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COVID-19 Diarrhea

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Abstract In 2019, a novel virus emerged in Wuhan, China that caused a febrile respiratory illness, sometimes rapidly fatal and thought to be transmitted by droplet contact. It likely originated from another species (possibly the bat), but later, spread occurred from human-to-human. Over a period of months, this disease disseminated to more than 100 nations as a highly infectious pandemic, reminiscent of disease associated with other coronavirus agents in 2002 (SARS) and 2012 (MERS). This COVID-19 virus also caused other forms of clinical illness, albeit in the minority, and most infected patients (over 50%) had few symptoms or remained completely asymptomatic. Prominent in some patients was watery diarrhea, often lasting less than a week, but sometimes without any respiratory features, such as fever, cough or shortness of breath. It is believed that fecal-oral transmission may result. The virus attaches to the surface of human respiratory and intestinal cells, gains entry into these cells, ultimately leading to production of new virions intraluminally. Fecal shedding may occur for extended periods, even after respiratory secretions become negative. Apart from preventive measures, vaccine development remains the most important strategy.

Keywords: *Covid-19, coronavirus, ACE-2 Receptors, fecal shedding*

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1. COVID-19 and Other Coronavirus Agents

COVID-19 is a newly recognized single-stranded, positive-sense RNA virus that belongs to the coronavirus family initially reported in a patient with pneumonia from Wuhan, Hubei Province of China in late 2019 [1]. After clinical illness had spread to over 100 countries, the World Health Organization (WHO) declared a pandemic, recognizing the agent to be a highly infectious viral agent, sometimes fatal [2].

COVID-19 is caused by an enveloped RNA-containing betacoronavirus [3]. This viral agent may cause a variety of clinical effects, some potentially fatal, including a severe acute respiratory syndrome. The agent, coronavirus-2 (SARS-CoV-2), is phylogenetically similar to SARS-CoV [4] with an estimated 79% sequence identity, demonstrating that the 2 viral agents are homologous [5]. In 2002, SARS-CoV had caused a severe acute respiratory syndrome outbreak in Guangdong Province, China [6,7,8]. Another coronavirus was identified in 2012 to cause a severe acute respiratory syndrome (MERS-CoV) in the Middle East, initially reported from Saudi Arabia [9]. Both of these coronavirus agents, like COVID-19, appeared to be spread by a droplet-contact type transmission.

2. Clinical Features of COVID-19 Infection

The characteristics of laboratory-confirmed coronavirus disease (COVID-19) were based on RT-PCR-based assays (real-time reverse-transcriptase-polymerase-chain-reaction) using nasal and pharyngeal swab specimens and established by WHO [10]. For example, an early report based on the first 2 months of the China outbreak included over 1000 patients [11]. Overall, 5% required ICU admission, 2.3% mechanical ventilation and 1.4% died. Although the initial source was thought to be a fish market in Wuhan and later suspected to be a coronavirus from bats, only 1.9% of affected patients were observed to have any direct contact with wildlife. Indeed, the majority had contact with Wuhan residents, including visitors to Wuhan. Median incubation was defined as 4 days with an interquartile range 2 to 7 days. The most common recorded symptoms were fever, cough and dyspnea, sometimes, but not always, associated with ground-glass radiological CT imaging changes. Nausea or vomiting and diarrhea were not common, estimated at only 5% and 3.8%, respectively. Interestingly, in the overall population of patients 23.7% had at least one co-existing illness, including hypertension. Other large studies subsequently reported from China generally confirmed these findings, except that diarrhea was recorded more frequently to about 15% or more [12].

To summarize, these early data strongly suggested a highly infectious viral agent derived from a non-human species and capable of human-to-human transmission with a high mortality. Most, but not all, hospitalized patients suffered a febrile respiratory illness, however, a large percentage of patients had no or minimal symptoms, including atypical features, such as diarrhea. Initially, most vulnerable patients were elderly, often residents of long-term care facilities, frequently with underlying diseases. In less than 6 months, this pandemic spread through Europe and North America, and later South America and the Indian sub-continent. Precise numbers of confirmed cases are difficult to fully ascertain or may not have even been reported, but over 500,000 of confirmed cases have died. Although the elderly have been most affected, particularly early in the pandemic, no age group has been spared. Recent experiences indicate a lowering of the mean age, possibly related to a relaxation of preventive measures and working in employment necessitating close contact of persons (eg., meat processing facilities).

3. Other COVID-19 Symptoms

Studies from China also indicated that this virus infects respiratory epithelial cells and appears to spread from human-to-human via the respiratory tract in exhaled droplets. Other viral targets, however, have also been considered. For example, a number of reports described olfactory and taste dysfunction, particularly in females [13,14,15] noting the finding in transgenic mice of possible retrograde tracking of the virus and entry via the olfactory nerve into the brain [16]. In addition, acute neurological events with imaging abnormalities have also resulted in speculation regarding central nervous system infection [17]. Cardiovascular events may be a further manifestation of direct viral tissue infection [18]. A hyper-coaguable state may occur associated with a risk for venous thrombotic events and pulmonary embolism [19]. Conjunctival effects, including hyperaemia have been associated with detection of the viral RNA in tears [20].

4. Fecal Samples in COVID-19 Diarrhea

Detection of SARS-CoV-2 RNA in a fecal specimen suggested viral gastrointestinal infection and possible transmission via the fecal-oral route [21]. In one early report focused on positive fecal specimens [22], SARS-CoV-2 RNA was detected in over 50% of hospitalized patients, some for up to 12 days duration. In some, the viral agent persisted in fecal material even after negative results were noted in respiratory samples [22].

5. ACE2 Viral Receptors in Intestinal Epithelial Cells

Interestingly, some have indicated that SARS-CoV-2 employs angiotensin converting enzyme (ACE) 2 as a specialized viral receptor for epithelial cell entry [23], similar to SARS-CoV. This ACE2 messenger RNA is expressed throughout the gastrointestinal tract and is intimately associated with the neutral amino acid transport system [24,25]. Given reports of hypertensive disease in the early clinical series of COVID-19 from China, this was intriguing. Further population-based studies were done to determine use of angiotensin-converting enzyme (ACE) and angiotensin-receptor blockers (ARBs) in this population. Although use of these agents were recorded more often in COVID-19 patients from the Lombardy region of Italy, there was no evidence that use increased risk of COVID-19 (26). Similarly, in a New York study, risk was not increased for COVID-19 test positive patients including groups using 5 common classes of antihypertensive medications [27].

6. Mucosal Pathology in COVID-19 Infection

To date, there is little in the way of published studies that systematically evaluate the mucosal histopathologic effects of COVID-19. However, some preliminary endoscopic-biopsy studies demonstrated limited pathological changes in the esophagus, stomach, small and large intestine consisting largely of increased numbers of plasma cells and lymphocytes in the mucosal lamina propria [22]. Little other significant change was reported. Using an immunofluorescent method, however, staining for viral host receptor ACE2 in epithelial cell cytoplasm was strongly positive in patients with positive fecal SARS-CoV-2. In addition, immunofluorescent staining for viral nucleocapsid protein was positive in gastric, small and large intestinal epithelial cells, but not esophageal mucosa [22]. These descriptive observations suggested that the ACE2 receptor may be an important means of epithelial cell entry for the virus, theoretically allowing viral infection and assembly of new virions that may be shed into the lumen. Again, in these patients, fecal studies remained positive by PCR testing even after shedding had ceased in the respiratory tract.

7. Pathogenesis of COVID-19 Diarrhea

The etiopathogenesis of SARS-CoV-2 associated diarrhea has been considered by others elsewhere [28]. SARS-CoV is thought to enter the epithelial cell by interaction with an envelope-anchored spike glycoprotein and ACE2. This spike protein has 2 subunits, S1 and S2, for epithelial cell entry. One subtype mediates virus attachment to the host cell membrane while the other subtype is involved in cell membrane fusion. Cellular serine proteases (TMPRSS2), highly co-expressed in respiratory and intestinal epithelia, initiate spike protein cleavage to regulate the process [29]. Infectivity is dependent on ACE2 binding affinity that is 10-20 times higher for SARS-CoV-2 than for SARS-CoV. It has been hypothesized that viral infection results in altered intestinal permeability and nutrient malabsorption [5]. Other hypothetical mechanisms involve altered uptake of

dietary amino acid and peptides resulting in changes to luminal antimicrobial peptides and the gut microbiome [30].

8. Clinical Features of COVID-19 Diarrhea

Clinical and epidemiological characteristics of COVID-19 diarrhea have been reported in several studies [28]. Importantly, diarrhea, usually loose, watery and non-bloody, has been recorded in some patients with and critically, even without respiratory symptoms. Indeed, bloody stools is unusual and may suggest a co-existing disorder. Diarrhea may be associated with nausea vomiting and abdominal pain. Retrospective series have also recorded diarrhea as the sole symptom at disease onset in about 10%. Some series have noted development of diarrhea later, during the disease course. The median diarrhea duration is about 4 days, ranging from 5 to 8 days [31]. Diarrhea initially seemed to accompany more severe disease, including those patients requiring mechanical ventilation, but data was inadequate to suggest a negative prognosis if diarrhea was present [32]. Similarly, with SARS-CoV and MERS, diarrhea was documented in most series, usually less than 20%.

9. Future Focus

In the immediate future, most focus will centre on preventive measures and the development of an effective vaccine [33]. So far, none are available although there are many current candidates being developed in China, United States, Canada and some European countries. In addition to development of a candidate vaccine, clinical trials will need to be completed (to include long-term effectiveness and safety) followed by mass manufacturing of vaccine and global distribution. Each of these phases will take significant time with the overall goal of vaccinating sufficient numbers of susceptible people to promote herd immunity. Much of this process has yet to be defined, and may be stalled at different stages.

Gastroenterologists need to correctly pay attention to preventive measures including masks, gloves, gowns and goggles, hand hygiene and careful processing of endoscopes and other reusable accessories. Attention to fecal SARS-CoV-2 will be critical, recognizing that PCR based detection methods only indicate the prior presence of the virus, rather than infectious virus *per se*. Watching for food-borne illness will be essential, including cruise ship clusters, hospital and care home clusters. Rapid point-of-care testing, tracking, contact tracing with public health and serological testing will be essential along with universal precautions during endoscopy and, possibly, for periods after endoscopy to ensure clearance of viral aerosols from procedure facilities. Processing of patients will simply require more time. Education and re-education of ourselves and our trainees will be needed. Special implications for patients with pre-existing intestinal disease, including celiac disease, will require exploration. We have unexpectedly and rapidly entered a new era of research and patient care in Gastroenterology.

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