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CORONAVIRAL INFECTIONS

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Synonyms: Coronavirus enteritis, coronavirus pneumonia, coronavirus encephalitis, feline infectious peritonitis, canine coronavirus, bovine coronavirus, porcine coronavirus, elk coronavirus

INTRODUCTION. The coronaviruses have emerged over the past 30 years to become one of the most widely studied virus groups affecting animals (Saif and Heckert 1990; Holmes and Lai 1996). The viruses were initially named based on the disease syndrome they were isolated from, and subsequently shown to cause following experimental inoculation (Pensaert et al. 1970; Stair et al. 1972; Mebus et al. 1975). Coronaviruses are currently placed in the family *Coronaviridae*, and together with the family *Arteriviridae*, comprise a new order: *Nidovirales* (Cavanagh 1997).

Virtually every animal species that has been studied has been shown to be infected by a coronavirus. These viruses are well documented to cause diarrhea and respiratory disease in domestic ungulates, including sheep *Ovis aries*, cattle *Bos taurus*, swine *Sus scrofa*, and horses *Equus caballus*. The coronaviruses infect predominantly neonatal animals, but older cattle and swine are also infected (Collins et al. 1987; Saif and Heckert 1990). The role of coronavirus in causing morbidity and mortality in wild animals is just beginning to be recognized. Notable among the coronavirus infections of wild mammals are feline coronavirus/feline infectious peritonitis (FIP) of large felids, primarily cheetahs *Acinonyx jubatus*, and enteric coronaviral infections of captive wild ruminants and swine (Chasey et al. 1984; Evermann et al. 1988; Heeney et al. 1990; Tsunemitsu et al. 1995; Majhdi et al. 1997). Due to the sparsity of information on coronaviral infections of wildlife, a comparative approach has been taken in this chapter. Important coronaviral infections of ungulates and carnivores are discussed and, whenever applicable, correlated with wildlife species.

HISTORY. The actual prevalence of coronavirus in wild populations has been underestimated due to studies that rely on serologic results to assess prevalence of infection (Gardner et al. 1996). Coronaviral infections are generally limited to the mucosal surfaces of either the respiratory tract or the gastrointestinal tract and therefore may not stimulate high levels of circulating

antibodies (Saif and Heckert 1990; Holmes and Lai 1996). A 1978 serologic survey of caribou *Rangifer tarandus* from the George River area in Northern Quebec, Canada, indicated that 13% had antibodies that neutralized bovine coronaviruses (Tsunemitsu et al. 1995). Lower seroprevalence in wild mammals contrasts with domestic herds, where prevalence of adult animals with antibodies to coronavirus is usually greater than 80% (Rodak et al. 1982). True assessment of coronavirus prevalence would require more frequent testing and/or more sensitive assays, such as polymerase chain reaction (PCR), that detect low levels of virus in feces or respiratory secretions (Shockley et al. 1987; Benfield et al. 1991; Herrewegh et al. 1995). Alternatively, coronavirus infections of wild mammals may be rare, or the animals are inherently resistant to infection and sufficient virus is not shed to infect large numbers of animals in the population at risk.

Coronavirus infections of domestic animals were initially recognized in 1951 and were primarily associated with enteric disease (Barker et al. 1993). The viruses were difficult to culture and, as a result, were primarily detected by histopathology and fluorescent antibody staining of gut sections (Mebus et al. 1975; Langpap et al. 1979). In 1968, the first reports of coronavirus associated with calf scours were noted. The enteric coronaviruses were frequently associated with concurrent infection with rotavirus and enterotoxigenic strains of *Escherichia coli*. It was during this time that electron microscopy (EM) was beginning to be used in the routine diagnosis of viral scours in domestic animals (Pass et al. 1982). Coronaviral infection was regarded as one of the primary causes of calf scours. In 1971, coronaviral infections were noted in domestic canids and felids. Enteric disease was the primary clinical and pathologic form of the canine disease. However, the disease that attracted primary attention in cats was an immune-mediated disorder: FIP. Based on EM of fixed lesions, this disease was considered to be caused by a coronavirus (Barker 1993). In subsequent years, FIP virus was cultured, and Koch's postulates were confirmed. Later, another coronavirus of cats was detected and referred to as feline enteric coronavirus. The first report of a bovine-like coronavirus in wild captive mammals was in sitatunga *Tragelaphus spekei* in 1984 (Chasey et al. 1984).

A parallel group of coronaviruses, murine hepatitis virus (MHV), was being studied in mice in the 1960s.

TABLE 13.1—Coronavirus infections of mammals

	Enteric	Respiratory	Neurologic	Other Manifestations
Bovidae	Bovine coronavirus	Bovine respiratory coronavirus	NR ^a	NR
	Ovine coronavirus	NR	NR	NR
Felidae	Feline enteric coronavirus	Feline infectious peritonitis	Feline infectious peritonitis	Feline infectious peritonitis (ocular)
Canidae	Canine coronavirus	NR	Canine infectious peritonitis ^b	NR
Muridae	Diarrhea virus of infant mice	NR	Murine hepatitis virus	Murine hepatitis virus (ocular)
	Sialodacryoadenitis virus	Sialodacryoadenitis virus	NR	NR
Leporidae	Rabbit enteric coronavirus	NR	NR	Rabbit pleuritis virus
Suidae	Transmissible gastroenteritis virus	Porcine respiratory coronavirus	Hemagglutinating encephalomyelitis virus	NR
Equidae	Equine coronavirus	NR	NR	NR
Primate	Simian coronavirus	NR	NR	NR
Mustelidae	Mink enteric coronavirus	NR	NR	NR

^aNR, not reported.

^bFollowing vaccination.

These viruses were recognized initially in mice held in captivity that had other viral infections, such as murine leukemia virus, and the studies were later expanded to include wild meadow voles *Microtus pennsylvanicus* (Descoteaux and Mihok 1986). The MHV group constitutes a wide range of pathogens from avirulent to virulent (Compton et al. 1993). The virulence of the strains is host genotype specific, suggesting that the host range of coronavirus-induced disease is related to the host genetics (Barthold et al. 1993).

The coronaviruses occupy a wide ecological niche in nature. Table 13.1 list the common coronaviral infections of animals. Although the diseases caused by coronaviruses were initially described in domesticated mammals, it became apparent that wildlife were susceptible to infection and, in some cases, diseases associated with coronavirus (Evermann et al. 1980; Foreyt and Evermann 1985; Roelke et al. 1993; Tsunemitsu et al. 1995).

DISTRIBUTION AND HOSTS. Occurrence of coronaviruses in mammals is widespread. The viruses are enveloped and, as such, are highly labile outside the host (Tennant et al. 1994). Coronaviruses primarily persist in hosts as subclinical infections of the mucosal surfaces of adult animals (Collins et al. 1987). The viruses are intermittently shed in body secretions (saliva, aerosol, etc.) and excretions (feces) throughout life. Viral transmission is unusually high during periods of pregnancy and from young animals that acquire the infection and progress onto disease. It is for this reason that coronaviral diseases are noted in areas of high animal density and during times of parturition, when neonatal animals are at risk.

The host range of the coronaviruses is generally restricted to single or closely related animal species. Interspecies transmission has been reported for canine coronavirus between dogs *Canis familiaris* and cats

Felis catus, bovine coronavirus between cattle and elk *Cervus elaphus*, porcine coronavirus from pigs to dogs and foxes, etc. (McArdle et al. 1992). The host range of the coronaviruses is primarily restricted due to receptors on the surface of host mammalian cells (Holmes and Lai 1996).

ETIOLOGY. The coronaviruses constitute a genus within the family *Coronaviridae* (Cavanagh 1997). Coronaviruses are large, enveloped, positive-sense RNA viruses. The coronaviruses also have the largest genome (27–32 kb) of RNA viruses. The presence of the lipid envelope imparts pleomorphism to size and shape of the virion (Fig. 13.1). The virions mature by budding into intracellular membranes such as the rough endoplasmic reticulum and Golgi apparatus to acquire the lipid envelope containing inserted viral proteins and glycoproteins (Compton et al. 1993). Most coronavirions contain one row of club-shaped peplomers or surface (S) projections approximately 12–15 nm in length, and others contain a second row of short spikes that compose the hemagglutinin-esterase (HE) glycoprotein on the envelope. The coronaviruses have a unique method of replication producing six to seven subgenomic messenger RNAs (mRNAs) with common 3' ends and a 5' leader. The genomic RNA, like the mRNAs, contains a 5' cap and 3' polyadenylated tail. The viral genome encodes for 3–4 structural proteins and several nonstructural proteins. Most of the genome (20 kb) consists of two overlapping open reading frames ORF1a and ORF1b that encode the viral RNA-dependent-RNA polymerase, proteases, and other unrecognized proteins. The remaining 7–12 kb encode for the structural proteins. The coding sequence of the structural proteins is highly conserved in most coronaviruses with the 5'-pol-S-M-N-3'. The unique replication method of a coronaviruses imparts a high rate of mutation due to recombination (Lai 1996). Although a

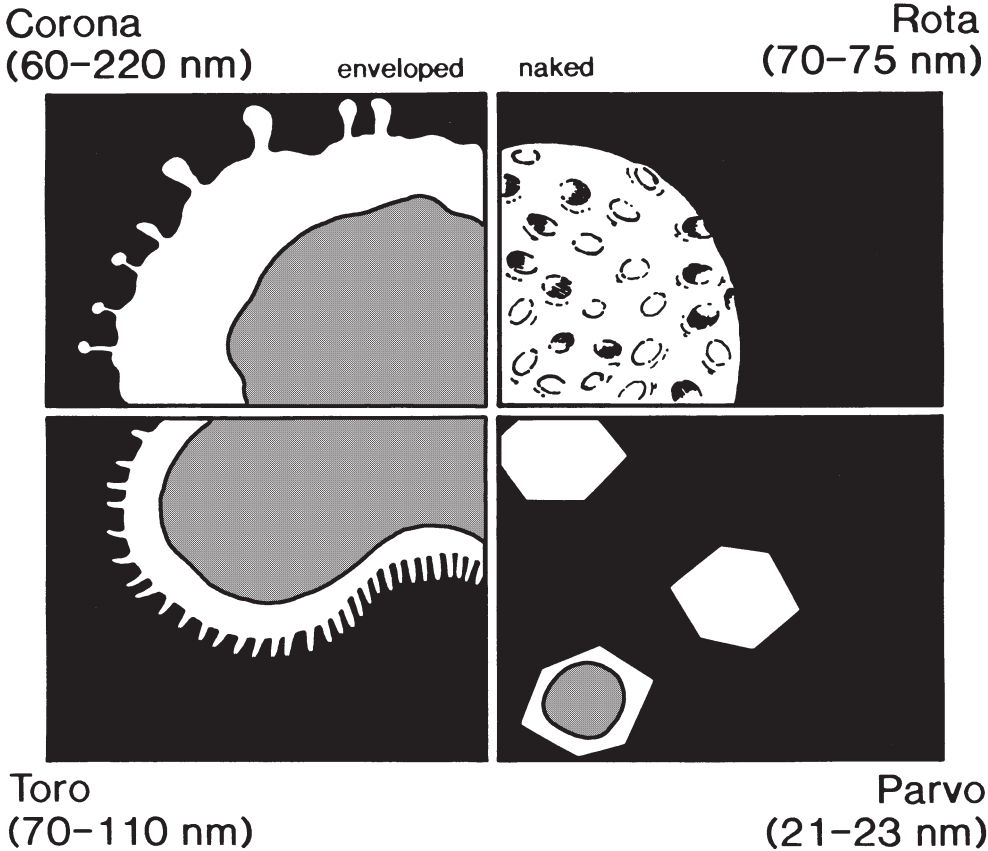


FIG. 13.1— Schematic diagram of the four major enteric viruses of mammals: coronavirus, rotavirus, torovirus, and parvovirus.

majority of the recombinations or mutations are silent, a rare escape mutant may occur and result in altered virulence. It is likely that feline enteric coronavirus mutates to the lethal FIP virus (Evermann et al. 1995; Poland et al. 1996). Once mutation occurs, the susceptibility of the host to disease is regulated by the host genotype and subsequent immune response (Foley and Pedersen 1996).

The mature coronavirus virion includes the nucleocapsid or N protein of 50–60 kDa. The N protein is a phosphoprotein that interacts with viral RNA to form an icosahedral ribonucleoprotein complex, and may also elicit cell-mediated immunity. The glycoprotein M (20–35 kDa) is a membrane-spanning glycoprotein that penetrates the lipid bilayer of the virion envelope three times. The M glycoprotein has a single accessible glycosylation site that is either N- or O-glycosylated, depending on the coronavirus. Antibody to the external domain of the M glycoprotein neutralizes virus in the presence of complement. The M protein may also function to bind the nucleocapsid to the viral envelope during virus budding. The M protein of some coronaviruses can also induce interferon- α . The S

glycoprotein (90–180 kDa) is the structural protein of the peplomers on the surface of the virion. Functions attributed to the S glycoprotein include cell attachment, membrane fusion to mediate entry of the nucleocapsid, and induction of complement-independent neutralizing antibodies. The HE glycoprotein is primarily restricted to some group-II coronaviruses. The protein is a 130–140-kDa disulfide-linked dimer of a 65–70-kDa protein that forms short spikes. Coronaviruses that express the HE bind to 9-O-acetylated neuraminic acid residue on glycoproteins or glycolipids and cause hemagglutination and hemadsorption. The HE also contains acetyl esterase activity that cleaves acetyl groups from the substrate, potentially eluting adsorbed virions and destroying the HE-binding activity of the glycans on the cell membrane. The HE glycoproteins permit initial adsorption of the virus to cell membranes, but subsequent interaction of the S glycoprotein with its glycoprotein receptor may be required for fusion of the viral envelope with cell membranes. The HE is not required for infectivity *in vitro*.

Coronaviruses are not exceptionally stable in the environment (Holmes and Lai 1996). These viruses are

thermolabile and highly photosensitive. Storage at refrigerator or room temperature will result in loss of infectivity over days or months while storage at -20°C – 80°C for 12 years results in minimal loss of virus titer. The more common occurrence of coronavirus infections in the winter months may relate to the fact that these viruses are best preserved by lower temperatures and lower ultraviolet light levels that are prevalent in winter. The lipid envelope of the coronaviruses also makes virions susceptible to chemical inactivation by formalin, phenol, beta-propiolactone, quaternary ammonium compounds, and the lipid solvents ether and chloroform. Most coronaviruses are resistant to trypsin and low pH, which allows for passage through the stomach and upper small intestine to the target cells in the middle to lower small intestine and colon.

Currently, there are three distinct antigenic groups of coronaviruses. Most of the related viruses share common antigenic epitopes on the nucleocapsid of the virus and nucleocapsid gene sequences. There is also cross-reactivity observed for the S and M structural proteins.

TRANSMISSION. Coronaviruses are shed in mucosal secretions from the upper respiratory tract and in excretions from the gastrointestinal tract (Collins et al. 1987; Kapil and Goyal 1995). Transmission is generally regarded as horizontal from parent to offspring postnatally. It may also occur from one adult to another adult in close proximity. This may be the likely scenario with cattle, elk, deer, and muskox *Ovibos moschatus* that commingle. Evidence for vertical transmission has not been reported for the coronavirus family.

EPIDEMIOLOGY. There have been limited prevalence studies for coronaviral infections of wild mammals. Coronavirus infections of domestic cattle, pigs, dogs, and cats are regarded as endemic, with greater than 80% of the populations seropositive by 1 year of age (Barker et al. 1993). In wild populations, several factors might limit coronavirus infection. These include low animal density, limited interspecies transmission, no insect vectors, high lability of the virus outside the host, and restricted host range due to specific viral receptors. This is generally reflected in seroprevalence studies of wild animals, such as canids to canine coronavirus (1.7%), felids to felid coronavirus (2%), and various bovines to bovine coronavirus (range, 6.6%–13.3%) (Evermann et al. 1980, 1988; Foreyt and Evermann 1985; Tsunemitsu et al. 1995). There are exceptions, and one may argue that when wild mammals are managed to any extent, such as on common winter feeding grounds, the risk of infection increases accordingly. The cheetah's exposure to feline coronavirus varies according to the habitat and may reflect incursion by domestic cats or dietary exposure to cross-reacting coronaviruses of feral swine (Evermann et al. 1988; Heeney et al. 1990).

CLINICAL SIGNS. Coronavirus infections of mammals result in at least three major disease manifesta-

tions. The first, and most common, is enteritis, followed by respiratory dysfunction ranging from rhinitis to pneumonia, and then systematic disease characterized by hepatitis and/or peritonitis (Barker et al. 1993).

The hallmarks of enteric coronavirus infections are tropism for gastrointestinal epithelial cells and failure to spread systemically. The enteric coronaviruses infect and destroy enterocytes, resulting in villous atrophy and fusion of adjacent villi. The loss of function of the mature absorptive cells leads to reduced absorptive surfaces in the intestine (Barker et al. 1993).

The clinical signs are a direct result of intestinal cell damage and manifested as a malabsorptive, maldigestive diarrhea. In case of severe diarrhea, dehydration occurs and death ensues within 24–48 hours after onset of clinical signs.

The respiratory coronaviruses are unique in that the viruses may have adapted to entry via the upper respiratory mucosa to ensure persistence in the host (Kapil and Goyal 1995). Porcine respiratory coronavirus (PRCV), for example, is a deletion mutant of the more virulent enteric coronavirus, transmissible gastroenteritis virus. Thus, PRCV isolates have lost their tropism for the enteric tract and preferentially replicate in the respiratory tract (Rasschaert et al. 1990; Wesley et al. 1990; Sanchez et al. 1992).

The systemic coronaviruses are best characterized by virulent strains of MHV and FIP virus (Evermann et al. 1988; Barthold et al. 1993). Both of these diseases appear to have an immune component that augments the disease. These viruses have a propensity to infect and persist in macrophages. In the case of FIP and captive felids such as cheetahs, the disease is characterized by a fatal immune-mediated vasculitis. Other large felids, such as the lion *Panthera leo*, do not appear susceptible to disease, although evidence of infection has been reported, based on serologic studies (Heeney et al. 1990).

PATHOGENESIS AND PATHOLOGY. The enteric coronaviruses infect enterocytes throughout the length of the villi and the length of the small intestine (Saif and Heckert 1990; Holmes and Lai 1996). The lesions are a direct result of the cytolytic nature of the virus (Barker et al. 1993). Absorptive epithelial cells, which line the small intestinal villi, are destroyed by the coronavirus and exfoliate. Epithelial cells on villi are constantly being replaced by cells that originate in the crypts and migrate up the sides of the villi. The turnover rate of these cells is slower in immature animals, leading to less rapid repair of villous atrophy. Loss of virus-infected cells results in marked shortening of villi, reduced absorptive capacity of the small intestine, and malabsorptive diarrhea. Lesions and consequences are most severe in young animals. Bovine enteric coronaviruses produce a persistent infection of villous enterocytes throughout the distal portion of the small intestine and colon.

Gross lesions include milk- or bile-stained fluid in the stomach. The small intestine is usually thin walled,

flaccid, and contains yellow fluid with flecks of mucus. There is an absence of fat absorption in the mesenteric lymphatics. The colon and cecum are often filled with watery fluid. Microscopically, the principal lesion is marked shortening or atrophy of the villi due to the exfoliation of the absorptive epithelial cells. Villi appear stumpy and club shaped, and fusion between villi is common. The virus does not replicate in crypt cells, which provide the replacement cells for the villi. Crypt epithelium is usually hyperplastic, indicating increased mitotic activity. In bovids, the colon may contain exfoliated, flattened, squamous epithelium and mild inflammation in colonic glands (Barker et al. 1993).

Lesions of FIP are markedly different than those described for enteric coronavirus infections. At necropsy, these cats are in poor to emaciated body condition and have abdominal distension due to fluid accumulation. Peritonitis occurs in most but not all animals with FIP. Serosal surfaces are often covered with fibrin, giving them a granular appearance, and granulomas in liver, spleen, kidney, and small intestine are common. Abdominal and thoracic lymph nodes may be enlarged. In some cases, lesions are restricted to inflammation in the eyes and nervous system. The characteristic microscopic lesion is generalized vasculitis and perivasculitis especially of venules. Neutrophils, lymphocytes, plasma cells, and macrophages accumulate in and around affected vessels. Lesions in the various organs result primarily from vascular damage (Barker 1993).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSES.

Methods for diagnosis of coronavirus infections in wild mammals are similar to those used to detect viral infections in domestic animals (Benfield and Saif 1990; Crouch et al. 1984; Gorham et al. 1990; Deeb et al. 1993). Diagnosis is based on clinical signs; detection of virus, viral antigen, or viral nucleic acid; serology; and microscopic lesions. Clinical signs are of little diagnostic value, because coronaviral infections cause signs that mimic other enteric infections. Virus isolation is often unsuccessful, because coronaviruses are difficult to adapt to cell culture and are present in excretions and secretions that contain bacteria and other compounds cytotoxic to cell cultures (Benfield and Saif 1990). Detection of coronavirus particles by EM and immunoelectron microscopy (IEM) of fecal material continues to be the "gold standard" for diagnosis of enteric coronavirus infection in domestic mammals (Stair et al. 1972; Langpap et al. 1979; Heckert et al. 1989) and wild mammals (Chasey et al. 1984; Tsunemitsu et al. 1995) (Fig. 13.2). Detection of viral antigens in the cytoplasm of infected cells in frozen intestinal or fixed sections by immunofluorescence (IF) or immunohistochemistry (IHC) is also economical and reliable for diagnosis of coronavirus infections (Pensaert et al. 1970; Mebus et al. 1975; Shoup et al. 1996). Other techniques such as enzyme-linked immunosorbent assays (ELISA) (Crouch et al. 1984; Reynolds et al. 1984; Smith et al. 1996) and cDNA probes (Shockey

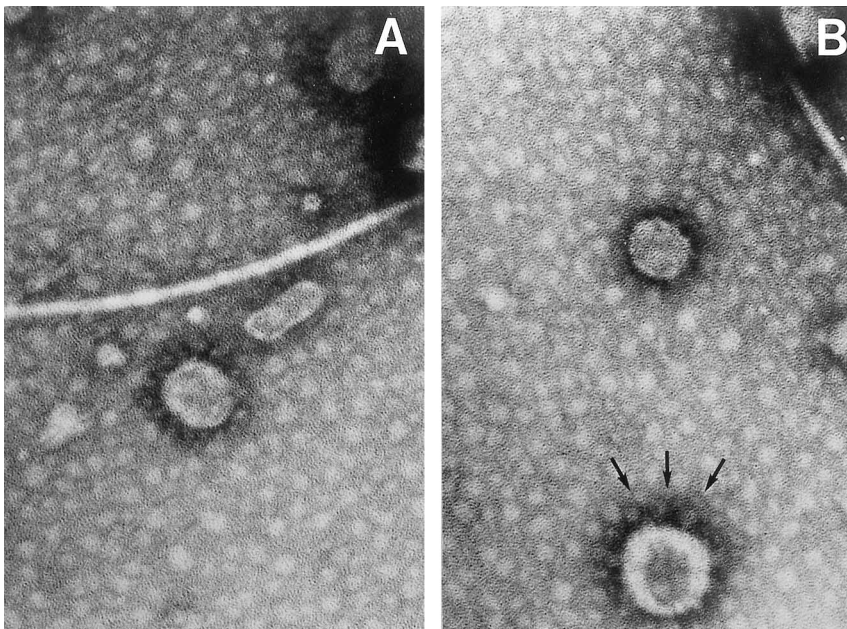


FIG. 13.2—Cheetah coronavirus particles. Size ranges from 120 nm (A) to 150 nm (B). Note peplomers extending from the intact virion (arrows). The virus particles are in a fecal sample obtained from clinically normal cheetah. $\times 210,000$.

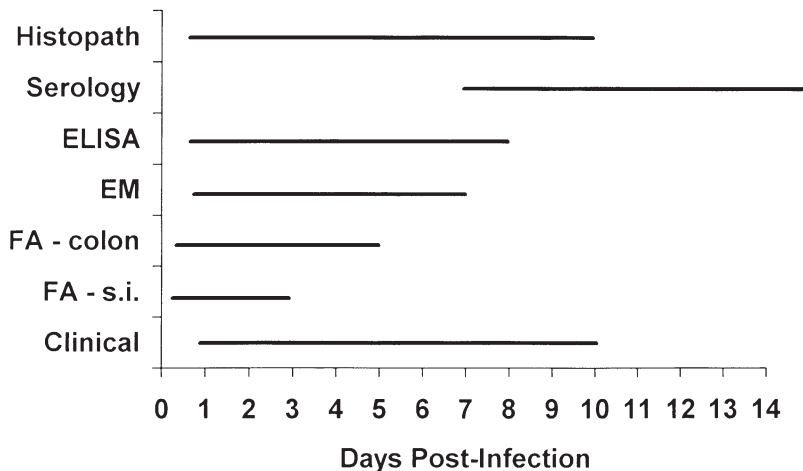


FIG. 13.3—Schematic depicting the most opportune times to diagnose coronaviral infections: Histopath, histopathology; ELISA, enzyme-linked immunosorbent assay; EM, direct or immunoelectron microscopy; FA, fluorescent antibody; s.i., small intestine; and *clinical* means signs of diarrhea, vomiting, respiratory dysfunction. Days after infection indicates the days following exposure.

et al. 1987; Benfield et al. 1991), have not been as reliable as EM and IEM for detection of coronavirus particles in fecal material. Microscopic lesions of villous atrophy are not specific for coronavirus infections and need to be confirmed by additional tests such as IF or IHC to detect the presence of coronaviral antigens in the remaining enterocytes.

Each of the various diagnostic assays mentioned have specific windows of sensitivity for detection of virus and viral antigens (Fig. 13.3). Coronaviruses are cytolytic, and the exfoliation of infected cells into the intestinal lumen limits the usefulness of techniques such as IF and IHC too early in the infection, whereas EM and ELISA can detect virions or viral antigens in fecal material for longer periods. Loss of epithelial cells especially narrows the window of opportunity for detection of coronaviruses by techniques such as IF and IHC that require the structural integrity of the complete cell for identification of viral antigen.

There is a need to develop more sensitive and reliable assays for detection of coronaviruses in the excretions and secretions in which the virus is shed in nature. Recent use of PCR technology, such as that used to detect feline coronavirus in body fluids of cats, may offer a possible method of viral detection (Herrewegh et al. 1995). Serology (neutralization and hemagglutination-inhibition assays) are useful only for retrospective diagnosis and epidemiologic surveys. Serologic surveys have been most commonly used to detect the presence of coronaviruses in wild mammals, such as caribou (Elazhary et al. 1981).

Coronaviruses produce few clinical signs or lesions that are specific to these viruses only (Barker et al. 1993). Differential diagnosis includes other enteropathogenic viruses (rotavirus, adenovirus, torovirus,

parvovirus, and bovine viral diarrheal virus), bacteria (*Campylobacter*, *Clostridium*, enterotoxigenic and enterohemorrhagic *Escherichia coli*, *Salmonella* spp., and *Serpulina* spp.), parasites (various nematodes and trematodes), and protozoa (coccidia and *Cryptosporidium*) that induce diarrhea (Evermann et al. 1980; Saif and Heckert 1990; Martin and Zeidner 1992; Koopmans and Horzinek 1995).

IMMUNITY. Localized immunity is critical to minimizing the impact of coronaviral infections at the respiratory and gastrointestinal mucosal surfaces (Gustafsson et al. 1996). During the first few weeks of life, neonatal mammals depend on colostral immunoglobulin G (IgG) for passive immunity (Kapil et al. 1994). This form of protection has been referred to as *lactogenic immunity* and persists for several weeks after colostral immunoglobulins have waned. The predominant immunoglobulin in milk is IgA in species with simple stomachs and IgG1 in ruminants (Lamm et al. 1996). Eventually, secretory IgA is generated by the host in the form of active immunity. This form of immunity is antigen dependent and is constantly in stages of reinfection, restimulation, and localized protection (El-Kanawati et al. 1996; Lamm et al. 1996).

TREATMENT AND CONTROL. The control of coronaviruses depends heavily on adequate intake of colostral antibody and maintaining the neonate on the dam for sustained periods. Neonates born to first-lactation animals are more prone to coronavirus-induced diarrhea due to lack of protective antibody.

Treatment of coronaviral diarrhea is usually symptomatic, with fluid rehydration, electrolyte therapy, and provision of a warm, dry environment (Barker et al. 1991; Saif and Heckert 1990). Modified-live vaccines have been used in commercial bovine and porcine herds with limited success.

Biosecurity is the main defense against coronavirus infections in domestic herds. The missing link in the epidemiology of coronaviral infection is where the virus "overwinters" during warmer months of the year, when the prevalence of infection is lower (Gulland 1996). Subclinically infected adult animals are suspected carriers (Collins et al. 1987; Tennant et al. 1994; Storz et al. 1996). High animal density and commingling with domestic species should be avoided with captive wild mammals.

PUBLIC AND DOMESTIC ANIMAL HEALTH CONCERNS. Although there are human strains of coronavirus, these are regarded as host specific. There is no recognized zoonotic potential of the animal coronaviruses in humans.

The potential for interspecies transmission of coronaviruses among domestic and wild animals is possible (Evermann et al. 1980; Ballou 1993; Cunningham 1996). The coronaviruses of animals are usually very species specific due to receptor specificity, resulting in cross-infection between closely related species such as wild felids and domestic cats, wild canids and domestic dogs, and less closely related species such as cattle and elk. The potential for interspecies transmission is minimal unless common range or habitat is utilized, since the coronaviruses are extremely labile outside the host animal (Tennant et al. 1994).

MANAGEMENT IMPLICATIONS. It is important to recognize the host range of the respective coronaviruses in order to take appropriate management steps when wild mammals are winter fed, captured for translocation, held captive for research purposes, maintained in zoologic collections, or farmed (Spalding and Forrester 1993). Coronaviruses are not known to be significant pathogens in free-ranging wildlife populations.

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