Austin Journal of Public Health and Epidemiology

Open Access

Austin Publishing Group

Review Article

Review on Canine Coronavirus Disease; Its Clinical Management and Zoonotic Spillover

Mulusew Tesfaye; Tadesse Mihret*; Gashaw Enbiyale; Daniel Workineh
University of Gondar, Ethiopia

***Corresponding author: Tadesse Mihret**
University of Gondar, PO Box. 196, Ethiopia.
Tel: +251932274818
Email: mihretadesse8@gmail.com

Received: November 23, 2023
Accepted: January 03, 2024
Published: January 10, 2024

Summary

Coronaviruses are a diverse group of viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans, as with the recently emerged spillover caused by COVID-19 (SARS-CoV2), which broke out in China's Wuhan seafood market. Human coronaviruses (HCoVs) often have animal origins. Canine coronavirus is a highly contagious viral disease which is a member of the broader coronavirus family with known pathogens in dogs. Both enteric and respiratory coronaviruses are the two common types of canine coronaviruses, and it often causes mild or hard-to-spot illness; however, it can be fatal under certain conditions, particularly in young puppies. Antibiotics are ineffective against coronavirus infection in dogs, but may be useful in controlling secondary bacterial infections and a dehydrated case requires adequate fluid therapy to maintain the fluid and electrolyte imbalances. Canine coronavirus is spread through contact with fecal material from infected dogs, so isolating infected dogs from healthy ones can help reduce disease distribution. The virus is susceptible to the household disinfectants, so cleaning virus contaminated areas and bedding enable to limit the spread of disease. Therefore, this literature review is designed to highlight about the canine coronavirus and its relation with other group of viruses including their public health importance.

Keywords: Coronavirus; Canine Coronavirus; Antibiotics; Dogs

Introduction

Coronaviruses cause respiratory and digestive diseases in vertebrates. The recent pandemic, caused by the novel Severe Acute Respiratory Syndrome (SARS) coronavirus 2, is taking a heavy toll on society and planetary health, and illustrates the threat emerging coronaviruses can pose to the well- being of humans and other animals. Coronaviruses are constantly evolving, crossing host species barriers, and expanding their host range. In the last few decades, several novel coronaviruses have emerged in humans and domestic animals. This is because of the high mutation frequency and broad host ranges of this virus [1]. Corona viruses are enveloped viruses with a large (27– 32kb) single-stranded, positive-sense RNA virus that are highly prevalent in animal and human population. The viral RNA is packaged by the nucleocapsid protein (N), which are themselves enclosed in an envelope containing at least three virally-encoded membrane proteins: the spike (S) glycoprotein, transmembrane protein (M) and small membrane protein (E) [2]. Different coronaviruses cause infections in many species of animals and birds [3] from these canine coronavirus is a coronavirus affecting dogs. Canine coronavirus (CCoV) and canine respiratory coronavirus (CRCoV) are common viral pathogens responsible for mild to severe enteritis or respiratory symptoms in dog populations [4].

Canine coronavirus (CCoV), a member of the family Coronaviridae, is an enveloped, positive- stranded RNA virus responsible for enteric disease in young puppies. CCoV has been detected in the feces of naturally infected puppies for up to180 days [5]. Canine Coronavirus disease is an intestinal infection of dogs that is usually short-lived, but may cause considerable abdominal discomfort for a few days. The cause is a virus of the Coronavirus family. The virus gets its name from the fact that when viewed from above under an electron microscope the virus has a ring of projections which appear like a coronet [3].The first observation of canine coronavirus (CCoV) infection was reported in 1971, when Binn and colleagues isolated a coronavirus (strain 1-71) from dogs with acute enteritis in a military canine unit in Germany [2]. Canine coronaviruses are well known pathogens in dogs causing usual mild local disease affecting the gastro-intestinal tract or the respiratory tract, but may also cause systemic infections [4]. More recently, strains of this enteric canine coronavirus have been identified with different properties, including pantropic strains of the enteric virus which causes fatal multisystemic illness. Constant continued evolution of canine coronavirus, through accumulation of point mutations. A point mutation occurs in a genome when a single base pair is added, deleted or changed. While most point mu-

Citation: Tesfaye M, Mihret T, Enbiyale G, Workineh D. Review on Canine Coronavirus Disease; Its Clinical Management and Zoonotic Spillover. Austin J Public Health Epidemiol. 2024; 11(1): 1156.

tations are benign, they can also have various functional consequences, including changes in gene expression or alterations in encoded proteins within the genome and genetic insertions or deletions, leads to the regular emergence of viruses with altered properties, including their tropism and virulence [6].

Coronaviruses in humans and domestic animals are closely related and have emerged recently and at an increasing rate [7]. The majority of human infectious diseases are caused by pathogens that first spread in non-human animal species. "Zoonotic spillover" refers to the spread of infections from wild animals to humans [8]. But still little is known about host ranges and cross-species transmissions of coronaviruses. Surveillance efforts of coronaviruses in the wild are underway [9], which are important for identifying new coronaviruses with zoonotic potential [10], tracking spillover pathways, and potentially filling in the host range gaps of known coronaviruses in humans and domestic mammals [1].

Alphacoronavirus 1 CoV resembling Canine CoV (CCoV; named CCoV-HuPn-2018), isolated from nasopharyngeal swabs of a small number of pediatric patients (8 of 301) in Sarawak, Malaysia, hospitalized with pneumonia between 2017 and 2018. CCoV-HuPn-2018 resembles a CCoV type II, but also shares high nucleotide sequence similarity with other type II *Alphacoronavirus* 1 CoVs: feline CoV (FCoV2) and porcine Transmissible Gastroenteritis Virus (TGEV). Subsequently to the original Vlasova *et al*. report, there was identification of a genetically similar virus (99.4% identical across the genome, compared to CCoV-HuPn-2018) from the urine samples of a medical worker returning from Haiti who was experiencing mild fever and malaise [11] named HuCCoV_Z19Haiti, suggesting that human infection with this CCoV virus may have occurred in multiple locations. Both studies report on genome-wide recombination history of the virus, implicating a FCoV type ll virus as a significant contributor [12].

Therefore, the main objective of this seminar paper is:

- To highlight about the canine corona virus disease and its clinical managements.
- To describe zoonotic spillover of canine corona virus
- To find out the relation between canine corona virus and other corona virus strains including human coronavirus.

Coronaviruses

Coronavirus Taxonomy and Genomic Oorganization

Coronaviruses cause a substantial fraction of human colds and a host of common respiratory infections in many other animals, including economically important diseases of livestock, poultry, and laboratory rodents. Moreover, although these viruses were not known for producing more than mild infections in humans prior to the SARS epidemic, veterinary corona virologists have long been aware of their potential for producing lethal infections in animals [13]. It constitutes the subfamily Orthocoronavirinae, which further belongs to the family Coronaviridae that lies within the suborder Coronavirineae, order Nidovirales. Based on the genetic and serological characteristics of coronaviruses, the subfamily Orthocoronavirinae is classified into four genera: Alpha coronavirus (αCoV), Beta coronavirus (βCoV), Gamma coronavirus (γCoV), and Delta coronavirus (δCoV) [14].

Currently, CoVs are classified into three different antigenic groups, although divergent CoVs have been identified in bats and wild carnivores in recent years, thus suggesting revision of CoV taxonomy [15]. Depending on their antigenic and genetic properties, CoVs are classified into three groups [16]. The major group of CoVs comprises porcine Transmissible Gastroenteritis Virus (TGEV), Feline Coronavirus (FCoV), Canine Coronavirus (CCoV), HCoV-229E, and Porcine Epidemic Diarrhea Virus (PEDV). The second group consists of Murine Hepatitis Virus (MHV), Bovine Coronavirus (BCoV), HCoV-OC43, Porcine Hemagglutinating Encephalomyelitis Virus (HEV), Rat Coronavirus (RtCoV), and Equine Coronavirus (ECoV). The third group comprises IBV, Turkey Coronavirus (TCoV), and Pheasant Coronavirue [17].

All coronavirus genomes are arranged similarly and are the largest known RNA genomes (27–32 kb). The replicase locus is encoded within the 5′ region of the genome that included two overlapping open reading frames [ORFs 1a and 1b with a Ribosomal Frame Shift (RFS) site and several non- structural proteins (nsp)] and the structural proteins within the 3′ region [16]. Structural proteins comprise spike (S), envelope (E), membrane (M), nucleocapsid (N) and internal proteins, as well as hemagglutinin esterase glycoprotein in the beta coronaviruses (forming a second type of surface projection). Structural proteins with functions

In virion structure and morphogenesis contribute significantly to viral spread in vivo and in antagonizing host cell responses. Conserved nonstructural proteins also have functions in antagonizing host responses and enzymatic activities in RNA metabolism or protein processing [18].

Coronaviruses –Host Interaction

Coronaviruses in humans and domestic animals are closely related, and have emerged recently and at an increasing rate. The circumstances associated with their emergence are high-animal-density environments that favor interspecies interactions, such as kennels, shelters, farms, and markets, which increase disease prevalence and promote cross-species transmission. Indeed, studies show that seroprevalence of CCoV is higher in kennels compared to the rest of the dog population, and shelters co-housing dogs with cats harbor recombinant canine-feline coronaviruses [19].

Corona viruses are constantly evolving, crossing host species barriers, and expanding their host range. In the last few decades, several novel corona viruses have emerged in humans and domestic animals. Novel corona viruses have also been discovered in captive wildlife or wild populations, raising conservation concerns. The evolution and emergence of novel viruses is enabled by frequent cross-species transmission. It is thus crucial to determine emerging coronaviruses' potential for infecting different host species, and to identify the circumstances under which cross- species transmission occurs in order to mitigate the rate of disease emergence [1]. Agriculture and industrialization expanded the global abundance of humans and domestic mammals (i.e., livestock and pets). Today, their combined biomass makes up 96% of all mammalian biomass on Earth. This may be the primary reason for disease emergence in humans and other animals. To help curb coronavirus disease emergence, it is important to identify current host ranges of existing coronaviruses in humans and domestic animals, and the circumstances associated with their cross-species transmission [20].

Coronavirus cause severe diseases in different animals such as dogs, cats, pigs, chicken, cows, camels and humans, as with the recently emerged spillover caused by COVID-19 (SARS-CoV2), This broke out in China's Wuhan seafood market in December 2019 [21]. Epithelial cells are the first line of host defenses against viral infection. CoVs pathogenesis is characterized by diff use alveolar damage to the lungs, epithelial cell proliferation, and elevation in macrophages. Moreover, CoV infections are associated with multinucleate giant cells, infiltration of macrophage, or epithelial cells known as putative syncytium-like formation [17].

Canine Coronavirus (Ccov)

History

Canine coronavirus infection was first reported in 1971, when Binn and colleagues first isolated a coronavirus (strain 1-71) from dogs with acute enteritis in a canine military unit in Germany. Then several CCoV outbreaks have been reported worldwide, showing that CCoV is an important enteropathogen of dogs. Serological and virological investigations have demonstrated that CCoV is widespread in dog population, mainly in kennels and animal shelters [16]. The main predilection site of CCoV infection is the gastrointestinal tract. Canine Enteric Coronavirus (CECoV) infection is associated with high morbidity and low mortality [17].

Historically, severe cases of canine coronavirus infection have been associated with coinfection with canine parvovirus, but deaths due to canine coronavirus have increased recently in the absence of known coinfection, especially in high-density housing situations. Because there are many causes of diarrhea in dogs, clinical suspicion of canine coronavirus infection should be confirmed by laboratory-based procedure [6].

A novel coronavirus was associated with canine infectious respiratory disease, so-called "kennel cough". It was first discovered in 2003 in dogs housed at a rehoming kennel in the United Kingdom due to this CRCoV is considered an emerging infection [22]. The virus is genetically distinct from the enteric canine coronavirus; enteric canine coronavirus is classified as an alpha coronavirus whereas canine respiratory coronavirus is a beta coronavirus that is genetically similar to bovine coronavirus and the human "common cold" coronavirus OC43. Unlike the enteric canine coronavirus, canine respiratory coronavirus possesses a Hemagglutinin-Esterase (HE) gene [6].

Since 2004, more virulent CCoV strains with systemic disease have been reported without obvious co-infections. It is an emerging type of CCoV-IIa was found to be able to produce a generalized form of the diseases similar to Severe Acute Respiratory Syndrome coronavirus (SARS-CoV). Among these infections, CB/05 was identified as a pantropic, highly pathogenic variant of CCoV type II which could be detected in the internal organs and caused both enteric and systemic signs [23]. It was named as pantropic CCoV, because of its potential to cause a systemic infection. Some of the dogs were co-infected with parvovirus, which may contribute to the disease syndrome [24].

Etiology and Mmorphology

Canine coronavirus, named after their crown-shaped spike surface proteins [3].Two types of canine coronaviruses are known, canine coronavirus (CCoV) and canine respiratory coronavirus (CRCoV). Both are member of the family Coronaviridae, which represent single- stranded, positive-sense RNA enveloped viruses. (CCoV) belongs to the sub-family alpha coronavirus and CRCoV to beta coronavirus. CCoV has been detected in the feces of naturally infected puppies for up to 180 days [5] since the main predilection site of CCoV infection is epithelial cells in the gastrointestinal tract. CCoV is divided into two genotypes, CCoV type-I (CCoV-I) and type-II (CCoV-II). Canine Enteric Coronavirus (CECoV) infection is associated with high morbidity and low mortality [17].

Molecular Characterization and its Relation to Human Coronaviruses (Covid)

Molecular characterization is a broad term that refers to using molecular markers, including DNA, RNA, and proteins, to determine the genetic characteristics of cells or tissues. Molecular characterization can play an important role in how diseases are diagnosed and treated and how they respond to treatment. Coronaviruses have the largest genomes (27 to 32 kb) of all the RNA viruses and replicate by a unique mechanism that result in a high frequency of recombination. The genome includes 7 to 10 Open Reading Frames (ORF) that encode both structural and non-structural proteins. Gene 1 consists of two overlapping regions (ORF1a and ORF1b) that are translated into a polyprotein, the precursor of the viral replicase (Rep). The ORF differ markedly among coronaviruses in number, nucleotide (nt) sequence, gene order and in methods of expression [25].

The CCoV genes are organized in the following order: replicase complex (open reading frame 1ab [ORF1ab]), spike (S) gene, ORF3abc, envelope (E) gene, membrane (M) gene, nucleocapsid (N) gene and ORF7ab [26]. The CCoV is subdivided into two distinct serotypes CCoV-I and CCoV-II. The main differences between the two are present in the spike protein gene and, in addition, CCoV-I has a unique intact ORF 3 downstream of the S gene [2]. The genome of the CRCoV contains ORF1ab, Non-Structural (NS) protein, Hemagglutinin-Esterase (HE), S, NS protein, E, M, N, and internal N proteingene sequences with similarities of more than 95% to the BCoV [27].

CCoV, designated HLJ-071, from a dead 5-week-old female Welsh corgi with severe diarrhea and vomit. Sequence analysis suggested that HLJ-071 bearing a complete ORF3abc compared with classic CCoV isolates (1-71, K378 and S378). In addition, a variable region was located between S gene and ORF 3a gene, in which a deletion with 104 nts for HLJ-071 when compared with classic CCoV strains 1-71, S378 and K378. Phylogenetic analysis based on the S gene and complete sequences showed that HLJ-071 was closely related to FCoV II. Based on major structural protein spike protein, HLJ-071 was closely related to FCoV WSU79-1683 and domestic strain HLJ-073, but it is different from other Chinese strains B135/JS/2018, B194/GZ/2019, B639/ZJ/2019, B203/GZ/2019 and B447/ZJ/2019 [23].

Sequence analysis of CCoV detected in fecal samples from diarrheic dogs in the South of Italy shows multiple substitutions accumulating over a fragment of the M gene. These preliminary observations gave a meaningful impulse to the study of the CCoV genetic evolution. In addition, a genetic drift to FCoV type II was also observed in the sequence of CCoV detected in the faeces of two naturally infected pups during the late stages of long-term viral shedding. It was thus postulated that the dogs might have been infected by a mixed population of genetically different CCoV, or that the viruses detected in both the pups were the result of mutation/recombination [28].

Various mutations were detected at five different sites in the partial amino acid sequences of the S gene (approximately 222 amino acids). Substitutions were found at position 70 (D→E, S, N), 127 (E→D, A), 159 (T→P), 189 (V→L), and 193 (V→I, T). Some of these mutations might be used to distinguish pantropic from enteric strains [29]. The molecular basis of the change of virulence and tropism is being investigated through the assessment of a reverse genetics system similar to that established for feline infectious peritonitis virus [30].

Canine respiratory corona virus possesses the canonical genome organization of the group 2 CoVs [31] Briefly, proceeding from the 5'end of the genome are the genes encoding for the replicase complex and for the structural proteins (hemagglutinin-esterase, HE; spike, S; envelope, E; membrane, M; nucleocapsid, N), expressed through a 3'coterminal nested set of subgenomic mRNAs by a process of discontinuous transcription [32].

Sequence analysis of the viral RNA 3'end of an Italian CRCoV, strain 240/05, together with the sequence comparison with extant bovine-like viruses including the sole CRCoV strain 4182 previously described. Interestingly, although the structural proteins show the same features of CRCoV 4182, the genomic region between the spike and the envelope protein genes of CRCoV 240/05 encodes for three distinct products, including the equivalent bovine 4.9 kDa non-structural protein and a truncated form of the 4.8 kDa protein, whereas CRCoV 4182 has a unique 8.8 kDa protein [33]. In recent years, an emerging type of CCoV-IIa was found to be able to produce a generalized form of the diseases similar to Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) [4].

The study by indicates CCoV-BJ70 and CRCoV-BJ202 belong to two distinctly different subgroups with close relationships with strains isolated from relatively near regions, based on the N gene phylogenetic tree. The CCoV-BJ70 clustered with other CCoVs in the Alphacoronavirus genus, including a Chinese strain isolated from deceased giant pandas, but was distinct from heterologous coronaviruses HCoV-229E and NL63. CRCoV-BJ202 was closely related to a Korean strain: CRCoV-K37, as well as HCoV-OC43. Furthermore, N protein identity between CCoVs and HCoVs also confirmed the phylogeny. Notably, the N protein identity observed between CCoV-BJ70 and HCoVs was only 25.5% to 39.9%, but was highly similar with other CCoV strains. However, CRCoV-BJ202 has a high identity of 96.7% to HCoV-OC43, suggesting that CRCoV might share the same origin with HCoV-OC43 or recombination has occurred between them. Although the phylogenic relationship and amino acid sequence similarity was observed, the potential of cross- reactivity between these coronaviruses is still unclear [34].

Genomic Relationship among the Different Coronaviruses

The scientific community has searched in diverse areas to understand the viral–host interactions to work in treatment alternatives and stop the disease progression mainly since the COVID-19 pandemic began, although there are non- genetic and genetic factors associated with these interactions. From the epigenetic studies is possible to evaluate the mechanisms as the virus interferes with the host immune response and quickly spread infection highlighted the importance of host-virus interactions through the SARS-CoV-2 epigenetics, however, coronavirus pathogenesis results from the complex epigenetic mechanisms and depends on the virus ability to enter, replicate and affect the host immune system. These mechanisms that modulate and regulate host gene expression include histone modifications chromatin remodeling, non-coding RNAs, and DNA methylation [35]

For many years, the CoVs have been known in both animal and human medicine. CoVs posse large genomes and show an exceptional genetic plasticity with rapid genetic evolution and a change of the antigenic profile, demonstrating adaption to a variety of new hosts or reservoirs and tissue tropism. These characteristics results of the viral replicase mechanism, such as RNA dependent-RNA polymerase and helicase, due to the inclusion of error nucleotides at each replication cycle, accumulating changes or mutations in the viral genome or the recombination mechanism allowing the CoVs acquire new biological properties [36].

In coronaviruses, the selection of CpG suppressed clones and cytosine deamination are the main biological factors responsible by codon usage bias. Recombination was frequently observed between different strains of the same CoV or other CoVs. The described ideal hosts for Alpha- and Betac-oronaviruses are mammals, bats, and rodents, including several zoonotic and human CoVs, and the Gamma- and Delta- coronaviruses are mainly detected in birds, demonstrating some genomic differences among these genera. Although all CoVs present a similar organization of the genome, some conserved genes present additional ORFs [37].

All members of Betacoronaviruses possess two papain like proteases (PL1 pro and PL2 pro), Haemagglutinin Esterase (HE) genes and the S proteins are cleaved into the S1 and S2 domains, except for SARS-CoV and bat-CoVs that only contain one PL pro, no encode HE, unique S domain and the sequence for the TRS is ACGAAC in the E gene instead of CUA AAC. From the CoV genomes, the proteins that demonstrate more variability is the S proteins, and when there are two domains from these, the S1 domain is the most variable [38].

Recombination and Emergence of CCoV Variants with Altered Pathogenicity

Coronaviruses have high potential for emergence of novel variants with altered tropism and pathogenesis. In large part this can be explained by several factors: a combination of recombination and mutation within the viral genome and that many coronaviruses exist as quasi-species, the availability of natural reservoirs for the virus and the modular nature of the viral spike protein [39]. Recent studies have highlighted the extraordinary complexity of canine coronavirus genomics. The increased likelihood of high-density housing for dogs increases the viral load of coronavirus in the population, and increases the likelihood of novel viruses emerging within dogs. It is now well-established that the feline coronavirus FIPV WSU-79-1146 arose following recombination with a canine coronavirus, and other recombinant canine-feline viruses have been identified [40]. Increased co-housing of dogs with other species, Particularly cats, also increases the chance of novel recombinant coronaviruses emerging across species [41].

Pathophysiology

Viral Lifecycle: The cell tropism CCoVs has been studied by experiments conducted in host species. The life cycle of canine coronavirus has been essentially studied in the canine fibrosarcoma cell line (A-72 cells). Infection led to apoptosis, which may be responsible for pathology induced by CCoV infection, the enteric CCoV is thought to infect enterocytes. Blood

monocytes may also support viral replication, as suggested by the presence of viral RNA in blood leucocytes [2].

Pathogenesis: The factors that determine the course of the natural disease caused by CCoV are not well understood. The natural route of transmission is faecal-oral and virus in faeces is the major source of infection. In neonatal dogs the virus appears to replicate primarily in the villus tips of the enterocytes of the small intestine [42]. Infected villous enterocytes undergo degeneration characterized by shortening, distortion and loss of microvilli of the brush border, leading to sloughing of necrotic cells into the lumen. The loss of mature villous enterocytes causes atrophy of intestinal villi, which become attenuated in an attempt to maintain the integrity of the intestinal barrier [43].

Production of local antibodies (IgAs) restricts the spread of the virus within the intestine and arrests the progress of infection. Infected dogs generally shed CCoV in the faeces for 6–9 days post infection, but some naturally infected dogs have shed virus for a period as long as 6 months after clinical signs had ceased [44].

Clinical Findings

Canine Enteric Coronavirus: CCoV is responsible for mild or moderate enteritis in dogs. The symptoms may vary, but are more severe in young pups, or in combination with other pathogens. Dual infections by CCoV and CPV2 and/or other pathogens are especially severe when infections occur simultaneously [45]. Therefore, the range of clinical signs from loose stools to severe watery diarrhea with high morbidity and variable mortality is mainly determined by the age at the onset of infection, the level and type of pathogen exposure, and the degree of maternal transfer of immunity. In recent years, an increasing number of reports of infections by highly virulent CCoVs have also been documented in puppies without apparent coinfections [46]. Coronavirus diarrhea is typically sudden in onset, and is accompanied by lethargy and decreased appetite. The stool is loose, with a fetid odor and orange tint. It may contain blood or mucus [3].

Canine Respiratory Coronavirus: CRCoV is one of the CIRD which is a highly contagious; polymicrobial respiratory disease syndrome associated with a number of bacterial and viral agents and is readily transmitted via aerosols between dogs housed in relatively high-density groups, like shelters or kennels. Dry cough and nasal discharge were reported during infection with CRCoV. The virus has preferences for the nasal cavity, nasal tonsil and trachea, but is rarely detected in lung, bronchial lymph nodes, and palatine tonsil [47].

Canine Respiratory CoV has also been shown to be capable of causing disease on its own and is thought to play a role in early CIRD infection by damaging the mucociliary elevator. Affected dogs have an impaired ability to clear pathogens and foreign material from the lower respiratory tract, predisposing them to secondary infections and more severe clinical disease [48]. Canine Respiratory CoV is most commonly associated with mild signs of upper respiratory disease, including nasal discharge, sneezing, and coughing. As is true of SARS CoV-2, CRCoV can also be associated with more severe clinical signs, inappetance, and bronchopneumonia.

Disease occurs most frequently in fall to winter months, and populations most at risk are dogs densely housed in shelter, kennel, or group environments [49]. CRCoV has been proposed as a naturally occurring animal model of SARS-CoV-2 infection in humans, due to parallels in pathogenesis and early host immune response [48].

Canine Pantropic Coronavirus

In 2005, a highly virulent variant of CCoV type II (strain CB/05) was reported in Italy which causes a systemic disease followed by a fatal outcome in pups [50]. In the case of the pantropic CCoV-IIa viruses, infection results in a fatal multisystemic illness, with various clinical signs similar to canine parvovirus infection, and including high fever, hemorrhagic gastroenteritis, neurological signs, and lymphopenia. The most consistent clinical sign of pantropic CCoV-IIa is leukopenia [51]. Some features of systemic infections that are similar to Severe Acute Respiratory Syndrome (SARS) in humans and Feline Infectious Peritonitis (FIP) in cats, have been documented for systemic fatal CCoV-II infections, including pulmonary alveolar damage, fibrinous exudation and macrophage involvement [52].

Diagnosis and Differential Diagnosis

Diagnosis

Detection of CCoV antibodies can be performed by Virus Neutralization (VN) tests and ELISA. But some studies shown that VN tests may fail to detect antibodies in some positive sera and thus provide misleading information on the epidemiology of the infection. A recently developed ELISA was found to be more sensitive than the VN test, even though the antigen prepared from CCoV infected cells might yield variable results, depending on the method of antigen preparation [53].

The virological diagnosis of CCoV requires laboratory confirmation. Virological and bacteriological investigations on the parenchymatous organs failed to detect common canine pathogens, whereas CCoV type I and type II were identified in the intestinal content of all pups by genotype-specific real-time RT-PCR assays. Unexpectedly, CCoV type II RNAwas also detected at high titres in lungs, spleen, liver, kidney and brain. A CCoV type II strain (CB/05) was isolated on A-72 cells from all the examined tissues but brain [54].

The diagnostic techniques employed for the detection of CCoV in faecal samples include electron microscopy, isolation in cell cultures and RT-PCR. Electron microscopy appears to be a valuable diagnostic tool for the detection of coronaviruses [55]. Definitive diagnosis of CCoV-induced disease is currently difficult; thus, it is not commonly done or available. The virus can be identified by visualization of viral particles in stool specimens following negative staining and examination by transmission electron microscopy; however, this is not a routinely available diagnostic tool. Virus isolation can be achieved for CCoV-II, but not for CCoV-I viruses, and again, this is not commonly available. The definitive test is post-mortem identification of viral antigen by immunofluorescence or immunohistochemical staining of tissue sections. The most useful ante-mortem tests are RT-PCR-based, which are highly sensitive assays [56].

A taqMan® fluorogenic RT-PCR assay was developed for the detection and quantification of CCoV RNA in the faeces of dogs. The test which is targeted the M gene too, is more sensitive than a conventional RT-PCR assay, with a detection limit of about 10 copies of standard CCoV RNA. This method allows quantification of samples with a wide range of CCoV RNA loads. Recently, two genotype-specific fluorogenic RT-PCR assays were developed for the detection and quantification of CCoV type I and type II RNA in the faeces of dogs with diarrhoea. Both the

fluorogenic assays allowed the quantification of specific RNA in the faecal samples collected from dogs naturally or experimentally infected with CCoV type I, CCoV type II or both CCoV genotypes. The high sensitivity, simplicity and reproducibility of the fluorogenic RT-PCR assays make these methods especially suitable for efficacy trials on CCoV vaccines [57].

Differential Diagnosis

There are many causes of diarrhea in dogs. Parasitic: *helminths, protozoa*, bacterial: *Salmonella, Campylobacter, Clostridium perfringens, Clostridium difficile* and *E. coli* and viral: *parvovirus* and *coronavirus*. Severe cases of coronavirus can be easily confused with parvovirus, and they may occur at the same time. Be sure to see, if the dog has diarrhea that does not resolve within twenty-four hours or is associated with significant lethargy or loss of appetite [3]. CCoV-positive puppies exhibit hemorrhagic enteritis like that observed in CPV-2 infections [58].

Pathology

Canine Enteric Coronavirus: Like the pathology of other enteric coronaviruses, CCoV infects and replicates in the apical and lateral enterocytes of the intestinal villi (mature enterocytes), resulting in cellular degeneration and/or necrosis characterized by atrophy of enterocytes, loss of the cellular brush border, and sloughing of necrotic cells into the intestinal lumen. Degeneration and destruction of mature enterocytes at the villous tips can lead to villous atrophy, ultimately resulting clinically in maldigestion, malabsorption and diarrhea [7].

A more severe form of enteritis in puppies infected with CCoV has also been reported in the absence of co-infection. Gross pathology in one case revealed moderate, diff use, hemorrhagic enteritis, and in another, severe ileo-cecal intussusception and segmental necrotic enteritis. Histologically, mild, lymphocytic and plasmacytic enteritis was present in the first case, along with necrosis and enteric and splenic lymphoid depletion. In the second case, depletion of gut associated lymphoid tissues was also noted, along with disuse villous blunting and crypt necrosis [59].

Canine Respiratory Coronavirus: Histopathological lesions are most significant in the upper respiratory tract like trachea and nasal cavity, where infection with CRCoV causes inflammation and damage to the ciliated respiratory epithelium, impairing the clearance of particulate matter in the lower respiratory tract and predisposing individuals to secondary bacterial infection of the lungs. Histological examination following experimental infection with CRCoV has demonstrated that the epithelium of the respiratory tract is disordered and devoid of cilia and goblet cells, and inflammatory cells infiltrate within the epithelium and adjacent lamina propria [60].

The trachea and nasal tonsil are the most common sites of CRCoV infection and are reported to have the highest viral loads, detected by quantitative RT-PCR. Though infrequently, CRCoV has also been detected in the spleen, mesenteric lymph node, and colon of infected dogs; while this may indicate the potential of CRCoV to display a dual tropism, it is likely that the detection of CRCoV outside the respiratory tract is a result of passive transport from the respiratory tract through the ingestion of saliva and respiratory secretions [61].

Canine Pantropic Coronavirus: A case report of pantropic CCoV described lesions in multiple organs, including a fibrinopurulent bronchopneumonia, renal cortical infarcts, severe coalescing centrilobular hepatic fatty change, and multifocal hemorrhage in the spleen with lymphoid depletion. Chronic diff use enteritis in this case was associated with the presence of adult ascarids in addition to CCoV [52]. Most studies of pantropic CCoV-IIa report the presence of viral RNA in various tissues, including lungs, lymph nodes, liver, spleen, kidneys, urinary bladder and brain. Evidence for replication of these pantropic viruses outside of the gastrointestinal tract is based on demonstration of CCoV antigen by immunohistochemical staining of lung tissue taken from a single dog, and reports of virus isolation from various visceral organs [51].

Amelioration (treatment and management): Dehydration is the most common problem with puppies that have CCoV. The puppy should be encouraged to drink independently if possible. Pedialyte can be a good fluid to hydrate puppies. If the puppy will not or cannot drink, fluids and electrolytes will need to be given intravenously. Various medications may be prescribed based on the symptoms. Metoclopramide can relax the intestine, and famotidine or another acid-blocker can help to coat the intestinal walls and protect them against inflammation. With puppies that are also vomiting, antiemetics like chlorpromazine and ondestron may be given [62]. Antibiotics like Enrofloxacin are commonly prescribed to control any concurrent bacterial infection which could present a bigger problem with a weakened immune system. Some puppies have hookworm (or other parasitic infestations) at the same time and need treatment for this as well. A heating pad may be helpful to maintain the proper temperature for young puppies. CCoV is also treated supportively. Antibiotics are given to prevent bacterial infections. Dogs that develop pneumonia along with the virus could need oxygen, but this is rare [63].

Consequences of Vomiting and Diarrhea and Their Treatment

Dehydration: Fluid loss from animals with vomiting and diarrhea can be severe, because large volumes of fluid are secreted and reabsorbed by the GI tract. Approximately 2.5 L of fluid enters the duodenal lumen of a 20-kg dog each day from diet and normal secretions, and more than 98% of this fluid is reabsorbed [64]. Fluid loss from GI disease thus can be extensive, and together with decreased intake leads to progressive dehydration. Severe complications, such as hypovolemia, may result. Dehydration often can be detected first on examination of the mucous membranes. Assessment may be confounded by nausea-induced hypersalivation. Physical examination may include depression, dry or tacky mucous membranes, and a prolonged skin tent. Dehydration in dogs with vomiting and diarrhea results from isotonic or hypertonic fluid loss and may be evident in changes to blood constituents. Loss of fluid from the blood results in hemoconcentration, demonstrated by a simultaneous increase in packed cell volume and plasma total protein concentration or total solids by refractometry [65].

Dehydration from vomiting and diarrhea can be corrected with oral, subcutaneous, or intravenous administration of fluids. Moderate to severe dehydration, electrolyte or acid-base derangements, and hypovolemia should be corrected by intravenous fluid therapy. Correction of interstitial fluid loss should begin during fluid resuscitation for hypovolemia. Crystalloid fluid in the intravascular space rapidly equilibrates with the interstitial space, with only 20% to 25% of the infused volume remaining within the intravascular space after 1 hour [66].

Hypovolemia: Fluid loss with vomiting and diarrhea may lead to hypovolemia and compromised perfusion of organs and tissues. Hypovolemic shock is one of the most life-threatening consequences of vomiting and diarrhea. Activation of normal physiologic responses protects against impaired tissue perfusion associated with hypovolemia. First, dietary sodium intake and water intake normally are greater than basal needs and second, the kidney is able to enhance sodium and water reabsorption to expand circulating volume. Hypovolemia is the result of such severe volume loss that fluid shifts and renal compensatory responses are unable to maintain circulating blood volume. Relatively large volumes of fluid must be lost, or the rate of loss must exceed the potential for compensatory responses, before a patient becomes hypovolemic [67].

The restoration of fluid volume and electrolyte balance is very important, especially in puppies that have had severe vomiting and diarrhea and that present in hypovolemic shock. IV fluids should be started immediately; if the patient is in hypovolemic shock, fluid deficits may be replaced in the first 1 to 2 hours to help prevent further deterioration of the patient's condition as well as death. The fluids can be given as "quickly" as 90 mL/kg/h; however, the patient's degree of dehydration and physiologic end points should be considered when choosing a fluid rate [63].

Vomiting and diarrhea can cause a large loss of GI protein. This can lead to a decrease in plasma Colloid Oncotic Pressure (COP), and fluid resuscitation reduces the COP even more. COP is important for holding fluid in the vasculature [68]. When the COP decreases, fluid leaks into the interstitial space, causing edema. When perfusion improves, the fluid rate can be decreased to a maintenance rate and, if necessary, a colloid (e.g., synthetic colloid, Fresh Frozen Plasma [FFP], whole blood) can be added to the fluid regimen. Administration of a colloid should be considered if the albumin level decreases to <2g/dL (normal: 2.6 to 4.0g/dL) or the total protein level decreases to <4g/dL (normal: 5.8 to 7.2g/dL) [67].

Electrolyte Disorders: Vomiting and diarrhea can cause a patient to lose not only fluids and proteins but also electrolytes. Hypokalemia (secondary to vomiting and diarrhea) is a common complication in puppies. Diarrhea caused by infectious diseases can have serious consequences for puppies' health, and in severe cases, it can lead to death [69]. In these cases, metabolic acidosis is the expected acid-base imbalance [70], initially due to a greater loss of sodium ions (Na+) than chlorides (Cl-), with a consequent decrease in the strong Ions Difference (SID). Simultaneously, bicarbonate (HCO3-) present in pancreatic juice secretion in the duodenum is not reabsorbed and is lost in feces along with Na+ [67]. Hypokalemia can cause muscle weakness and paralysis, ileus, cardiac arrhythmias, and polyuria. Potassium chloride can be added to fluid therapy to treat or prevent hypokalemia Vomiting and diarrhea can also cause hypoglycemia, which should be Prevented, especially in young puppies, by adding 2.5% to 5% dextrose to fluid therapy [62].

Prevention and Control

CCoV is highly contagious and once the virus has become established in the environment, the spread of the infection is difficult to control. Avoiding contact with infected dogs and their excretions is the only way to ensure disease prevention. Crowding, unsanitary conditions, stress during training and other conditions appear to favour development of clinical disease. CCoV is inactivated by most germicidal agents but they do not prevent dog to dog transmission. The value of CCoV vaccines in providing adequate immunity, under field conditions is controversial [25]. The study by [71] demonstrated the low efficacy of a widely used inactivated commercial vaccine (Duramune PC, Fort Dodge) in reducing faecal shedding after challenge with a field virus. Although the efficacy and the duration of immunity engendered by inactivated vaccines have not been substantiated, only killed vaccines are licensed for the control of the infection. Modified Live (ML) vaccines have been licensed in the past, but they often resulted in a high frequency adverse of post-vaccinal reactions [72].

Prevention of CCoV infection is related to the production of protective levels of IgAs in the intestine. Considering the long period of CCoV shedding after infection, effective control of CCoV, especially in animal shelters, requires the prevention of infection. Recently, the safety and the efficacy of an ML CCoV vaccine was evaluated in three groups of dogs: two groups were vaccinated by the intramuscular and oronasal routes, respectively, and their responses were compared with a third group of unvaccinated dogs [73]. A vaccine is available to prevent canine coronavirus infection. The coronavirus vaccine is not required for all dogs, but it may sometimes be included in combination vaccines for other, more serious diseases, such as infections with canine distemper virus, canine parvovirus, and canine adenovirus type 2 [74].

Canine Coronaviruse Vaccine

The value of vaccination against CCoV is controversial. Although both inactivated and modified live vaccines against the group 1 virus are available, their use is not recommended because this virus usually only causes a mild, self- limiting or inapparent gastroenteritis with anorexia, fever and diarrhea. It usually affects puppies less than 6 weeks old and lasts for a few days. It is believed that protection against CCoV is mainly dependent on the production of IgA, and therefore parenteral vaccination was not favored because it does not produce prime mucosal IgA in the intestine. As a result, vaccination at the normal time of 8–12 weeks of age is too late to prevent the disease. The vaccine appears to protect dogs from disease but not from infection. It is generally accepted that protection against CCoV is dependent on the presence of IgA in the intestine. Dogs vaccinated by the parenteral route do not mount an IgA response and so shed virus in their feces [75].Two types of vaccine have been developed against CCoV; inactivated and live-attenuated. Vaccination of dogs with the inactivated CCoV vaccine reduced the level of viral shedding in feces and was eff ective against experimental challenge [5]. A small number of vaccinated dogs (15%) show very mild diarrhea while 80% of the non-vaccinated dogs show severe watery or bloody diarrhea experience with an average of about10.8 days compared to 1.4 days for vaccinated animals. However, the mild status of the disease discouraged the wide application of the vaccine [76].

As of mid-2020, three monovalent coronavirus vaccines are licensed in the United States. Two are inactivated products given by the subcutaneous or intramuscular routes to dogs over six weeks of age. The duration of immunity has not been established. The other is a modified live product. The first dose is given by the subcutaneous or intramuscular routes to dogs over 6 weeks of age with a second dose 2–3 weeks later. Dogs under 12 weeks should be revaccinated every 2–3 weeks until they reach 12 weeks of age. Maternal antibodies will interfere with vaccination responses prior to that time. There are also a large number of multivalent licensed vaccines available

that contain coronavirus combined with diverse other canine pathogens such as parvovirus, adenovirus, canine dis- temper and parainfluenza. These are all inactivated products given by injection [75].

Canine Coronavirus in Humans

The majority of human infectious diseases are caused by pathogens that first spread in non-human animal species. "Zoonotic spillover" refers to the spread of infections from wild animals to humans. Increased risk of spillover occurrences is linked to activities and variables that increase human connection with various animal species and the pathogens that they might harbor. Over the last two decades, the ongoing coronavirus disease 2019 (COVID-19) is the third reported animal- to-human CoV spillover to have resulted in a severe epidemic. Coronavirus (CoV) zoonotic transmissions pose a significant threat to human health, with a large number of unknown reservoir hosts [8].

A study posted on 20 May 2021 investigated samples collected between 2017 and 2018 from eight patients with pneumonia (seven of whom were children) in Malaysia and discovered a new coronavirus strain CCoV-HuPn-2018. It's different from SARS-CoV-2, the coronavirus that caused the COVID-19 pandemic. This study confirmed that the presence of CCoV with different, less sensitive 1-step RT-PCR assays in 2 specimens, grew a virus in A72 cells from 1 specimen, and conducted a complete genome sequence analysis of the CCoV. Our results demonstrated that CCoV-HuPn-2018 is a novel canine-feline–like recombinant strain with a unique N. To our knowledge, this is the first report suggesting that a CCoV without major genomic rearrangements or adaptive modifications in the S protein might replicate in association with pneumonia in a human host [77]. Another sequence of CCoV strain Z19 (MZ420153) was found in a NCBI database which was detected in a Haitian human in 2017 from a medical team member presenting with fever and malaise after travel to Haiti. If the association of CCoV with human disease is confirmed, it would become the eighth known coronavirus to cause human disease [11].

The conducted analyses by Vlasova et al, demonstrated that the newly identified CCoV-HuPn- 2018 was most closely related to CCoV TN-449, while its S1 and S2 domains shared the highest nucleotide identity with CCoV UCD-1 and FCoV WSU 79-1683, respectively. These findings are suggestive of the recombinant nature of this strain, similar to many previously characterized CCoVs [59]. Phylogenetic and recombinational analyses confirmed that CCoV-HuPn-2018 was only distantly related to other *Alphacoronavirus* species, including HCoVs (229E and NL63) and bat CoVs, and likely originated via multiple recombination events between different *Alphacoronavirus 1* strains, but not other alphacoronaviruses. The ability of the novel strain to replicate in A72 canine cells, the absence of ORF3, the higher overall similarity with CCoV-II strains (TN-449 and HLJ-073), and the lack of the furin cleavage site between S1 and S2 domains suggest that the strain belongs to CCoV genotype II [26].

Conclusion and Recommendations

According to different studies, coronavirus infections are highly distributed and commonly encountered in the wide areas of the world, and it cause mild to severe diseases in different animals including dogs, cats, pigs, chicken, cows, camels and human. The emergence of novel variants with altered tropism and pathogenesis were reported in the different areas with in various host range. Canine coronavirus infection is one of the diseases known to cause enteric and respiratory disorders in Dog. Therefore, further review should be done on other coronaviruse infections in terms of their livestock and public health impact.

References

1. Nova N. Cross-species transmission of coronaviruses in humans and domestic mammals, what are the ecological mechanisms driving transmission, spillover, and disease emergence? Front Public Health. 2021; 9: 717941.
2. Le Poder S. Feline and canine coronaviruses: common genetic and pathobiological features. Adv Virol. 2011; 2011: 609465.
3. Studer RA. canine coronavirus disease. 2007; 2.
4. Decaro N, Buonavoglia C. Canine coronavirus: not only an enteric pathogen. Vet Clin North Am Small Anim Pract. 2011; 41: 1121-32.
5. Pratelli A, Tinelli A, Decaro N, Martella V, Camero M, Tempesta M. Safety and efficacy of a modified-live canine coronavirus vaccine in dogs. Vet Microbiol. 2004; 99: 43-9.
6. MacLachlan NJ, Dubovi EJ. Fenner's veterinary virology. 5th ed. Boston: Elsevier. 2017.
7. Licitra BN, Duhamel GE, Whittaker GR. Canine enteric coronaviruses: emerging viral pathogens with distinct recombinant spike proteins. Viruses. 2014; 6: 3363-76.
8. Saha N. A canine coronavirus zoonotic spillover and tropism shift. Saved from URL. 2021.
9. Carlson CJ. From PREDICT to prevention, one pandemic later. Lancet Microbe. 2020; 1: e6-7.
10. Jelinek HF, Mousa M, Alefishat E, Osman W, Spence I, Bu D. Evolution, ecology, and zoonotic transmission of betacoronaviruses: a review. Front Vet Sci. 2021; 8: 644414.
11. Lednicky JA, Tagliamonte MS, White SK, Blohm GM, Alam M, Iovine NM, et al. Isolation of a Novel Recombinant Canine Coronavirus from a Visitor to Haiti: Further Evidence of Transmission of Coronaviruses of Zoonotic Origin to Humans. Clin Infect Dis. 2021; ciab924.
12. Tortorici MA, Walls AC, Joshi A, Park YJ, Eguia RT, Stevens-Ayers T, et al. Structure, receptor recognition and antigenicity of the human coronavirus CCoV-HuPn-2018 spike glycoprotein. bioRxiv. 2021.
13. Priestnall SL. Canine respiratory coronavirus: A naturally occurring model of COVID-19? Vet Pathol. 2020; 57: 467-71.
14. Yang H, Peng Q, Lang Y, Du SY, Cao SJ, Wu R, et al. Phylogeny, evolution, and transmission dynamics of canine and feline coronaviruses: A retro-prospective study. Front Microbiol. 2022; 13: 850516.
15. Dong BQ, Liu W, Fan XH, Vijaykrishna D, Tang XC, Gao F, et al. Detection of a novel and highly divergent coronavirus from Asian leopard cats and Chinese ferret. 2007; 81: 6920-6.
16. Decaro N, Buonavoglia C. An update on canine coronaviruses: viral evolution and pathobiology. Vet Microbiol. 2008; 132: 221-34.
17. Alluwaimi AM, Alshubaith IH, Al-Ali AM, Abohelaika S. The coronaviruses of animals and birds: their zoonosis, vaccines, and models for SARS-CoV and SARS- CoV2. Front Vet Sci. 2020; 7: 582287.
18. Miranda C, Silva V, Igrejas G, Poeta P. Genomic evolution of the human and animal coronavirus diseases. Mol Biol Rep. 2021; 48: 6645-53.

19. Nguyen TT, Woo HJ, Kang HK, Nguyen VD, Kim YM, Kim DW, et al. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in pichia pastoris. Biotechnol Lett. 2012; 34: 831-8.

20. Harper KN, Armelagos GJ. Genomics, the origins of agriculture, and our changing microbe-scape: time to revisit some old tales and tell some new ones. Am J Phys Anthropol. 2013; 152: 135-52.

21. Zhang X, Tan Y, Ling Y, Lu G, Liu F, Yi Z, et al. Viral and host factors related to the clinical outcome of COVID-19. Nature. 2020; 583: 437-40.

22. Erles K, Brownlie J. Canine respiratory coronavirus: an emerging pathogen in the canine infectious respiratory disease complex. Vet Clin North Am Small Anim Pract. 2008; 38: 815-82.

23. Tian Z, Pan Q, Zheng M, Deng Y, Guo P, Cong F, et al. Molecular characterization of the FCoV-like canine coronavirus HLJ-071 in China. BMC Vet Res. 2021; 17: 364.

24. Alfano F, Fusco G, Mari V, Occhiogrosso L, Miletti G, Brunetti R, et al. Circulation of pantropic canine coronavirus in autochthonous and imported dogs, Italy. Transbound Emerg Dis. 2020; 67: 1991-9.

25. Annamaria P. Genetic evolution of canine coronavirus and recent advances in prophylaxis. 2006; 37: 191-200.

26. Decaro N, Mari V, Dowgier G, Elia G, Lanave G, Colaianni ML, et al. Full-genome sequence of pantropic canine coronavirus. Genome Announc. 2015; 3: e00401-15.

27. Lim SI, Choi S, Lim JA, Jeoung HY, Song JY, Dela Pena RC, et al. Complete genome analysis of canine respiratory coronavirus. Genome Announc. 2013; 1: e00093.

28. Pratelli A, Martella V, Elia G, Decaro N, Aliberti A, Buonavoglia D, et al. Variation of the sequence in the gene encoding for transmembrane protein M of Canine Coronavirus (CCV). Mol Cell Probes. 2001; 15: 229-33.

29. Timurkan MO, Aydin H, Dincer E, Coskun N. Molecular characterization of canine coronaviruses: an enteric and pantropic approach. 2020; 166: 35-42.

30. Haijema BJ, Volders H, Rottier PJ. Switching species tropism: an effective way to manipulate the feline coronavirus genome. J Virol. 2003; 77: 4528-38.

31. Erles K, Shiu KB, Brownlie J. Isolation and sequence analysis of canine respiratory coronavirus. Virus Res. 2007; 124: 78-87.

32. De Vries AAF, Horzinek MC, Rottier PJM, De Groot RJ. The genome organization of the nidovirales: similarities and differences between arteri-, toro-, and coronaviruses. Semin Virol. 1997; 8: 33-47.

33. Lorusso A, Desario C, Mari V, Campolo M, Lorusso E, Elia G, et al. Molecular characterization of a canine respiratory coronavirus strain detected in Italy. J Homepage. 2008.

34. Lu S, Chen Y, Qin K, Zhou J, Lou Y, Tan W. Genetic and antigenic characterization of recombinant nucleocapsid proteins derived from canine coronavirus and canine respiratsory coronavirus in China. Sci China Life Sci. 2016; 59: 615-21.

35. Krammer F, Srivastava K, Alshammary H, Amoako AA, Awawda MH, Beach KF, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. N Engl J Med. 2021; 384: 1372-4.

36. Decaro N, Lorusso A. Novel human coronavirus (SARS-CoV-2): A lesson from animal coronaviruses. Vet Microbiol. 2020; 244: 108693.

37. Woo PCY, Huang Y, Lau SKP, Yuen KY. Coronavirus genomics and bioinformatics analysis. Viruses. 2010; 2: 1804-20.

38. Woo PC, Lau SK, Huang Y, Yuen KY. Coronavirus diversity, phylogeny and interspecies jumping. Exp biol Med (may-wood). 2009; 234: 1117-27.

39. Graham RL, Baric RS. Recombination, reservoirs, and the modular spike: mechanisms of coronavirus cross-species transmission. J Virol. 2010; 84: 3134-46.

40. Le Poder S, Pham-Hung d'Alexandry d'Orangiani AL, Duarte L, Fournier A, Horhogea C, Pinhas C, et al. Infection of cats with atypical feline coronaviruses harboring a truncated form of the canine type I nonstructural ORF3 gene. Infect Genet Evol. 2013; 20: 488-94.

41. El Wahed AA, Patel P, Maier M, Pietsch C, Rüster D, Böhlken-Fascher S, et al. Suitcase lab for rapid detection of SARS-CoV-2 based on recombinase polymerase amplification assay. Anal Chem. 2021; 93: 2627-34.

42. Appel MJ. Canine coronavirus. In: Appel MJ, editor. Virus infections of carnivores. The Netherlands: Elsevier Science Publishers. 1987; 115-22.

43. Greene CE, Decaro N. Canine viral enteritis. In: Greene CE, editor. Infectious diseases of the dog and cat. St. Louis: Elsevier Saunders. 2012.

44. Keenan KP, Jervis HR, Marchwicki RH, Binn LN. Intestinal infection of neonatal dogs with canine coronavirus 1-71: studies by virologic, histologic, histochemical and immunofluorescent techniques. Am J Vet Res. 1976; 37: 247-56.

45. Decaro N, Camero M, Greco G, Zizzo N, Tinelli A, Campolo M, et al. Canine distemper and related diseases: report of a severe outbreak in a kennel. New Microbiol. 2004; 27: 177-81.

46. Ntafis V, Mari V, Decaro N, Papanastassopoulou M, Papaioannou N, Mpatziou R, et al. Isolation, tissue distribution and molecular characterization of two recombinant canine coronavirus strains. Vet Microbiol. 2011; 151: 238-44.

47. Lavan R, Knesl O. Prevalence of canine infectious respiratory pathogens in asymptomatic dogs presented at US animal shelters. J Small Anim Pract. 2015; 56: 572-6.

48. Priestnall SL, Mitchell JA, Brooks HW, Brownlie J, Erles K. Quantification of mRNA encoding cytokines and chemokines and assessment of ciliary function in canine tracheal epithelium during infection with canine respiratory coronavirus (CRCoV). Vet Immunol Immunopathol. 2009; 127: 38-46.

49. Wille M, Wensman JJ, Larsson S, van Damme R, Theelke AK, Hayer J, et al. Evolutionary genetics of canine respiratory coronavirus and recent introduction in to Swedish dogs. Infect Genet Evol. 2020; 82: 104290.

50. Buonavoglia C, Decaro N, Martella V, Elia G, Campolo M, Desario C, et al. Canine coronavirus highly pathogenic for dogs. Emerg Infect Dis. 2006; 12: 492-4.

51. Decaro N, Campolo M, Lorusso A, Desario C, Mari V, Colaianni ML et al. Experimental infection of dogs with a novel strain of canine coronavirus causing systemic disease and lymphopenia. Vet Microbiol. 2008; 128: 253-60.

52. Zappulli V, Caliari D, Cavicchioli L, Tinelli A, Castagnaro M. Systemic fatal type II coronavirus infection in a dog: pathological findings and immunohistochemistry. Res Vet Sci. 2008; 84: 278-82.

53. Pratelli A, Elia G, Martella V, Palmieri A, Cirone F, Tinelli A et al. Prevalence of canine coronavirus (CCoV) antibodies in dog in Bari, Italy, by an enzymelinked immunosorbent assay. J Virol Methods. 2002; 102: 67-71.

54. Decaro N, Martella V, Elia G, Campolo M, Desario C, Cirone F, et al. Molecular characterization of the virulent canine coronavirus CB/05 strain. Virus Res. 2007d; 125: 54-60.

55. Pratelli A, Tempesta M, Greco G, Martella V, Buonavoglia C. Development of a nested PCR assay for the detection of canine coronavirus. J Virol Methods. 1999; 80: 11-5.

56. Gizzi AB, Oliveira ST, Leutenegger CM, Estrada M, Kozemjakin DA, Stedile R, et al. Presence of infectious agents and co-infections in diarrheic dogs determined with a real-time polymerase chain reaction-based panel. BMC Vet Res. 2014; 10: 23.

57. Decaro N, Martella V, Ricci D, Elia G, Desario C, Campolo M, et al. Genotype-specific fluorogenic RT-PCR assays for the detection and quantitation of canine coronavirus type I and type II RNA in faecal samples of dogs. J Virol Methods. 2005; 130: 72-8.

58. Pinto LD, Barros IN, Budaszewski RF, Weber MN, Mata H, Antunes JR, et al. Characterization of pantropic canine coronavirus from Brazil. Vet J. 2014; 202: 659-62.

59. Evermann JF, Abbott JR, Han S. Canine coronavirus-associated puppy mortality without evidence of concurrent canine parvovirus infection. J Vet Diagn Investig. 2005; 17: 610-4.

60. Mitchell JA, Brooks HW, Szladovits B, Erles K, Gibbons R, Shields S, et al. Tropism and pathological findings associated with canine respiratory coronavirus (CRCoV). Vet Microbiol. 2013; 162: 582-94.

61. Mitchell JA, Brooks H, Shiu KB, Brownlie J, Erles K. Development of a quantitative real-time PCR for the detection of canine respiratory coronavirus. J Virol Methods. 2009; 155: 136-42.

62. Prittie J. Canine parvoviral enteritis: a review of diagnosis, management, and prevention. J Vet Emerg Crit Care. 2004; 14: 167-76.

63. Linda S. Canine coronavirus infection in dogs. 2021.

64. Strombeck DR, Guilford WG. Classification, pathophysiology, and symptomatic treatment of diarrheal diseases. In: Strombeck DR, Guilford WG, editors. Small animal gastroenterology. 2nd ed. CA: Davis. Stonegate Publishing Company. 1990; 277-95.

65. Hughes D, Boag AK. Fluid therapy with macromolecular plasma volume expanders. In: DiBartola SP, editor. Fluid, electrolytes, and acid-base disorders in small animal practice. 3rd ed. St. Louis: Elsevier Saunders. 2006; 621-34.

66. Brown AJ, Otto CM. Fluid therapy in vomiting and diarrhea. Vet Clin North Am Small Anim Pract. 2008; 38: 653-75.

67. Hackett TB. Hemorrhagic diarrhea in Wingfield WE, Raffe MR. the Veterinary ICU Book. Jackson, Wyoming. Teton. 2002; 763-70.

68. Duijvestijn M, Mughini-Gras L, Schuurman N, Schijf W, Wagenaar JA, Egberink HN, et al. Enteropathogen infections in canine puppies: (Co-)occurrence, clinical relevance and risk factors. Vet Microbiol. 2016; 195: 115-22.

69. Tello L, Perez-freytes R. Fluid and electrolyte therapy during vomiting and diarrhea. Vet Clin North Am Small Anim Pract. 2017; 47: 505-19.

70. Pratelli A, Tinelli A, Decaro N, Cirone F, Elia G, Roperto S, et al. Efficacy of an inactivated canine coronavirus vaccine in pups. New Microbiol. 2003; 26: 151-5.

71. Stull JW, et al. Disease prevention at canine group settings. Includes content on disinfectants effective against parvovirus; 2016.

72. Pratelli A, Decaro N, Buonavoglia C, Martella V, Elia G, Tempesta M et al. Two Genotypes of canine coronavirus simultaneously detected in the fecal samples of dogs with diarrhea. J Clin Microbiol. 2004; 42: 1797-9.

73. Day MJ, et al. WSAVA Guidelines for the vaccination of dogs and cats. J Small Anim Pract. 2016; 57: E1-E45.

74. Tizard IR. Vaccination against coronaviruses in domestic animals. Vaccine. 2020; 38: 5123-30.

75. Fulker R, Wasmoen T, Atchison R, Chu H-J, Acree W. Efficacy of an inactivated vaccine against clinical disease caused by canine coronavirus. In: Talbot PJ, Levy GA, editors. Corona and related viruses: current concepts in molecular biology and pathogenesis. Boston: Springer US. 1995; 229-34.

76. Vlasova AN, Diaz A, Damtie D, Xiu L, Toh T-H, Lee JS-Y, et al. Novel canine coronavirus isolated from a hospitalized pneumonia patient, East Malaysia. Clin Infect Dis Ciab. 2022; 74: 446-456.