CANINE PARVOVIRUS

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Perhaps the most dramatic change that occurred in veterinary gastroenterology in the decade of the 1980s was the emergence of viral enteritis as a common clinical problem. Prior to 1978, contagious enteritis was virtually unknown in the dog. Clinicians occasionally encountered colibacillosis affecting an entire litter, but otherwise enteritis was most often an individual animal problem and most often of noninfectious origin.

Then, beginning in 1978, and peaking in 1979 and 1980, clinicians began to encounter outbreaks of severe gastroenteritis among groups of dogs. Entire litters or even colonies would be affected; the epidemiologic profile was clearly one of an infectious agent with a relatively short incubation period. The causal agent was shown to be canine parvovirus, a previously undescribed pathogen of dogs.[2, 10] Subsequent work has shown that canine parvovirus was a newly evolved pathogen: the clinical pattern observed was typical of a new pathogen spreading rapidly through a completely susceptible population.

Now, nearly 15 years after its initial appearance, both canine parvovirus and the pattern of disease seen clinically have changed. This article reviews current knowledge about the virus, its epidemiology, clinical manifestation, diagnosis, management, and prevention.

THE VIRUS

The virus commonly known as canine parvovirus is better termed canine parvovirus type-2 (CPV-2), because it is the second parvovirus described in dogs. The first, termed CPV-1 or the Minute Virus of

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Canines, was described in 1970 and originally believed to be nonpathogenic.[3] Recent work has shown that CPV-1 can cause resorption and abortion in pregnant bitches—an outcome not reported for the enteritis-causing CPV-2.[4, 22]

A large body of literature is now available on the genetic structure of CPV-2.[26] CPV-2 differs from the closely related feline panleukopenia virus (FPV) by only three or four DNA sequence changes.[26] It is feasible that CPV-2 could have been derived from FPV or from some other closely related parvovirus by a relatively small number of DNA mutations. The nature of the ancestral virus is not known.

Once CPV-2 acquired the properties that permitted it to infect dogs, it was able to spread rapidly, because there was no preexisting immunity in the dog population in the late 1970s. Serologic analyses of stored serum samples have been conducted by a number of investigators in different countries. The earliest reported CPV-positive sera are from Greece in 1974.[11] Positive sera were first identified in Europe in 1976 and 1977, and in the United States in 1978.[4, 24, 25, 37] By 1979, cases had been diagnosed worldwide.

Genomic analysis has demonstrated that canine parvovirus has continued to evolve. Parrish et al[29] reported that all isolates examined from 1978 to 1980 were of a single type. Post-1980 isolates, however, could be distinguished by their reactivity to specific monoclonal antibodies and restriction-endonuclease cleavage patterns. Moreover, these latter strains apparently had some selective advantage over the parental strain such that they had virtually replaced it by the mid 1980s. Parrish et al proposed naming the new strain CPV-2a to indicate that it is a subtype of CPV-2.[28] Serum from dogs exposed to either CPV-2 or CPV-2a cross-reacts with both viruses and vaccines to cross-protect. Subsequent studies in the mid-1980s revealed the emergence of a third subtype, CPV-2b, which has now become the predominant type isolated in the United States.[28] The small size of the parvovirus genome and the availability of exquisitely sensitive molecular probes have made it possible to track this evolution in remarkable detail. The entire three-dimensional surface of the virus has been mapped and the location of individual amino acids identified.[27]

EPIDEMIOLOGY

Initially, outbreaks of canine parvovirus were characterized by high morbidity and high mortality, with the majority of dogs in a group becoming clinically ill. Such outbreaks no longer occur, and the disease is encountered almost exclusively in puppies between the ages of about 6 weeks to 6 months. Virtually all adult dogs are immune, either as a result of vaccination or natural infection. Immunity to canine parvovirus following infection or modified live vaccines is long-lived—more than 2 years, and perhaps life-long.[5] Therefore, the only pool of susceptible animals are puppies born into the population. These are protected

against infection for the first few weeks of life by maternal antibody so that disease is no longer encountered in neonates.[22, 33] As their maternal antibody titers decline, however, they become susceptible to infection, and if they are not adequately immunized, they become infected in the first year of life. Canine parvovirus persists for long periods in the environment (5–7 months) and is ubiquitous. Endemic parvovirus cycles exist among wild canids and in large breeding colonies.[22, 40, 44]

Instances of fatal disease are still encountered, but subclinical infections are common, especially in adults, as evidenced by seroconversion without evidence of clinical disease.[18] Clinical cases in practice are generally milder with better survival rates than a decade ago, possibly due in part to a lower challenge dose. Initially, when large numbers of dogs were susceptible, the amount of virus in the environment was amplified as more and more dogs became infected so that the challenge dose increased over time until all susceptible dogs had become infected. Nowadays, except in very large colonies, there is little opportunity for such amplification to occur because of a high level of population immunity.

Two disease entities associated with CPV-2 infection were initially described, enteritis and myocarditis.[2, 8, 9, 12, 36] The latter form has virtually disappeared as a result of population immunity. Parvoviral myocarditis only develops if puppies become infected very near the time of birth when their myocardial cells are still rapidly proliferating. (The autonomous parvoviruses including CPV-2 replicate only in dividing cells.)[17, 38, 39] Because virtually all bitches are now immune and pass that immunity to their pups through the colostrum, virtually all puppies are refractory to infection during the critical period when infection of the myocardium is possible. As a result, the myocardial form of the disease is no longer seen.

PATHOGENESIS

The pathogenesis of canine parvovirus infection has been studied in great detail by Meunier et al[19–21] and MacCartney et al.[14–16] Infection is acquired by ingestion of infectious virus.[14–16, 19–21] The minimal infectious dose is not known but appears to be very small, perhaps as few as a hundred tissue culture infective doses (TCID). This, taken together with the enormous amounts of virus shed by infected animals (up to 10 billion $TCID_{50}/g$ of feces) and the hardiness of the virus in the environment, are sufficient to account for the rapid world wide spread of infection in the late 1970s.[31]

After ingestion, viral replication occurs in the oropharynx during the first 2 days of infection, spreading to other organs by way of the blood stream (Fig. 1). By the third to fifth days, viremia is marked. Although usually manifest as enteric disease, parvoviral infection is systemic. The virus reaches the intestinal mucosa from the blood stream rather than from the intestinal lumen.[20, 21] For this reason, serum

Ingestion

↓

Viral replication
Oropharyngeal lymph nodes

↓

Viremia

Lymph nodes ← Bone marrow → Intestine
Spleen

Lymphoid cell necrosis

↓

Lymphopenia

Necrosis of
germinal epithelium

↓

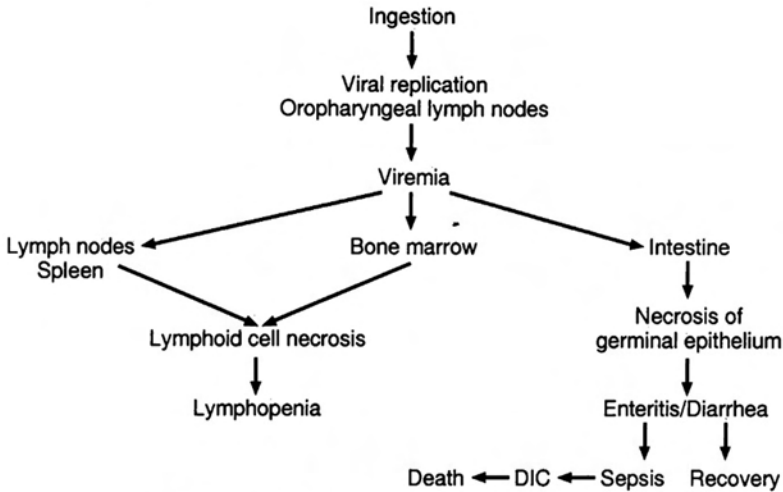Enteritis/Diarrhea

Death ← DIC ← Sepsis Recovery

Figure 1. Pathogenesis of canine parvovirus.

antibody titers are strongly correlated with protection, and passively derived antibody is completely protective in sufficient amounts.[20] Intestinal IgA is not essential for protection. Clinical signs of CPV enteritis are not manifest until 4 to 5 days after oral exposure.[31] The incubation period is believed to range from 3 to 7 or 8 days, with virus first shed on day 3, often before clinical signs appear.

The lesions resulting from canine parvovirus are determined primarily by the autonomous parvoviruses' requirement for actively dividing cells. Hence, viral replication occurs principally in tissues with high rates of cell turnover—the intestine, lymphoid tissues, and bone marrow. Cells must also possess appropriate viral receptors, as not all tissues with proliferating cell populations are affected.[26] Conditions that increase cell turnover favor viral replication and increase the severity of the resulting lesions and clinical disease. Hence, if exposure to canine coronavirus, which stimulates proliferation of the germinal epithelium of the intestinal crypts by destroying more mature villous epitheliocytes, precedes canine parvovirus infection, the resulting dual infection is more severe than that produced by either virus individually.[1]

In the intestinal tract, parvoviral replication kills cells of the germinal epithelium of the intestinal crypts, leading to epithelial loss, villus shortening, vomiting, and diarrhea. Lymphoid necrosis and destruction of myeloproliferative cells results in lymphopenia and, in severe, cases, panleukopenia.

Immunity to canine parvovirus develops rapidly. Circulating antibody to canine parvovirus is usually detectable by the time clinical signs commence and peaks rapidly during the course of clinical illness.[31] The rapidity of the immune response is a key determinant in the severity of the clinical manifestation of disease. Animals that are able to limit the magnitude and duration of viremia have milder disease and

greater chance for recovery.[21] This may explain why killed vaccines, while failing to prevent infection, nevertheless appear to protect dogs from clinical illness; the anamnestic response to infection is sufficiently rapid to curtail viremia.[32]

If dogs survive the acute stage of infection, recovery from the enteric form is usually rapid and complete. Even in fatal cases, there is evidence of intestinal regeneration.[7] Only the now extinct myocardial form leads to chronic progressive disease as a result of myocardial damage. Immunity is long-lived and complete; dogs kept in isolation for 2 years and rechallenged were completely refractory to infection.[5]

CLINICAL PRESENTATION

The clinical presentation of canine parvovirus is now well known—prodromal signs of lethargy and inappetence followed by an acute onset of diarrhea, vomiting, and fever—although the syndrome was inexplicable and unprecedented when it was first described. One of the observations that lead to the link with feline panleukopenia was the observation of profound leukopenia in severely affected dogs. In some cases, white blood cell counts as low as 300 cells/mm^3 were reported.[43]

The first cases of the myocardial form of CPV-2 disease were even more perplexing; affected puppies were either found dead or died after short episodes of signs indicative of heart failure. Entire litters would be affected, most dying within a few days, whereas survivors often went on to develop chronic heart failure within a few months of birth. The link to canine parvovirus was finally made by the discovery that myocardial cell nuclei from infected dogs were stained by fluorescent antibodies against canine parvovirus.[36]

DIAGNOSIS

The diagnosis of fulminant cases of canine parvovirus is relatively easy. Few diseases in dogs cause the constellation of acute enteritis, fever, and leukopenia. Less severe cases, which are more common than the classic "textbook" presentation, pose a diagnostic dilemma: in most instances, it is impossible to differentiate canine parvovirosis from the myriad of other causes of acute enteritis in dogs on the basis of clinical signs alone. The telltale leukopenia is transient when present, and in milder cases, may never drop below the lower limit of the "normal" range.[14–16, 18–21, 31]

Definitive diagnosis is most easily made by demonstrating canine parvovirus in the stool, a relatively simple task in acute cases because of the amount of virus present. A number of different methods are available to diagnostic laboratories—viral isolation, stool hemagglutination, electron microscopy, and so forth.[34] Perhaps the most practical method for practitioners is an in-office ELISA test (Cite test, IDDEXX,

Portland, ME). A few cautionary comments apply to all tests for virus in the feces. The period of fecal viral shed is brief: virus is seldom detectable by 10 to 12 days after infection.[20, 21, 31] Also, all modified live canine parvovirus vaccines shed in the feces and could yield a false-positive result in dogs 4 to 10 days after vaccination.

MANAGEMENT

Supportive care remains the cornerstone of therapy for patients with canine parvovirus and follows the general guidelines for management of any acute enteritis.[35] Animals presenting with acute-onset vomiting and diarrhea should be triaged into those that can be managed as outpatients and those that require hospitalization and intensive therapy. If the patient has only minimal vomiting and diarrhea with no other significant clinical findings, then it should be given supportive therapy and can be sent home. If the patient's condition worsens or if it fails to respond to supportive therapy within a day or two, the animal should be hospitalized and given a more complete workup and more intensive therapy.

Patients that present with acute vomiting and diarrhea accompanied by other significant clinical signs, such as high fever, moderate to severe abdominal pain or dehydration, blood in the diarrhea or vomit, or severe depression, should be hospitalized immediately. Such patients need a thorough diagnostic evaluation and intensive therapy.

Outpatient Supportive Therapy

The clinical management of acute enteritis in dogs without other systemic signs includes dietary restriction, subcutaneous fluid therapy, and, in some cases, gastrointestinal medications. Patients should be reevaluated in 1 to 3 days, either by an office visit or by a telephone call to the owner.

Dietary restriction is the single most effective measure in the symptomatic treatment of acute enteritis. The goal is to rest the inflamed gastrointestinal tract. All food should be withheld for 12 to 24 hours. If vomiting has been severe, then water should also be withheld. If water is withheld, subcutaneous fluids must be given and the animal must be monitored for signs of dehydration.

After 24 hours, small amounts of warm, bland diet should be offered. Commercial bland diets are available, but a homemade diet of boiled rice and low-fat cottage cheese is simple to prepare.

If feeding causes the vomiting or diarrhea to worsen, then food should be withheld for an additional 12 to 24 hours; then, it can be tried again. Small amounts of the bland diet should be offered several times a day for the next 2 to 3 days. Once the animal can eat successfully, gradually reintroduce the normal diet.

Subcutaneous fluids should be administered to patients that are mildly to moderately dehydrated. (Severely dehydrated animals need intravenous fluids). Subcutaneous fluid administration is rapid and easy; absorption continues over several hours, so it is suitable for outpatients. Lactated Ringer's solution supplemented with 10 to 20 mEq/L of potassium chloride can be instilled in multiple sites. It is important not to give an excessive amount in one place; this can result in local areas of necrosis and skin sloughing in dogs with parvoviral enteritis.

Many locally acting intestinal preparations are available. Most have been used for years, although controlled scientific experiments have failed to show that they have any beneficial effect. For example, kaolin-pectin preparations fail to reduce either the severity or duration of clinical signs in humans with traveller's diarrhea and are no longer recommended by most gastroenterologists.[35] In clinical trials in humans, preparations that contain bismuth subsalicylate did reduce the severity and duration of diarrhea and are recommended for use in dogs. Their benefit is believed to derive principally from the subsalicylate moiety, which has a local antiprostaglandin effect in the intestinal tract. Bismuth preparations may be used to help control diarrhea in patients that can tolerate oral medications.

Followup is an important, but often overlooked, aspect of care for acute enteritis. The owner should be contacted 24 to 48 hours after the first visit to check on the animal's progress. Followup is most effective if the owner is instructed to watch and record specific parameters. It may be helpful to prepare a small chart for them to complete, listing items such as number of bowel movements, amount eaten, body temperature, and so forth. By quickly reviewing the chart, you can get an objective assessment of whether the animal's condition is getting better or worse. This approach is both faster and results in better care than just asking "How is your dog doing today?"

In-Hospital Care

If the animal is brought to the clinic with a high fever, severe depression, bloody diarrhea, or other signs of more serious disease, then it should be hospitalized at once and treated vigorously. Fatal dehydration and irreversible shock can develop rapidly in patients with severe enteritis, especially in young puppies with small body mass.

Again, fasting is an essential aspect of treatment. Food should be withheld until the underlying problem has been diagnosed and treated or until the animal's clinical condition has improved.

Intravenous fluid therapy is mandatory in severely dehydrated patients and in patients in which fluid loss in the vomit and watery diarrhea is excessive. An indwelling intravenous catheter should be placed to allow rapid infusion of the large volume of fluids these animals may require.

Ideally, the fluid therapy should be based on analysis of the serum electrolyte and acid-base concentrations, but when these are not available, the use of a balanced salt solution alone can be life saving.[42] Initial fluid therapy should be planned to correct dehydration over 18 to 24 hours. Maintenance of 70 mL/kg body weight should be supplied. The packed cell volume and total solids and body weight should be used to monitor hydration. Continued water loss in the feces and vomit may require infusion rates of two to three times normal maintenance requirements.

The routine use of antibiotics in patients with enteritis is considered unnecessary and potentially harmful, potentially leading to bacterial overgrowth.[35] Broad-spectrum parenteral antibiotics are recommended in patients with parvoviral enteritis, however, because of the disruption of the mucosal barrier and the frequency of secondary septicemia.[35] Antibiotic selection should cover both gram-positive and gram-negative aerobic and anaerobic bacteria.[41] A combination of ampicillin (10–20 mg/kg) and gentamicin (2.2 mg/kg) every 8 hours has been recommended.[35] Veterinarians should be careful about using aminoglycoside antibiotics in patients with poor renal function because of their inherent renal toxicity; the urine sediment should be monitored and if granular casts are detected—indicating the onset of tubular nephrosis—the aminoglycoside should be discontinued.

Oral antibiotics should not be used in patients with gastroenteritis. Vomiting, delayed gastric emptying, impaired peristalsis, and altered intestinal mucosa all occur with gastroenteritis and make the absorption and effect of oral medications unpredictable and unreliable.

There is controversy regarding the use of motility modifiers in an attempt to control the diarrhea. Most gastroenterologists now recommend against the use of anticholinergic antidiarrheal medications because they suppress segmental contractions more than peristaltic contractions, which may actually hasten transit times. Narcotic analgesics and synthetic opiates are considered to be better choices. They should probably be reserved only for severe or prolonged cases, however, because slowing the flow through the intestine may increase toxin absorption. There is some evidence that in canine parvoviral enteritis some of the clinical signs are due to endotoxin absorption through the intestinal tract.[26]

Antiemetics should be prescribed in severe cases in which continued vomiting makes it difficult to maintain hydration or electrolyte balance or in which the animal is becoming exhausted.[13] Metoclopramide is a dopamine antagonist antiemetic that blocks the chemoreceptor trigger zone and increases the tone of the caudal esophageal sphincter while relaxing the pylorus and duodenum. The recommended dose is 0.2 to 0.4 mg/kg intramuscularly or subcutaneously every 8 hours. In very severe cases, metoclopramide can be given continuously by intravenous drip at the rate of 1 to 2 mg/kg per 24 hour period.

The phenothiazine derivative antiemetics block both the chemoreceptor trigger zone and the vomiting center in the brain. Chlorpromazine at a dose of 0.5 mg/kg intramuscularly or subcutaneously every 6

to 8 hours or prochlorperazine 0.1 to 0.5 mg/kg intramuscularly or subcutaneously every 6 to 8 hours will help control vomiting without causing excessive sedation. The phenothiazine derivatives should not be used in dehydrated patients, however, because they block alpha-adrenergic receptors, causing arteriolar vasodilation that further complicates the hypotension resulting from dehydration and shock.

PREVENTION

A variety of vaccines against canine parvovirus are available from commercial sources, both alone and in combination with other canine pathogens. All are effective when administered to seronegative dogs. Both killed and modified live vaccines appear to provide adequate immunity against clinical disease, but it appears that dogs immunized with killed vaccines can be subclinically infected within a few weeks after vaccination.[32] Such subclinically infected dogs shed virus and are a source of contagion for other animals.

The principal challenge for practitioners is to provide protection for young puppies. Even in endemic colonies, puppies do not seroconvert to canine parvovirus until their maternal antibody titers drop below a protective level between 6 to 15 weeks of age, indicating that maternal antibody is itself sufficient to prevent active infection.[22, 23, 30, 33] Similarly, puppies vaccinated while their maternal antibody titers are still high have no evidence of an active immune response. Unfortunately, the amount of maternal antibody required to prevent infection is greater than the amount that interferes with vaccination.[33] As a result, there is a period of several days to several weeks during which the pup is susceptible if exposed to wild-strain parvovirus, but not yet immunizable.

The timing and duration of this critical period of susceptibility are affected by two factors: the immune status of the bitch and the nature of the vaccine used. After ingesting colostrum, puppies have an antibody titer approximating that of their dam, although their is some variability within litters depending on the amount of colostrum ingested. Maternal antibody declines at a fairly predictable rate, with a half-life of approximately 10 days.[33] This means that the age at which a puppy becomes susceptible to infection (or responsive to vaccination) is determined principally by the bitch's antibody titer. Puppies from bitches with low titers may be susceptible as early as 4 to 6 weeks after birth, whereas puppies from bitches with high titers may be refractory to infection for 12 to 16 weeks (Figs. 2 and 3).

The difference between the amount of antibody necessary to protect and the minimum amount that prevents active immunization is determined by the nature of the vaccine. As a general rule, it requires less maternal antibody to suppress response to a killed vaccine (Fig. 3). As a result, the period of susceptibility is longer. Live vaccines vary in their ability to immunize in the face of maternal antibody. In general,
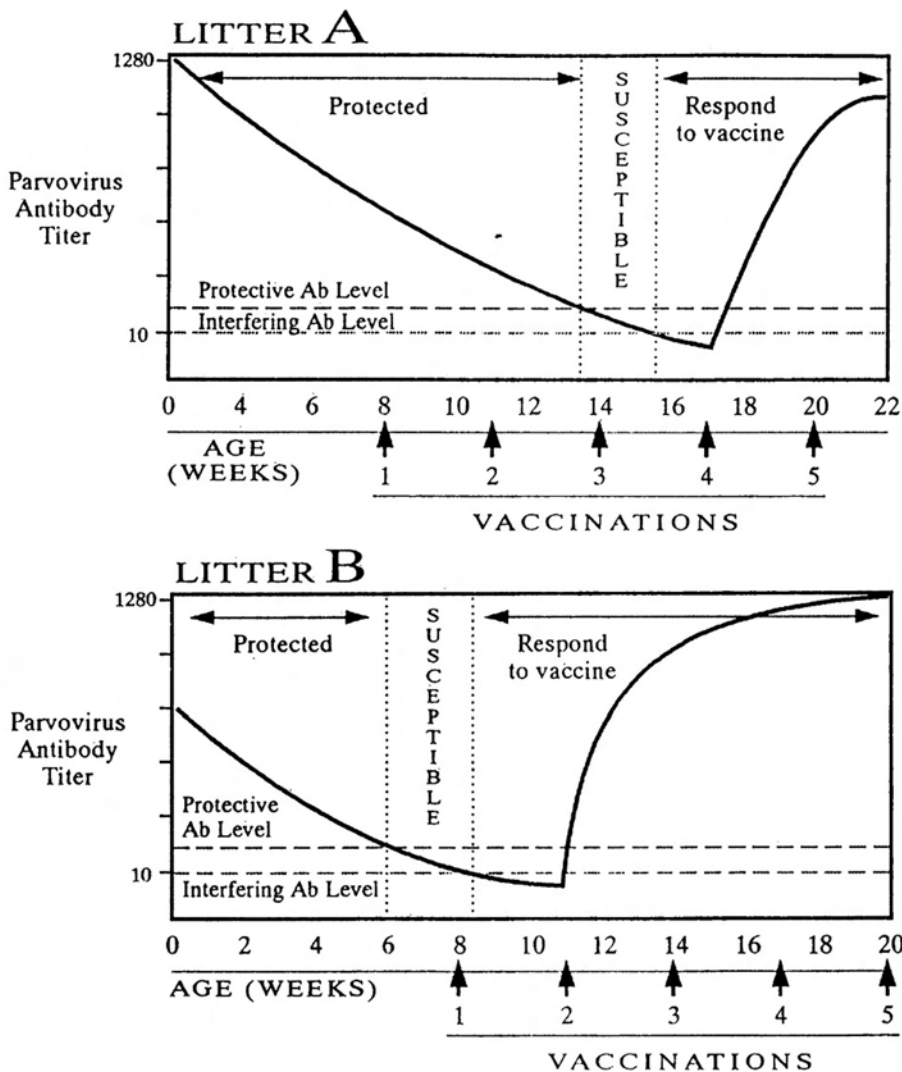
LITTER A

LITTER B

Figure 2. The effect of maternal antibody levels on the susceptibility to infection or vaccination with a modified live vaccine. Two hypothetical litters are illustrated. Puppies with low maternal antibody levels are susceptible to infection and vaccination at an earlier age than puppies with high maternal antibody levels. Only a single successful inoculation with a modified live vaccine is needed to adequately immunize a puppy.

the higher the virus titer in the vaccine and the lower the degree of attenuation, the greater the vaccine's ability to immunize in the presence of antibody. This implies a certain trade-off between safety and immunizing ability; a general rule for vaccines.

Extravagant claims about the ability to "override" maternal antibody have been made for a number of commercial vaccines. In most
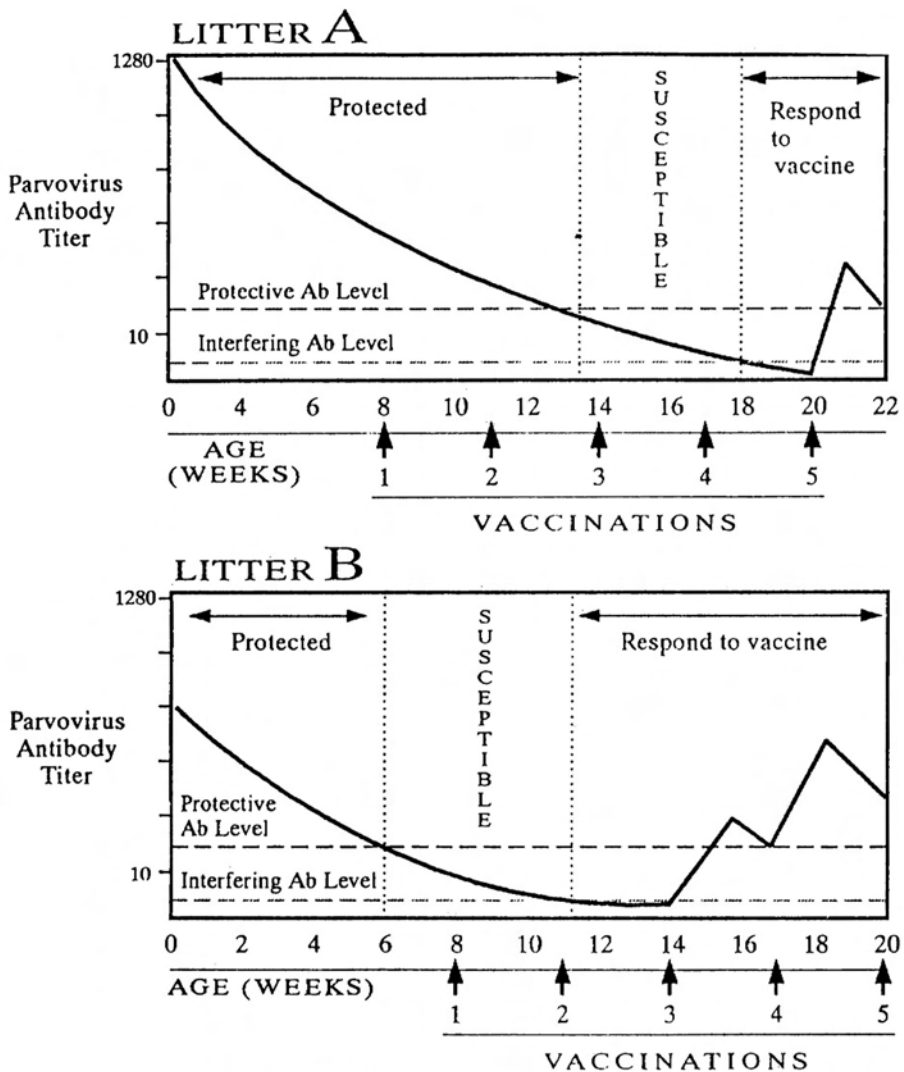
LITTER A

Parvovirus Antibody Titer

1280

Protected

SUSCEPTIBLE

Respond to vaccine

Protective Ab Level

Interfering Ab Level

10

0   4   6   8   10   12   14   16   18   20   22

AGE (WEEKS)

1   2   3   4   5

VACCINATIONS

LITTER B

Parvovirus Antibody Titer

1280

Protected

SUSCEPTIBLE

Respond to vaccine

Protective Ab Level

Interfering Ab Level

10

0   2   4   6   8   10   12   14   16   18   20

AGE (WEEKS)

1   2   3   4   5

VACCINATIONS

Figure 3. The effect of maternal antibody levels on the susceptibility to infection or vaccination with a killed vaccine. Two hypothetical litters are illustrated. Lower maternal antibody levels are required to suppress response to a killed vaccine as compared to a modified live vaccine. The period of susceptibility to infection is longer and the age at which successful immunization occurs is later.

instances, the data presented have been inadequate to substantiate the claims. As a general rule, no commercially available vaccine will immunize before a puppy becomes susceptible to infection. As a result, vaccination alone is inadequate to break an endemic parvovirus cycle in an infected colony, no matter how frequently they are given or what brand is used. Likewise, all practitioners will continue to encounter

cases of parvoviral enteritis in puppies who have received one to several inoculations of CPV-2 vaccines. In such cases, vaccinations failed to protect because an immune response was suppressed by maternal antibodies before the puppies were exposed to virulent CPV-2.

The practical import of these findings is (1) regardless of what vaccine is used, owners and breeders must take steps to minimize the potential exposure of puppies to CPV-2 prior to 20 weeks of age; (2) veterinarians must give a series of inoculations, beginning at the time of first presentation (6 to 8 weeks of age) and continuing through 18 to 20 weeks of age; and (3) veterinarians must be prepared to explain to owners that even the most rigorous vaccination protocol cannot completely eliminate the risk of infection. Although only a single successful inoculation is needed to adequately immunize an animal, it is impossible to predict which inoculation will successfully immunize. The optimal interval between vaccinations will depend on the value of the animal and the assessment of the cost-benefit relationship afforded by more frequent vaccinations. Shorter intervals increase the probability of vaccinating the puppy at the earliest immunizable moment, but they are also increasingly expensive.

The recognition of the 2a and 2b subtypes of CPV-2 raised the specter that current vaccines were inadequate to protect against these new strains. This claim has not been supported experimentally. The differences among the various subtypes of CPV-2 are minor; current vaccines cross-protect against all known strains. The clear consensus is that maternal antibody interference accounts for virtually all supposed "vaccine" failures.

SUMMARY

Canine parvovirus is a truly new pathogen of dogs that emerged in the late 1970s. Initially seen as epidemic disease in all dogs, parvoviral enteritis is now primarily a disease of 1- to 6-month-old dogs. Maternal antibody interference with immunization accounts for the vast majority of vaccine "breaks." Molecular virologic methods have revealed continued evolution of the virus, but this appears to be of greater academic than practical interest. Clinical diagnosis can be definitive in fulminant cases but requires laboratory support—usually demonstration of virus in the feces—in less clear-cut cases. Treatment remains symptomatic, based simply on principles of good supportive care. As the virus is firmly entrenched in both the wild and domestic canine population, elimination of the virus is impossible, and CPV-2 will remain a concern for the small animal practitioner indefinitely.

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