitro.

Epizootiology
Canine distemper is enzootic worldwide and has a wide host range. Most terrestrial carnivores are susceptible to natural CDV infection. All animals in the Canidae family (e.g. dog, dingo, fox, coyote, wolf, jackal), the Mustelidae family (e.g. weasel, ferret, mink, skunk, badger, stoat, marten, otter), the Procyonidae family (e.g. kinkajou, coati, bassariscus, raccoon, red panda) may succumb to CDV infection. More recently, large cats (lions, leopards and tigers in California in 1992, and lions in Tanzania in 1994) were found to be susceptible to CDV infection and disease. In addition, CDV has been isolated from the brains of javelinas (collared peccaries) with clinical signs of encephalitis.

CDV affects susceptible dogs of all ages, but puppies are most susceptible when maternal antibody is lost.
Acutely infected dogs shed virus in all body excretions, regardless of whether they show clinical signs or not. Aerosol transmission from respiratory secretions is the main route of transmission. Virus shedding begins approximately seven days post infection. The virus is unstable outside the host and deteriorates fast. Dogs that recover from CDV infection are immune for life. They are not persistently infected and they do not shed virus. Puppies from apparently healthy bitches raised under gnotobiotic conditions have developed CDV infections without postnatal exposure, indicating that transplacental infection can occur.

**Pathogenesis**

Inhalation of airborne virus leads to infection of macrophages in the respiratory tract (Fig. 2). The virus spreads first to local lymph nodes and within seven days to all lymphatic tissues (Fig. 3). During this period, usually between three and six days post-infection (DPI), the first temperature elevation occurs along with the appearance of interferon in circulation.

During the second and third weeks post-infection (PI), dogs either initiate vigorous humoral and cellular immune responses and they recover without further clinical signs, or have weak immune responses and develop acute or subacute disease. In dogs that fail to recover early, infected lymphocytes and macrophages carry the virus to surface epithelium of the alimentary (Fig. 4), respiratory, and urogenital tracts and to the central nervous system (CNS) (Fig. 5). Clinical signs follow the local infection.

Virus strains that induce acute fatal infection appear to predominantly affect the grey matter of the CNS and cause neuronal destruction. By 3 weeks PI dogs have either succumbed or are fully recovered. Virus strains that cause a more delayed disease affect the white matter of the CNS, causing demyelination. Recovery or fatal infection may be delayed for 2 or 3 months. CNS signs without previous signs of generalized disease are possible.

After a delayed onset of humoral and cellular immune responses, virus may disappear from lymphatic tissues and surface epithelium but may persist in the CNS, eyes, and foot pads.

**Clinical Signs**

There is great variation in the duration and severity of clinical disease. Signs may range from no visible signs to severe disease, with or without CNS signs, with approximately 50% mortality. The first pyrexia (3-6 DPI) may pass unnoticed, the second peak (several days later and intermittent thereafter) is usually connected with serous (later mucopurulent) nasal and ocular discharge, depression and anorexia. Lymphopenia is always present during the early infection. Gastrointestinal and/or respiratory signs may follow, often enhanced by secondary bacterial infection. However, about 50% of CDV infections in dogs are probably subclinical or very mild.

Some dogs develop CNS signs, often, but not always, following systemic disease. Depending on the virus strain, the signs may be more related to acute grey matter or subacute white matter disease. Seizures and myoclonus with hyperesthesia and depression predominate in grey matter disease; incoordination ataxia,
paresis, paralysis and muscle tremors in white matter disease. Meningeal signs of hyperesthesia and cervical
trigidity may be seen in both. Optic neuritis and retinal lesions in dogs with CDV are not uncommon.
Hyperkeratosis of the foot pads and nose is produced by some virus strains. In growing dogs enamel
hypoplasia of the teeth after CD infection is a common observation. Post-vaccinal encephalitis usually causes
central nervous signs including behavioral changes, seizures, and blindness one or two weeks post vaccination
with a high mortality rate.

Immune Response
During the first week of infection, dogs always have a lymphopenia and are immuno-suppressed. Depletion of
T and B cells and necrosis in lymphatic tissues appears to be a direct effect of CDV infection.
Dogs that recover early with minimal clinical signs respond with vigorous humoral and cellular immune
reactions. Antibody to core proteins (NP and P) may be found 6 to 8 DPI by ELISA or immune precipitation.
Antibody to envelope proteins (H and F) corresponding with the onset of virus neutralizing (VN) antibody,
appears 10 to 20 DPI depending on the virus strain. VN antibody persists for years. Virus specific IgM
(ELISA) may be found from 6 or 8 DPI up to three months PI depending on the severity of infection and the
virus strain (IgM in vaccinated dogs lasts for approximately three weeks).
Cell mediated immune responses by circulating cytotoxic T cells appear 10 to 14 DPI and are maximal by 14
to 28 DPI. They gradually decline thereafter and disappear by 6 to 10 weeks PI. Dogs which develop acute or
subacute disease have little or no humoral neutralizing antibody and cell mediated immune responses are
either absent or the onset is delayed. Antibody to viral NP and P proteins may be found in these dogs. Dogs
with a more chronic CNS infection may develop strong immune responses later. Cerebrospinal fluid (CSF) of
dogs which recover early is usually free of antibody and interferon. Dogs which die from acute CNS infection
have interferon but no VN antibody in the CSF. Dogs with subacute or chronic CNS signs have interferon and
may have VN antibody in the CSF. Concentrations of IgM and IgG in the CSF may be high.

Diagnosis
Hematology - In acute cases, lymphopenia and thrombocytopenia may be found, monocytes may increase.
Immunocytochemistry - In acute cases, viral antigen and/or inclusion bodies may be seen in buffy coat cells,
in conjunctival or vaginal imprints, in cells from bronchial washings and urine sediments, or from the CSF.
Virus particles have been seen by electron microscopy in fecal preparations. In subacute or chronic cases these
tests may be negative, and negative tests do not rule out distemper.
Virus Isolation - Virus isolation can be attempted from the same specimens used for immunofluorescence.
However, virus isolation is usually not performed in veterinary diagnostic laboratories.
Polymerase Chain Reaction (PCR) - Demonstration of viral nucleic acid may still be positive when virus
isolation and immunocytochemistry fail to detect the agent.
CSF Analysis - Increased protein and mononuclear cell concentration in the CSF is common in dogs with
CNS involvement. CDV antigen in CSF cells is found during the acute stages of encephalitis. Presence of
CDV specific antibody in the CSF is pathognomonic in dogs with an intact blood-brain barrier, however, its
absence does not rule out distemper. As long as CDV persists in the CNS, interferon can be demonstrated in
the CSF. Antibody in CSF is not present in dogs after vaccination.
Serology - Measurement of CDV specific neutralizing, precipitating, or cytotoxic antibody is not sufficient for
a diagnosis. Acutely infected dogs may die without neutralizing antibody and subacutely or chronically
infected dogs may have antibody levels comparable to vaccinated dogs.
ELISA Tests for CDV Specific IgM - ELISA tests are useful. IgM persists in dogs with distemper for 5 weeks
to 3 months, depending on virus strain and host response. IgM in vaccinated dogs persists for approximately 3
weeks.

Treatment
Specific antiviral drugs having an effect on CDV in dogs are not available. Treatment of CD, therefore, is
nonspecific. Antibiotic therapy is indicated because of the common occurrence of secondary bacterial
infections of the respiratory and alimentary tracts. Because dogs with CD and diarrhea are often dehydrated,
fluid and electrolyte support may be the most important therapy for CD.
Treatment of dogs with neurologic signs is not rewarding. Sedatives and anticonvulsants may ameliorate
clinical signs, but they do not have a curative effect. However, dogs with signs of CNS involvement
occasionally recover and myoclonus or optic neuritis may improve with time. If CNS signs are progressive
and dogs become recumbent, euthanasia is indicated.

**Prophylaxis and Control**
Immunization by controlled vaccination is the only effective approach to CD prophylaxis at the present time. Active immunization with modified-live virus vaccines induces long-lasting immunity and has kept the disease in dogs under control during the last 35 years.

**Modified-Live CDV Vaccines** - With few exceptions the modified-live CDV vaccines available today are derived from either avian cell or canine cell culture adaptations. Both methods of adaptation produce vaccines that are very effective in inducing an immunity that lasts for at least 1 year and probably for several years in most dogs. There are minor disadvantages to both products: Canine cell-adapted strains immunize virtually 100% of susceptible dogs but sporadically may induce post-vaccinal encephalitis. The avian cell-adapted strains are safer for dogs, but the onset of the immune response in dogs may be 2 or 3 days later than with the canine cell-adapted vaccines, and not all susceptible dogs may become immunized. Any modified live CDV vaccine may be fatal for certain wildlife and zoo animals (e.g. red pandas or black footed ferrets). Inactivated virus vaccines must be used in these species.

**Inactivated CDV Vaccines** - Inactivated CDV vaccines, that were used earlier in this century, have not been able to control the disease of dogs and are no longer commercially available.

**Heterotypic (Measles) Virus Vaccination** - Heterotypic (measles) virus vaccination has been the best approach to overcome maternal antibody interference with immunization. As with inactivated CDV vaccines, MV induces a limited immunity that can protect dogs against CDV disease but not against CDV infection. A combination of attenuated MV and CDV is still commonly used in 6-10-week-old pups. It offers the advantage of complete protection in the absence of, and partial protection in the presence of, maternal antibody.

**Recombinant CDV and DNA Vaccines** - With the advancements in biotechnology, work is in progress to produce recombinant vaccines for CD. Carrier viruses (e.g. vaccinia, canary pox, adeno or baculovirus) have been found to be suitable for dogs. Genes coding for the H and F proteins of CDV are being used as inserts. Immunity to the CDV H and F proteins has been found to be protective. A canary pox recombinant vaccine with H and F inserts is now available commercially. Although safety would be assured by such products, it will be difficult to match the efficacy and duration of immunity of current modified live virus vaccines. Immune stimulating complexes (ISCOMS) and DNA vaccines would have similar effects.

**Maternal Antibodies** - Maternal antibodies interfere with immunization, and the persistence of maternal antibodies in young pups greatly influences the proper time of vaccination. Transplacental uptake of maternal antibodies may range from 3% to 20% of the bitch's serum level. The predominant portion (approximately 80%) is absorbed in the intestine from colostral antibody, mainly during the first day of life. The half-life of maternally derived antibody has been estimated to be 8.4 days.

**Vaccination Schedule** - A vaccination schedule for pups against CD should include a combined modified-live MV-CDV vaccination at 6-8 weeks of age. Two additional CDV vaccinations at 3 to 4 week intervals should be given. Annual booster inoculations are commonly recommended by veterinarians because some dogs may lose antibody titers in that time period since vaccines vary as well as dog immune responses. However, vaccination at 2 - 3 year intervals is probably sufficient in the majority dogs. Neutralizing antibody levels may be tested to confirm immunity. Colostrum-deprived pups should not be vaccinated with modified-live CDV before they are 4 weeks of age. Modified-live CDV can cause fatal post-vaccinal encephalitis in unprotected younger pups, as it can be in certain wild or zoo species.

**Homeopathy** - In recent years, homeopathic prevention of CD for dogs by use of 'nosodes' has been advocated in the lay press, and by some holistic veterinarians. However, claims of prevention are completely unsubstantiated. Such methods are not recommended. Recently, several kennels who had used homeopathic nosodes lost pups to CDV infection (unpublished observations).

**Other Control Measures** - In addition to immunization, strict isolation of dogs with CD appears to be the most important step in controlling the disease. Virus is shed in all body excretions during the acute systemic disease and direct dog-to-dog contact appears to be the main route of viral spread. Dogs with subacute CD encephalitis still may infect susceptible contact dogs. Disinfection of CDV in the environment can be accomplished with commonly used products because the enveloped virus is rapidly destroyed outside the host.
Public Health Considerations
There was speculation several years ago that CDV might cause multiple sclerosis (MS) in humans. The speculation was based on epidemiologic observations involving prior exposure of MS patients to dogs and to dogs with CD. This proposition has not been substantiated in many subsequent reports published over the past 15 years. Another point of concern has been the possible shedding of modified-live MV from vaccinated dogs. The concern was that dogs may excrete a mutant virus that is virulent for humans. This concern is not justified because MV replicates only to a very limited extent in dogs and only in lymphoid tissues; dogs vaccinated with modified-live MV, like those vaccinated with modified-live CDV, do not shed vaccine virus. More recently, CDV transcripts have been detected in bone cells of dogs with metaphyseal osteopathy. It has been speculated that CDV may play a role in human Paget's Disease, but proof is lacking.

References


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