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Transmission of severe acute respiratory syndrome coronavirus 2 via fecal-oral: Current knowledge

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Abstract

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in more than 93 million cases and 2 million deaths in the world. SARS-CoV-2 respiratory tract infection and its main clinical manifestations such as cough and shortness of breath are well known to the scientific community. However, a growing number of studies have reported SARS-CoV-2-related gastrointestinal involvement based on clinical manifestations, such as diarrhea, nausea, vomiting, and abdominal pain as well as on the pathophysiological mechanisms associated with coronavirus disease 2019. Furthermore, current evidence suggests SARS-CoV-2 transmission *via* the fecal-oral route and aerosol dissemination. Moreover, studies have shown a high risk of contamination through hospital surfaces and personal fomites. Indeed, viable SARS-CoV-2 specimens can be obtained from aerosols, which raises the possibility of transmission through aerosolized viral particles from feces. Therefore, the infection by SARS-CoV-2 *via* fecal-oral route or aerosolized particles should be

conceptualization, methodology, formal analysis, investigation, and supervision.

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considered. In addition, a possible viral spread to sources of drinking water, sewage, and rivers as well as the possible risk of viral transmission in shared toilets become a major public health concern, especially in the least developed countries. Since authors have emphasized the presence of viral RNA and even viable SARS-CoV-2 in human feces, studies on the possible fecal-oral coronavirus disease 2019 transmission become essential to understand better the dynamics of its transmission and, then, to reinforce preventive measures against this infection, leading to a more satisfactory control of the incidence of the infection.

Key Words: COVID-19; SARS-CoV-2, Transmission; *Via* fecal-oral

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Core Tip: The pandemic caused by severe acute respiratory syndrome coronavirus 2 has become a global health problem. Transmission *via* the respiratory tract and the clinical manifestations related to that organ system are well known to the scientific community. In addition, current knowledge about the viral infection strongly suggests a possible transmission of the severe acute respiratory syndrome coronavirus 2 *via* the fecal-oral route. In addition, a possible spread of the virus to sources of drinking water, sewage, and rivers as well as the possibility of viral transmission in shared toilets become a major public health problem, especially in underdeveloped countries.

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INTRODUCTION

In December 2019, cases of pneumonia of unknown etiology were reported in Wuhan, China. The disease would be later named corona virus disease 2019 (COVID-19), and researchers found that it is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. According to the World Health Organization, from the beginning of the pandemic to the writing of this article, more than 93 million cases and 2 million deaths were reported globally[2]. The SARS-CoV-2 belongs to the β -genus of the Coronaviridae family. Its main target is the human respiratory system, and its transmission occurs mainly with personal contact through droplets originated from infected individuals. Droplet transmission involves exposure of an entry point such as mucosa or conjunctiva to potentially infectious particles[3,4]. This infection classically involves respiratory tract symptoms such as dry cough and shortness of breath as well as associated fever, myalgia, myalgia, and fatigue[5]. The patients can also present with gastrointestinal (GI) manifestations, including diarrhea, nausea, abdominal pain, and GI bleeding[6,7]. Interestingly, in January 2020, the first COVID-19 case in the Americas presented with diarrhea. Stools were collected from the patient, underwent analyses, and were later found to be positive for SARS-CoV-2 RNA through reverse transcriptase polymerase chain reaction (RT-PCR) test[8].

The angiotensin-converting enzyme type 2 (ACE2) receptor, which is expressed in alveolar[9], gastric, and rectal epithelial cells as well as in enterocytes from the small intestine[10,11], seems to play a crucial role in the infection pathogenesis[12,13]. Viral binding to ACE2 allows SARS-CoV-2 to enter host cells[14]. In addition, the viral presence in the feces of infected patients or asymptomatic people indicates a possible fecal-oral transmission route[11]. Studies have shown that the ACE2 receptor may contribute to this route, allowing the occurrence of GI infection. The colonization of the GIT *via* ACE2 may lead to viral spread through stools, which may or may not be preceded by the onset of diarrhea and occur before or after respiratory tract-related clinical manifestations[15,16]. RT-PCR tests of rectal and anal swabs collected from pediatric patients were positive within 10 d after hospital discharge following mild

COVID-19, even after patients turned asymptomatic and RT-PCR from nasopharyngeal samples were negative[17]. In asymptomatic adult patients, there was viral detection in the stools for up to 42 d as well, whereas nasopharyngeal samples were negative, showing a possible GI involvement regardless of the occurrence of respiratory complaints[18]. In this sense, it has to be emphasized the possible significant implications of this potential transmission route and the possibility of its use for early identification of the SARS-CoV-2 infection as well.

THEORY FOR PATHOPHYSIOLOGY OF GI TRACT INFECTION AND LIVER AND GI SYMPTOMS

Pathophysiology of GI tract infection

The way SARS-CoV-2 infects GI tract (GIT) remains unclear. Of note, there is an evident genetic similarity between this virus and the SARS-CoV (70%), which infects the human body by attaching to the ACE2. Therefore, researchers hypothesized that this receptor could also play a role in SARS-CoV-2 manifestations[19]. Indeed, ACE2 was subsequently identified as the operative receptor of SARS-CoV-2, and, since it is distributed throughout almost all organs, including the small intestine, colon, rectum, and liver epithelia, this receptor may explain the viral presence in the GIT[20,21]. Besides ACE2, serine protease TMPRSS2 seems to be important in the SARS-CoV-2 infection[22]. That enzyme activates the S protein, which facilitates the entry of the virus into cells through the action of its two subunits, S1 and S2. The S1 unit is responsible for binding cell receptors, whereas S2 promotes the fusion between viral and cell membranes[23]. Therefore, the virus depends on both ACE2 and TMPRSS2 to invade host cells[24], as illustrated in [Figure 1](#).

The pathophysiology in humans is not yet fully understood. Because clinical studies in humans are scarce, many experimental studies have been performed with mice. A study showed that a decrease in the levels of tryptophan absorption might be associated with the pathophysiology of the intestinal infection by SARS-CoV-2 in a murine model. This phenomenon can be explained by the need for ACE2 activation for the absorption of the aforementioned amino acid and the competitive binding of the receptor by the SARS-CoV-2. The mice that underwent the infection had an imbalance in their intestinal microbiota and a higher susceptibility to develop colitis, a condition that has been reversed with the administration of glycine tryptophan dipeptide during the study[25].

Another phenomenon that may contribute to the worsening of COVID-19 is the “cytokine storm”, an exacerbated expression of pro-inflammatory cytokines. Studies have observed higher levels of cytokines including interleukin (IL)1B, IL1RA, IL2, IL6, IL7, IL8, IL9, IL12p70, IL15, IL17A, interferon γ , and tumor necrosis factor α in patients with severe COVID-19 than individuals who experienced a milder disease[6]. *Ye et al* [26] highlighted the gut-lung axis as a potential cause of the intestinal manifestations in COVID-19. The effector CD4+ T cells play a role in GI immunity and chronic enteritis, using the C-C chemokine receptor type 9 to enter the GIT environment. Since C-C chemokine receptor type 9+ CD4+ T cells are highly expressed in the lung during infections with viral pathogens, this may explain intestinal damage and the onset of symptoms such as diarrhea. Moreover, the aggressions against the GIT mucosa can lead to damage to the intestinal barrier, which predisposes to infections by other external pathogens and the onset of GI symptoms[27].

Complementarily, the liver is also affected by the SARS-CoV-2 infection. The ACE2 is expressed in biliary epithelial cells, allowing viral access to the hepatobiliary system [28]. The most common repercussions associated with this organ are increased levels of alanine aminotransferase, aspartate aminotransferase, and aggravation of preexisting liver damage[29]. The intense systemic inflammatory response that can occur in COVID-19 patients, as previously discussed in this topic, may contribute to those repercussions[30,31]. Another important factor is the potential hepatotoxicity caused by drugs used in COVID-19 treatment. Medications such as lopinavir and ritonavir are associated with hepatic dysfunction among inpatients with SARS-CoV-2 infection[32].

GI symptoms

A study analyzing 4243 patients from six countries observed the occurrence of GI symptoms such as loss of appetite, nausea/vomiting, diarrhea, and abdominal pain in 17.6% of the cases. The lack of appetite was the most common symptom (26.8%),

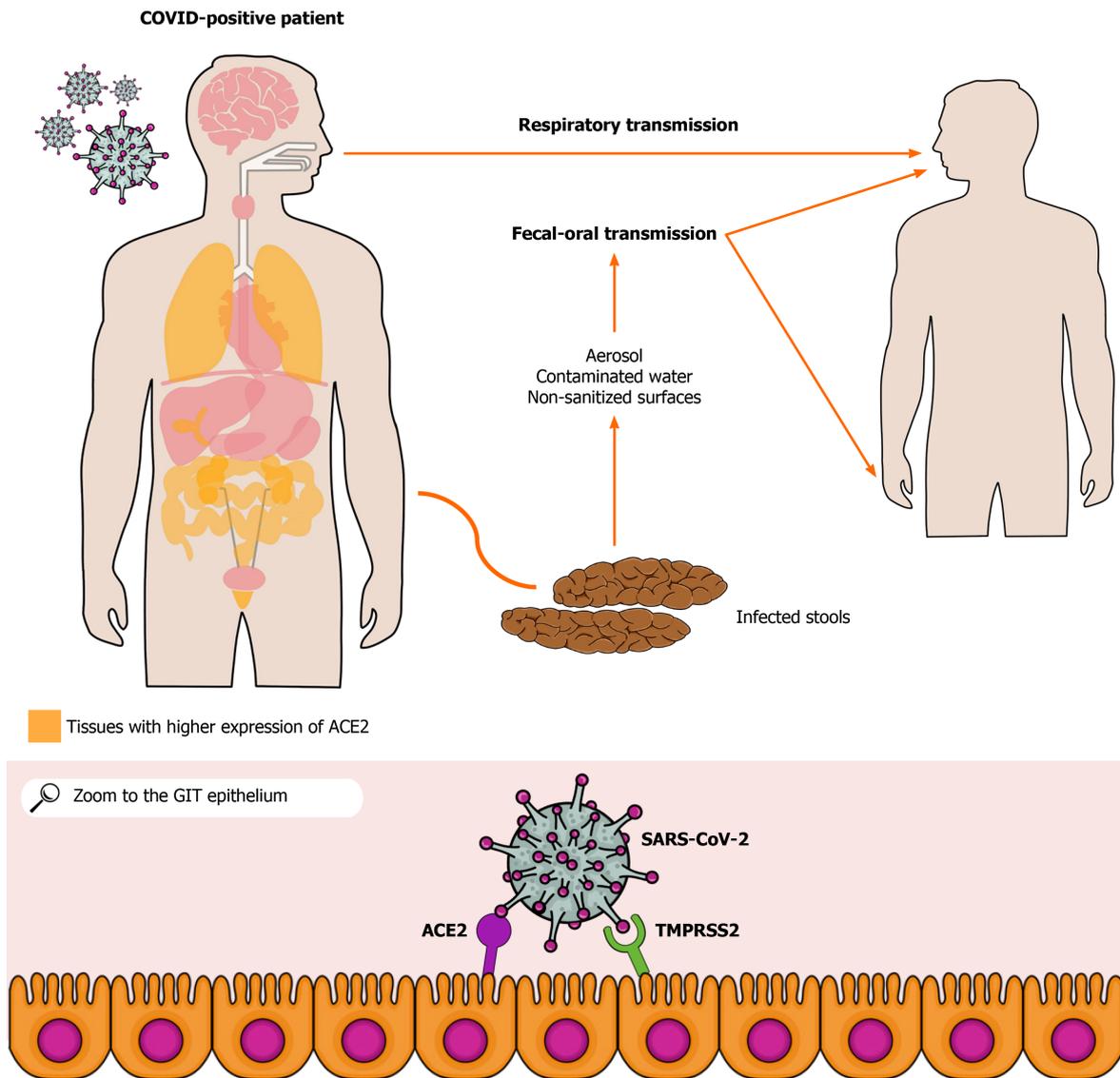


Figure 1 Global severe acute respiratory syndrome host infection scheme and molecular demonstration of the pathophysiology of gastrointestinal tract infection theory. ACE2: Angiotensin-converting enzyme 2; COVID: Coronavirus disease; GIT: Gastrointestinal tract; SARS-CoV-2: Severe acute respiratory syndrome by coronavirus 2.

followed by diarrhea (12.5%), nausea/vomiting (10.2%), and abdominal pain (9.2%) [33]. In another analysis including 6686 patients, the prevalence of digestive symptoms was 15%, and nausea/vomiting, diarrhea and loss of appetite were the most common manifestations, with incidences of 6%, 9%, and 21%, respectively. Of note, the symptoms are similar among adults and children. Moreover, patients with GI symptoms had their COVID-19 diagnosis delayed as compared to individuals without GI manifestations[34]. Concerning early GI manifestations of COVID-19, Redd *et al*[35] found that, among 318 patients, 61.8% reported at least one GI symptom at the time of hospital admission. Another study found that these manifestations were more common during hospitalization (49.5%) than at the moment of admission (11.6%)[36].

In a study performed with 1942 outpatients, 53.3% presented with at least one GI symptom, with loss of appetite affecting almost half of the patients (47%) and 24.2% of the individuals reporting diarrhea[37]. Pan *et al*[38] examined 204 patients with COVID-19 admitted to three hospitals in Hubei, China and noticed that 103 had digestive symptoms such as loss of appetite ($n = 81$), diarrhea ($n = 35$), vomiting ($n = 4$), and abdominal pain ($n = 2$) (Table 1). The diarrhea was the only GI symptom that occurred as a mild-to-severe manifestation in some patients, and, as the patients' condition worsened, the digestive symptoms tended to become more intense. Moreover, abdominal pain can be considered as an indicator of severity in patients with COVID-19, being it important for decision-making during clinical management. Kumar *et al*[39] observed that patients experiencing severe disease have a 7-fold higher

Table 1 Main gastrointestinal manifestations in the articles discussed in the text

Ref.	Any GI symptom	Diarrhea	Nausea/vomiting	Abdominal pain	Loss of appetite
Redd <i>et al</i> [35]	195	107	84	46	110
Lin <i>et al</i> [36]	58	23	17	ND	17
Pan <i>et al</i> [38]	103	35	4	2	81
Jin <i>et al</i> [40]	74	53	ND	ND	ND
Sulaiman <i>et al</i> [41]	78	41	32	42	40

GI: Gastrointestinal; ND: Not described.

chance to present with abdominal pain than non-serious cases.

In China, in an analysis with 651 patients, 74 had at least one digestive symptom, including nausea ($n = 10$), vomiting ($n = 11$), and diarrhea ($n = 53$). Only three cases had all the aforementioned digestive symptoms, and four individuals had both nausea and vomiting. Among patients with GI manifestations, the more frequent complication was liver damage, which was observed in 17.57% of the cases. Moreover, one person developed shock and five had severe acute respiratory syndrome[40]. Sulaiman *et al* [41] confirmed that GI manifestations are common among individuals infected with SARS-CoV-2, and that they are reported mainly as initial symptoms, preceding respiratory symptoms. This study estimates that about half of COVID-19 patients may have GI symptoms along with fever and/or respiratory symptoms.

Regarding hepatic damage, high levels of important markers were registered, such as elevated serum bilirubin in 9% of 1471 patients and prolonged prothrombin time in 7% of 750 cases[42]. Similarly, 243 out of 1450 patients had an abnormally high level of aspartate aminotransferase, and 197 out of 1347 individuals had a high level of alanine aminotransferase[43].

ANAL SWAB AND RNA DETECTION IN FECES

Since March 2020, the detection of SARS-CoV-2 in intestinal biopsies and stool samples has been reported in several studies[28]. Therefore, some authors have highlighted the possibility of fecal transmission of the virus[44].

Currently, there are studies that prove and validate the detection of SARS-CoV-2 RNA in stool samples[45]. In addition, anal swabs (AS) are used for the diagnosis and monitoring of COVID-19, especially to evaluate the possibility of hospital discharge of patients[46]. A timeline that compares the viral load detected in AS and throat smears (TS) during the stages of the disease found that, although TS samples detect viral load earlier, AS detects the virus for longer periods[47].

A Chinese study including 57 individuals has noticed the presence of SARS-CoV-2 viral RNA in extrapulmonary sites. They found that the RT-PCR detection of the viral RNA in stool samples or AS increased the likelihood of increased clinical severity[48]. A study from December 2020 indicates that the use of enteric samples may be effective for the monitoring of the natural course of COVID-19[49]. The findings regarding the detection of viral RNA in stool are shown in Figure 2. It demonstrates an evolution regarding the development of a new tool for the management of COVID-19 patients[1, 8,50-52].

The detection of viral RNA in feces has already been observed in individuals infected with another type of coronavirus, the Middle East respiratory syndrome coronavirus[53]. A study that included 3028 patients observed a positivity of 85.8% for SARS-CoV-2 in fecal nucleic acid tests with COVID-19 patients. It was also reported that 71.2% of the patients were still positive for fecal nucleic acid after samples from the respiratory tract became negative for the virus[54]. A study that included children with COVID-19 detected SARS-CoV-2 fecal RNA in more than 91% of the cases, with viral detection in feces for up to 70 d[55]. Data from studies evaluating the duration of positivity of stools for SARS-CoV-2 among infected individuals are shown in Table 2 [56-68]. These findings reinforce the hypothesis raised by several authors regarding possible transmission of SARS-CoV-2 *via* fecal-oral.

Table 2 Detection of severe acute respiratory syndrome by coronavirus 2 RNA in anal swabs or fecal sample

SARS-CoV-2 RNA										
<i>n</i>	Ref.	Country	<i>n</i>	Age	RT-PCR	Stool	PSDI	Respiratory	PRDI	Relevance information
1	Xie <i>et al</i> [56]	China	4	4-9 yr	AS-PS	4/4	8-33 d	4/4	11-21 d	One patient with positive stool RNA 54 d after hospital admission
2	Ge <i>et al</i> [57]	China	1	55 yr	FS-RS	1/1	18 d	1/1	7 d	Positive stool RNA 22 d after negative respiratory
3	Lo <i>et al</i> [58]	China	10	27-64 yr	FS-PS	10/10	5-19 d	10/10	9-24 d	Some patients had positive stool even with negative respiratory
4	Zhang <i>et al</i> [17]	China	3	6-9 yr	AS-PS	3/3	16-20 d	3/3	7-14 d	The anal swab was positive after 10 d of discharge
5	Liu <i>et al</i> [59]	China	9	NR	AS-PS	8/9	28-66 d	9/9	6-24 d	Positive stool RNA 46 d after discharge
6	Wang <i>et al</i> [60]	China	5	35-56 yr	FS-PS	5/5	11-30 d	5/5	5-9 d	Even after a negative respiratory test, IgM was positive on 2 consecutive occasions
7	Wang X <i>et al</i> [61]	China	3	24-42 yr	FS-PS	2/3	30-36 d	3/3	15-29 d	-
8	Xing <i>et al</i> [62]	China	3	ND	FS-PS	3/3	8 d-4 wk	3/3	2 wk	Positive stool RNA 8-20 d after negative respiratory
9	Chen <i>et al</i> [63]	China	42	42-62 yr	AS-FS	28/42	1-24 d	42/42	1-19 d	Eighteen patients remained positive for viral RNA in the feces after the pharyngeal swabs turned negative
10	Wu <i>et al</i> [64]	China	74	ND	FS-PS	33/74	27, 9 d	74/74	16, 7 d	Fecal positive 47 d after the onset of the first symptoms
11	Li <i>et al</i> [65]	China	13	33-73 yr	FS-RS	5/13	Until 38 d	13/13	5-14 d	Positive stool RNA 14-15 d after negative respiratory
12	Du <i>et al</i> [66]	China	10	9 mo-14 yr	FS-PS	7/10	Mean 34.43 d	10/10	Mean 9 d	Seven patients positive stool RNA 2 wk after discharge but negative respiratory and urine
13	Xiao <i>et al</i> [16]	China	73	10 mo-78 yr	FS-PS	39/73	1-12 d	ND	ND	Seventeen patients positive stool RNA after negative respiratory
14	Xu <i>et al</i> [67]	China	10	2 mo-15 yr	AS-PS	8/10	1-27 d	10/10	1-21	Eight patients positive stool RNA after negative respiratory
15	Fan <i>et al</i> [68]	China	1	3 mo	AS-PS	1/1	1-28 d	1/1	1-14	Positive stool RNA 14 d after negative respiratory

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; AS: Anal swabs; PS: Pharyngeal swabs; FS: Fecal sample; RS: Respiratory samples; PSDI: Positive stool duration interval; PRDI: Positive respiratory duration interval; ND: Not described; IgM: Immunoglobulin M.

TRANSMISSION VIA FECAL-ORAL AND VIA AEROSOLS

Since the first detection of SARS-CoV-2-positive stool samples[6,16,48,66,68-72], the possibility of viral transmission through the fecal-oral route and fecal aerosols has been widely debated. Scientists have gathered their efforts in order to elucidate these issues and to determine the viability of viral particles found in air and stool samples.

Fecal-oral transmission

Studies have emphasized the risk of COVID-19 contamination from hospital surfaces and personal fomites. In an evaluation of contaminated surfaces in hospital rooms, researchers found that most samples that were found to be positive for SARS-CoV-2 RNA were from bathrooms[73]. This could indicate the possibility of fecal viral loads being more likely to remain on surfaces than viral particles released from other biological secretions, reinforcing the possibility of fecal-oral transmissions. Another paper found that five out of 27 toilet flushes tested were positive for viral RNA and all the five patients that used these bathrooms had GI symptoms[74]. This could indicate a relationship between enteric manifestations and viral shedding through feces, but further studies are needed on the topic.

Complementarily, cytopathic effects have been observed in Vero cells infected by SARS-CoV-2 isolated from feces of COVID-19 patients[75]. Moreover, the latter

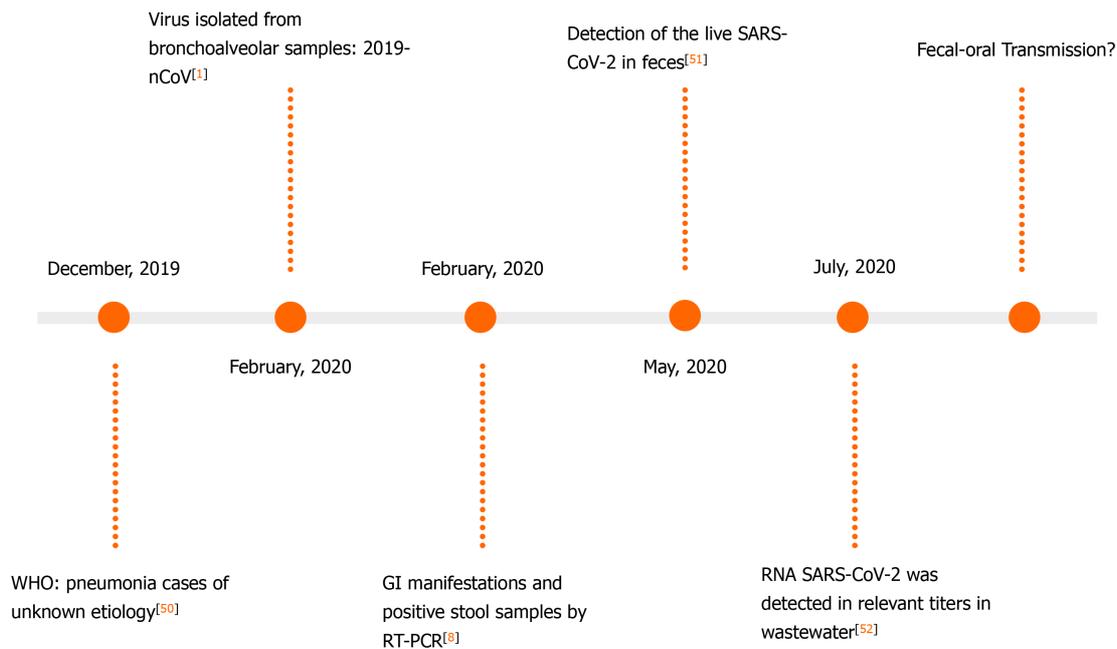


Figure 2 Timeline of studies representing the evolution of current knowledge about the possible transmission of severe acute respiratory syndrome by coronavirus 2 *via* fecal-oral. GI: Gastrointestinal; SARS-CoV-2: Severe acute respiratory syndrome by coronavirus 2; WHO: World Health Organization.

analysis through electron microscopy found viral particles with similar morphology to the novel coronavirus in fecal samples[75-77]. These studies were essential to elucidate if the positive results from RT-PCR tests in fecal samples were due to actual virions or only represent RNA from the inactivated virus.

Transmission through fecal aerosols

It is well established that SARS-CoV can be transmitted through fecal aerosols after the analysis of the Amoy Gardens incident in Hong Kong, in which multiple residents from an apartment complex were infected due to faulty pipelines that led to the spread of aerosols from the feces of infected patients[78]. The question raised with the new pandemic is whether or not SARS-CoV-2 is also able to remain viable through the process of aerosolization and to be transmitted.

Some works showed the presence of SARS-CoV-2 in air samples taken from patient’s rooms[74,79]. In two studies, researchers have observed cytopathic effects in Vero cells by viral particles collected in air samples. In one of these studies, the samples were observed through electron microscopy, which detected the presence of SARS-CoV-2 virions[80]. In the other investigation, a full genome sequencing was obtained from purified material from air samples and the viral genome was the same as the genome obtained from the infected patient’s nasopharyngeal swab[81]. This indicates that viable viral particles can be obtained from aerosols, and it raises the question of possible transmission from aerosolized virus shed through feces. Interestingly, in a study, researchers were not able to replicate viruses in Vero Cells from aerosol particles examined[82]. However, as Pan *et al*[83] have shown, the collection of viral particles using non-ideal air samplers could be the cause of viral inactivation of some specimens, which could impede the observation of cytopathic effects.

In two studies, researchers have tested the time of SARS-CoV-2 survival in aerosol suspensions. The first one found that the virus was able to survive for at least 3 h (the duration of the experiment)[84]. The second one searched for viral RNA through RT-quantitative PCR and found traces of the virus up to 16 h after the aerosolization of the particles, which were later visualized through an electron microscope and presented a shape consistent with the SARS-CoV-2 at the 10th minute of the experiment[85]. These studies show that SARS-CoV-2 is able to remain viable for long periods, and aerosols can be a dangerous form of infection.

Among studies evaluating the possibility of animal infection with virus from fecal samples, Jeong *et al*[86] intranasally inoculated viral particles that were isolated from the stool of confirmed COVID-19 patients in ferrets. Some animals showed an increase

in viral load throughout the period of infection and tested positive for the virus a few days later. All ferrets had symptoms of the disease after inoculation. In another study, Lee *et al*[87] used Syrian Golden Hamsters to inoculate intranasally and orally SARS-CoV-2 in variable doses. They found that hamsters that underwent intranasal inoculation developed more severe respiratory symptoms and similar GI inflammation to those that received the virus orally, but these results were not statistically significant ($P > 0.05$). Both groups tested positive for the virus in fecal samples and saliva[87]. This finding could indicate that in the case of fecal-oral transmission, COVID-19 manifestations could be less severe than through aerosols, but viral shedding from the infected patients would still be an important factor to consider.

Research has also shown that SARS-CoV-2 persistence time depends on multiple factors such as pH, temperature, and humidity, with the longest viability time at 4 °C temperature in a pH of 9[88]. Strategies with the use of this knowledge and standard disinfection procedures should be applied in order to reduce the risk of surface contamination, and special attention should be given to bathrooms in order to prevent transmission from their fomites. Ong *et al*[89] found contamination in 87% of surfaces in a patient's room before cleaning as opposed to no contamination in rooms of patients after the cleaning, showing the importance of precaution during the disinfecting process. In the case of the first SARS coronavirus from 2003, studies have reported that virus viability is highly affected by the pH of the patients' feces[90]. Analysis should be conducted to evaluate if this applies to SARS-CoV-2 as well.

Overall, although not totally proven, the possibility of infection by SARS-CoV-2 through the fecal-oral route or aerosolized particles should be considered. In any case, proper cleaning processes and prophylactic measures should be performed in order to avoid contact with the virus through fomites or aerosols until the possibility of both types of transmission are properly elucidated.

ENVIRONMENTAL FACTORS ASPECTS

Studies that evidence the detection of SARS-CoV-2 in fecal samples raise attention to the risks of human exposure in the environment[91]. The indirect transmission through fomites has been already well documented, especially when individuals touch contaminated surfaces and then take the hands to the mouth, nose, or eyes without first cleaning them[92]. Besides, it is assumed that improper disposal of solid waste associated with viral stability on solid surfaces could lead to contamination of surface water from household or hospital waste[93]. Furthermore, a possible spread of the virus to drinking water sources is assumed when an infected person defecates in open environments. In addition, there is a possible risk of viral transmission in shared toilets [94]. Moreover, Li *et al*[95] showed that the flow of water during flushing the toilet can spread viral particles through aerosols.

Although the transmission of SARS-CoV-2 by sewage aerosol is not yet confirmed [93], some studies (Table 3)[96-107] show the detection of SARS-CoV-2 RNA in wastewater. Arslan *et al*[108] and Pandey *et al*[93] highlight that this can be beneficial from a wastewater-based epidemiology perspective because the viral presence in wastewater can be an early warning as well as a monitoring and surveillance tool for COVID-19. However, they highlight the risk of recurrent outbreaks due to the continued presence of the virus in those media.

Recent surveys have shown that around 2.3 billion people do not have access to a basic sanitation service, and 844 million people do not have a drinking water service worldwide. Another study reports that developing countries have inefficient wastewater treatment[108]. In addition, Pandey *et al*[93] emphasized the difficulty of inspection in the least developed countries owing to the absence of a proper sewage system. Besides, Arslan *et al*[109] suggested that various societies do not have the basic conditions to inactivate the coronavirus from the water. Therefore, the treatment of water[93], the use of disinfection methods with high doses of disinfectant products [110], and public guidelines on hygienic measures[111] are convenient in that context.

CONCLUSION

The current knowledge about the dynamics of the infection in the GI tract strongly suggests a possible transmission through the fecal-oral route. In addition, the spread of infected aerosolized feces in hospital environments, bathrooms, and surfaces draws attention to this issue, which has not been considerably taken into account by health

Table 3 Detection of severe acute respiratory syndrome by coronavirus 2 RNA in water systems

Ref.	Country	Wastewater type	Main findings
Medema <i>et al</i> [96]	The Netherlands	Sewage	Sewage samples of six cities and the airport were tested: (1) February: No SARS-CoV-2 RNA was detected; and (2) March: SARS-CoV-2 RNA detection increased concomitant with the increase in COVID-19 prevalence
Ahmed <i>et al</i> [97]	Australia	Wastewater in a catchment	Two positive detections within a 6-d period from the same wastewater treatment plant
Kumar <i>et al</i> [98]	India	Wastewater Treatment Plant	Increase in SARS-CoV-2 RNA samples was concomitant with the increase in the number of active COVID-19 patients in the city
Wurtzer <i>et al</i> [99]	France	Wastewater treatment plant (raw and treated wastewater samples)	Raw wastewater samples: all positive for SARS-CoV2; Treated wastewater samples: 6 out of 8 positive for SARS-CoV2
Randazzo <i>et al</i> [100]	Spain	Wastewater treatments plants	(1) Influent samples: 35 of 42 were positive for SARS-CoV-2; (2) Effluent secondary treated samples: 2 of 18 were tested positive; and (3) Effluent tertiary treated samples: 0 of 12 tested positive
Kocamemi <i>et al</i> [101]	Turkey	Wastewater treatment plants (primary sludge and waste activated sludge)	SARS-CoV-2 RNA was detected quantitatively from all samples.
Guerrero-Latorre <i>et al</i> [102]	Ecuador	River	SARS-CoV-2 RNA was detected in the three locations
Zhang <i>et al</i> [103]	China	Septic tanks	SARS-CoV-2 RNA was detected in septic tanks after disinfection with sodium hypochlorite
Ahmed <i>et al</i> [104]	United States	Wastewater treatment plants	Two out of 15 wastewater samples tested positive
Haramoto <i>et al</i> [105]	Japan	River, wastewater treatment plants	One of 5 secondary-treated wastewater samples tested positive
La Rosa <i>et al</i> [106]	Italy	Sewage	Six out of 12 samples tested positive.
Hasan <i>et al</i> [107]	United Arab Emirates	Sewage, wastewater treatment plants, pumping stations	SARS-CoV-2 RNA was detected in 85% of untreated wastewater samples; SARS-CoV-2 RNA was not detected in wastewater treatment plants.

WHO: Pneumonia cases of unknown etiology[50]. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

agencies in discussions on infection prevention. The contamination of water by SARS-Cov-2 in sewers, wastewater treatment plants, and rivers, possibly from fecal samples, evidences a major public health problem, especially in developing countries. However, further studies are needed in order to elucidate completely the SARS-Cov-2 transmission *via* the fecal-oral route.

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