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MINIREVIEWS

Role of gastrointestinal system on transmission and pathogenesis of SARS-CoV-2

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Abstract

Coronavirus disease 2019 (COVID-19) continues to pose a significant threat to global health. Primary prevention remains as a major strategy against the pandemic. Current evidence proves that aerosol and droplet-based routes are the main means of transmission of COVID-19 but other ways should be sought in order to prevent possible collateral transmission. The gastrointestinal system may be one such route. Angiotensin converting enzyme 2 is the target entry receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is abundantly expressed in the gastrointestinal tract. SARS-CoV-2 is able to infect human enterocytes similar to severe acute respiratory syndrome and Middle Eastern respiratory syndrome. Herein this review, we discuss the current knowledge regarding the role of gastrointestinal transmission in transmission and pathophysiology of COVID-19.

Key Words: SARS-CoV-2; COVID-19; Gastrointestinal system; Transmission; Pathogenesis

Core Tip: Angiotensin converting enzyme 2 is the target entry receptor for severe acute respiratory syndrome coronavirus 2 which is abundantly expressed in lung as well as in the gastric, duodenal, and rectal epithelium. This raises the question on potential transmission of the virus through gut *via* fecal-oral route. In addition to many studies showing viral RNA in feces, studies with animal models strengthen the evidence that the virus can be transmitted through the fecal-oral route. We underline the importance of raising awareness for the control of the pandemic by updating the information about

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INTRODUCTION

In December 2019, a new type of coronavirus (novel coronavirus, nCoV), was first identified in a series of pneumonia cases in Wuhan, Hubei, China and declared as pandemic by the World Health Organization (WHO) on March 11, 2020[1,2]. Although respiratory transmission *via* droplet infection is accepted as the primary route, fecal-oral and blood transmission have been suspected[3].This issue is of a great concern for the course of pandemic as real time reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal swab is used to confirm the clinical diagnosis of coronavirus disease 2019 (COVID-19) and its negativity is sought in order to end isolation or discharge from hospital. Therefore, presence of fecal transmission as an alternative route will be consequential for the prevention of spread and therefore to control the pandemic.

Although our knowledge on the fecal transmission of COVID-19 is expanding, it still remains theoretical. In this paper, we summarize the current data on fecal-oral transmission to date and emphasize the urgent need for more insight regarding the pathogenesis and fecal-oral transmission as a possible route, in order to better understand the disease and take actions to counteract the virus.

LITERATURE SEARCH

We performed a systematic search of all published and in-press articles in PubMed, Web of Science, Google, EMBASE databases with search terms "COVID-19", "SARS-CoV-2", "Discharge criteria", "multiple specimens", "virus shedding'', "transmission", "RT-qPCR", "gastrointestinal", "digestive system", "transmission route", "fecal-oral transmission". We also searched Clinilaltrials.gov database for ongoing clinical studies. After removal of duplicate results, two authors (Erul E and Simsek C) filtered the remaining studies. We excluded abstracts, unavailable full-texts, non-English publications. All studies included in the first step were reviewed with full-text by two authors (Simsek C and Balaban HY).

LESSONS LEARNED FROM SEVERE ACUTE RESPIRATORY SYNDROME AND MIDDLE EASTERN RESPIRATORY SYNDROME

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, single-stranded RNA virus with a positively charged capsid, and taxonomically belongs to the same beta coronavirus genus with severe-acute respiratory syndrome-associated coronavirus (SARS) and Middle Eastern respiratory syndrome-related coronavirus (MERS) viruses[4]. Therefore, we can learn from previous outbreaks of SARS and MERS in terms of transmission, clinical features and disease management.

Both SARS and MERS viruses were shown to infect human enterocytes in both *in vitro* and *in vivo* studies. In an animal model of human DPP4 transgenic mice, an intragastric inoculation of MERS-CoV was shown to induce replication and following infection in the intestines[5]. In a human study, six fatal cases of SARS were investigated for the distribution of virus through an extensive analysis of various tissue samples with immunofluorescence-fluorescence *in-situ* hybridization (FISH), finally demonstrating infection of small intestinal epithelium[6]. In another study, a large cohort of SARS patients with gastrointestinal symptoms were included where positive nucleic acids were detected in the stool samples of 97% (65 / 67)[7]. This indicates the active involvement of gastrointestinal tract not only in the clinical presentation but

also viral replication and pathogenesis. In a similar study with MERS RNA was studied in 37 infected inpatients and demonstrated 14.6% positivity[8].

Notably, MERS-CoV and SARS-CoV studies to date have not demonstrated gastrointestinal transmission in human. Having said that, our findings from epidemiological and virological studies may indicate environmental contamination through respiratory droplets and feces, particularly in regions with poor sanitation. These could serve as an alternative route to acquire COVID-19[9].

PATHOGENICITY AND TRANSMISSION OF SARS-COV-2

SARS-CoV and SARS-CoV-2 have surface anchored Spike (S) glycoproteins that harbor receptor-binding domains (RBDs). These play critical roles for the viral entry into the human cell through the angiotensin converting enzyme 2 (ACE2) receptor and TMPRSS2 protein[10]. Therefore, expression of ACE2 is an important landmark to demonstrate potential susceptibility for SARS-CoV-2 infection. Four data sets with single cellular transcriptome of the lung, esophagus, stomach, ileum and colon were analyzed to examine the composition and proportion of cells expressing ACE2. ACE2 was found to be highly expressed not only in lung AT2 cells but also in the enterocytes of ileum and colon[11]. This study provided bioinformatic evidence of the potential pathway for SARS-CoV-2 infection in the digestive tract. As such, diarrhea may be caused by the invasion of ACE2-expressing enterocytes preceding fever and respiratory symptoms.

Other parts of the gastrointestinal tract might be susceptible to SARS-CoV-2 infection. This was demonstrated by histologic and immunofluorescent staining of gastrointestinal epithelial samples for ACE2 receptor expression, which was extensively expressed in the gastrointestinal system, mainly in the glandular cells of the stomach, duodenum, and rectum[12]. Notably, esophagus is rarely stained with ACE2, because it consists mainly of squamous epithelial cells rather than glandular cells. *In vivo* studies also show enterocytes can be infected by SARS-CoV-2. Human small intestinal organoids (hSIOs) interaction with SARS-CoV and SARS-CoV-2 was assessed by qRT-PCR, and then live virus titers were measured on VeroE6 cells enterocyte cell line. Although immunofluorescent staining of SARS-CoV-2 was observed only in a few intestinal organoid cell clusters at 24 h but infected nearly all organoids after 60 h[13].

Live SARS-CoV-2 was recently observed in the feces of a patient with COVID-19 [14]. If SARS-CoV-2 actively infect human enteroids and intestinal epithelial cells *in vivo* and viral RNA are shed in fecal specimens, whether the virus in feces is infectious and the fecal viral load is high enough for human transmission should be questioned. In line with this question, Vero E6 cells were inoculated with fecal samples of COVID-19 patients. After a second-round passage, a cytopathic effect in Vero E cells was observed. This indicates that infectious live virus in feces can transmit infective virions into enterocytes.

Beside these *in vitro* findings, there is also *in vivo* data for supporting fecal transmission of SARS-CoV-2. In a ferret animal model study to decode the transmission routes of the virus, centrifuged fecal specimens of infected ferrets were collected, their debris removed, and then inoculated into naive ferrets. After the nasal wash specimens of fecal-specimen-treated ferrets inoculate Vero E6 cells, the virus could be isolated from 2 out of 3 of samples. These results show how body fluids could be infectious for SARS-CoV-2[15]. Fecal-oral transmission of SARS-CoV-2 was also tested in large animal models. SARS-CoV-2 was inoculated to the intranasal and stomach of Rhesus monkeys. Viral RNA has been detected in both digestive and lung epithelium after intranasal inoculation with histopathological changes showing inflammation in both. Models were followed up with chest radiographs after intragastric inoculation. At the end, pulmonary infiltration and pneumonia were also observed in this group, however they could not detect viral RNA in the lung. CD 68 marker indicated macrophages were also increased in histopathological examination and inflammatory cytokine levels of the digestive system were elevated. This finding may be explained by the fact that inflammatory reactions can be originated or potentiated by the digestive system as the largest immune organ[16]. The inflammation caused by activated T cells, plasma cells, dendritic cells, and macrophages in the peyer plaques and lymphoid tissue of the digestive system may play a role in the pathogenesis of cytokine storm that frequently occurs in COVID-19 patients.

Another question that it brings up is whether the gastrointestinal tract could possibly be a viral reservoir, whether macrophages infected by SARS-CoV-2 could lay

there as an undetected reservoir, and then might lead to reinfection? A group of COVID-19 patients whose nasopharyngeal swabs had been found to be negative several times converted positive later on. The most common explanation for these instances is false negative results of earlier tests due to wrong sampling technique[17]. However, the question is if this is a reinfection with a new viral strain or if the gastrointestinal tract could be a viral reservoir where virus might reactivate, leading to recurrence of infection. As a result, these findings reveal that there is a very complex relationship between the lungs and the digestive system in the pathogenesis and transmission of the disease.

GASTROINTESTINAL SYMPTOMS IN COVID-19 AND POTENTIAL FECAL-ORAL TRANSMISSION

Whilst COVID-19 patients most frequently present with fever or respiratory illness, a group of patients experience digestive symptoms including diarrhea, nausea, vomiting, abdominal pain, abdominal discomfort, or gastrointestinal bleeding during disease progression. The incidence of these gastrointestinal symptoms was broadly different in the studies ranging from 5%-61%[18-23].

SARS-CoV-2 has already been detected in fecal specimens of COVID-19 patients even in the ones without any gastrointestinal signs or symptoms. Additionally, this fecal shedding of virus is known to persist for weeks after initial diagnosis and even after PCR negativity[21,24-26]. In one study, fecal samples tested by rRT-PCR for SARS-CoV-2 were 29% (44 of 153 patients) positive[27]. Another study showed that 55% (41 of 74 patients) of fecal specimen tested by SARS-CoV-2 RNA remained positive up to 33 d (for a mean of 27.9 d) following negative pharyngeal PCRs[28]. Similarly, in another study, using the next-generation sequencing of stool samples from COVID-19 patients, it was shown that the virus was excreted in the stool for a long time, and had different variants with many mutations[29]. Along with these studies, stool RT-PCR tests of three pediatric cases were positive after 10 d of recovery [30]. These studies imply that viral shedding *via* feces might occur for a long time after recovered, and so both child and adult post-COVID patients might be asymptomatic carriers of the virus. Based on this, it is recommended that a negative fecal viral RNA test should be added as discharge criteria in patients with negative oropharyngeal specimens[28,31].

One study found that the viral load of SARS-CoV-2 RNA excreted in the feces of some patients was 10^7 copies/g. This high amount indicates that it could not occur only by ingestion of viral particles in respiratory tract secretions. Transcription of subgenomic mRNA (sgmRNA) of SARS-CoV-2 shows active virus replication in the tissue due to its inability to be packaged into virions. Therefore, the presence of sgmRNA in the feces may be proof that SARS-CoV-2 productively infects intestines [32]. Fecal calprotectin is an established biomarker for gastrointestinal tract inflammation[33]. Fecal calprotectin level was also elevated in COVID-19 patients with diarrhea compared to those without diarrhea and correlated with another inflammatory marker IL 6[34]. This finding supports the intestinal inflammation in COVID-19 patients and indicates a transmission as well as pathophysiology of COVID-19.

All of these findings prompted us to investigate why and how the SARS-CoV-2 leads to gastrointestinal symptoms. If pharyngeal swabs of patients are negative for RNA, are they truly virus-free and should we get specimens from multiple sites such as feces? The most important question that remains unanswered is: Could fecal-oral transmission be one of the reasons for the rapid spread of the virus?

Anal swabs for detection COVID-19 patients have started to be used in some provinces of China. Viral RNA detection in anal swabs or stool samples of COVID-19 patients could be routinely performed for the decision about hospitalization, recovery and discharge. Transmission-based measures for patients may be considered to continue until there is negative transformation of viral RNA in stool[35,36]. Patients might have only gastrointestinal symptoms initially upon presentation to the hospital. If the patients come with only gastrointestinal symptoms, it may cause missed and late diagnosis and increase in the number of cases due to not taking necessary precautions. Clinicians should be aware of fecal-oral route and possibilities of COVID-19 if diarrhea is complaint of their patients[37].

GASTRIC ACIDITY AND COVID-19

Gastric mucosa and its pH below 3.0 protects against COVID-19 due to its enveloped structure[38]. Recently in a retrospective study, the epidemiological, clinical, and laboratory data of 420 patients with COVID-19 showed that patients with a history of *Helicobacter pylori* (*H. pylori*) infection had more upper and lower gastrointestinal symptoms. A study analyzing 34541 individual cells derived from 12 gastric mucosa samples by ScRNA-seq analysis found a clinical correlation between specific expression of ACE2 and TMPRSS2 in gastric mucosa and *H. pylori* infection and intestinal metaplasia. Therefore, it is suggested that intestinal metaplasia and *H. pylori* are risk factors for SARS-CoV-2 due to loss of gastric acidity that inactivates the virus.

Elderly people could be also more susceptible for SARS-CoV-2 due to decreased stomach acidity with atrophic gastritis[39-41]. There are reports indicating significant associations between blood type A and atrophic gastritis and *H. pylori* infection[42]. Similarly, there are reports suggesting that people with blood group A are more susceptible to SARS-CoV-2[43,44]. Therefore, hypotheses were developed stating blood group A persons are more likely to be infected with SARS-CoV-2, as they are also more susceptible to *H. pylori* infection, and they have higher possibility of gastrointestinal viral transmission[39]. Proton pump inhibitors (PPIs) usage may also be a risk factor affecting the natural course of COVID-19 and they should be used cautiously by clinicians[45]. The data from the Korean nationwide cohort were used to compare the clinical outcomes of COVID-19 patients in three groups: Current PPI user, in hospital PPIs user after diagnosis, and non-users. Patients who took twice daily PPI had significantly higher requirement for oxygen therapy, intensive care unit admission, invasive ventilation than patients who had never taken PPI [fully adjusted OR (aOR): 2.39; 95%CI: 1.08-5.10]. However, researchers also suggested that mucosal protective agents might be beneficial to prevent virus spreading from stomach to the intestine and reduce the occurrence of subsequent diarrhea. In 18 hospitalized patients with upper gastrointestinal symptoms, none of the 8 patients using mucosal protective agents (sucralfate suspension gel, hydrotalcite tablets) developed diarrhea, whereas 6 of 10 patients who did not use mucosal protective agents subsequently developed diarrhea[46].

CONTAMINATED FOOD AND COVID-19 INFECTIVITY

SARS-CoV-2 virus viability and infectivity in the food and feces are still not clear. In a recent study, foods prepared with chicken, salmon and pork were inoculated with SARS-COV-2 and then stored at 4 °C, -20 °C or -80 °C. After 3 wk, no reduction in virus titer and infectivity was observed between different temperatures[47]. Another case that might point to a potential transmission took place in Beijing. No new cases had been reported for 2 mo in Beijing until the diagnosis of a 52-year-old male. When the index case and contacts were searched, only environmental samples from the Xfandi Market were found to be positive for SARS-CoV-2 PCR. Detailed epidemiological investigations gave rise to the hypothesis that contamination from fish products stored in cold chains may cause another transmission route for the virus[48].

SARS-CoV-2 RNA has been detected in sewage in Australia using RT-qPCR assays and confirmed by sequencing. Sewage from hospitals must be properly disinfected as a precaution, specifically in areas with poor sanitation[9]. The possibility of SARS-CoV-2 transmission through the fecal-oral route is crucial for the control of the pandemic. We emphasize the importance of frequent and proper hand hygiene as well as wearing mask and social distancing. Particular measures should be taken by physicians in procedures such as endoscopy that may be exposed to the stools of COVID-19 patients in the hospital[49].

CONCLUSION

Although more than 1 year has passed since the first case, COVID-19 still causes morbidity and mortality led by mutations and new variants all over the world. There are many studies on the possibility of transmission of SARS-CoV-2 through the fecal-oral route, but none of them has proven this hypothesis yet. In real life it is difficult to prove or deny fecal-oral transmission, since transmission *via* droplets cannot be controlled, and human subjects cannot be ethically exposed by fecal-oral route[50]. However, research with ferret and Macaca Rhesus model regarding COVID-19 fecal-

oral transmission are milestones in the field. These studies should be analyzed carefully and fecal-oral transmission warrants further attention. The fecal-oral route should not be overlooked and many more studies are needed on this subject. The potential strategies for prevention of possible fecal-oral transmission might be a routine anal swab testing for detection of SARS-CoV-2 in hospitalized patients, especially in those with only gastrointestinal symptoms such as diarrhea and/or with negative nasopharyngeal PCR; and more frequent use of feces PCR test in order to detect those post COVID-19 carriers with negative nasopharyngeal swabs.

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