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A Review of the Gastrointestinal Effects Associated with COVID-19 Infections

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Abstract

SARS-CoV-2, the virus that causes COVID-19, has led to an ongoing worldwide pandemic that has afflicted nearly 46 million lives world. Current clinical evidence indicates that gastrointestinal symptoms may be more prevalent across COVID-19 infections than clinicians previously realized. Furthermore, these symptoms are common among patients who present with no other COVID-19 symptoms, suggesting that these individuals may be unknowingly spreading the disease to others. The ability of SARS-CoV-2 to invade cells depends on two key factors: Angiotensin Converting Enzyme-2 (ACE2) receptors and Transmembrane Serine Protease (TMPRSS2). Research has shown that both ACE2 and TMPRSS2 are highly expressed in the gastrointestinal tract, which is the likely mechanism by which SARS-CoV-2 invades the digestive system to induce symptoms that include diarrhea, nausea and vomiting. Further studies suggest that probiotics may serve as a means to combat COVID-19.

Keywords: COVID-19; Gastrointestinal symptoms; Angiotensin Converting Enzyme-2 (ACE2) receptors; Transmembrane Serine Protease (TMPRSS2); Gut microbiome; Fecal transmission; Probiotics.

Introduction

As the novel coronavirus, COVID-19, approaches nearly 11 million cases in the United States and 740,000 deaths worldwide, early identification of COVID-19 specific symptoms has become imperative to stop transmission [1,2]. Along with common COVID-19 symptoms (e.g., fever, cough and shortness of breath), there have also been reports of gastrointestinal symptoms, such as diarrhea, nausea and vomiting, and anorexia that accompany the virus. COVID-19 patients report these gastrointestinal symptoms occur either before, after, or completely independent of typical symptom [3,4]. COVID-19 is most commonly spread via person-to-person contact through respiratory droplets; however, spread via fecal-to-oral route has recently been discovered as well [4]. Identification of the most commonly observed gastrointestinal symptoms can assist in early diagnosis, thereby simultaneously halting transmission and potentially allowing for early treatment interventions. In this article, we will review the clinical presentation and pathophysiology of gastrointestinal symptoms frequently reported by COVID-19 positive patients.

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Clinical presentation

Preliminary studies have revealed that the Coronavirus Disease 2019 (i.e., COVID-19) may present with a variety of gastrointestinal symptoms, including diarrhea, nausea and vomiting, anorexia, abdominal pain, pharyngalgia and reduction or loss of taste (i.e., dysgeusia or ageusia) [5]. Clinical data regarding the prevalence of these symptoms is largely variable, with some studies suggesting as little as 11% of COVID-19 positive patients experience these symptoms, while other studies report as many as 68% of COVID-19 patients report gastrointestinal distress [3,6]. Similarly, reports vary regarding the most common gastrointestinal symptoms that occur, with some sources claiming diarrhea to be the most common while others claim anorexia is the most common [2-4]. However, in both children and pregnant women, nausea and vomiting are the most commonly reported [6]. Researchers and clinicians hypothesize that the incidence of gastrointestinal symptoms may be more prevalent than previously reported, especially since many patients may experience this gastrointestinal distress and unknowingly be infected with SARS-CoV-2, the virus that causes COVID-19 [7].

Although these gastrointestinal symptoms correlate with a more severe disease course and higher incidence of hospitalizations, some reports have indicated that mild COVID-19 cases often present with only gastrointestinal symptoms [5,7]. In fact, there have been multiple reports of patients experiencing gastrointestinal symptoms without the presence of fever, cough, or shortness of breath [3,4].

Patients who experience digestive symptoms take approximately 50% longer to seek medical care compared to those who have respiratory symptoms, indicating these individuals may be unwittingly spreading the disease to others. Recent research from China revealed that gastrointestinal symptoms were the only symptoms seen in approximately 25% of mild COVID-19 cases. Of these patients, an estimated one in five had diarrhea as their first symptom. The onset of gastrointestinal symptoms, particularly diarrhea, can occur as early as one day after contracting COVID-19 or as late as 10 days after exposure. The average duration of this diarrhea was five days, although some individuals experienced diarrhea for up to two weeks [4,7].

Pathophysiology

SARS-CoV-2 enters host cells via the Angiotensin Converting Enzyme-2 (ACE2) receptor [8]. This receptor is expressed in nearly all human organs, thus allowing the virus to induce a variety of symptoms as it targets each organ system. Not surprisingly, the expression level of ACE2 in each organ system correlates with the prevalence of observed symptoms in patient populations [6,9,10]. For example, ACE2 is primarily expressed on type II alveolar epithelial cells, which is not surprising, as one of the most widely reported COVID-19 symptoms is respiratory distress [3,9]. Although most prior studies focus on the interaction between SARS-CoV-2 and the ACE2 receptor population found within the lungs [11-13], additional studies have examined the relationship this interaction may play in the pathological characteristics underlying the gastrointestinal symptoms seen in many COVID-19 cases [8,14,15].

Researchers recently examined the quantitative expression map for ACE2 across 72 human tissues, including the testicular, cardiovascular, renal and gastrointestinal expression levels. They found that ACE2 showed comparably high expression levels in the surface epithelial cells of the gastrointestinal system, especially in the ileum, duodenum, jejunum, caecum, colon and stomach [16]. Further studies demonstrated that ACE2 expression levels are actually higher in the digestive tract than the lung, suggesting that the gastrointestinal system should also be considered a highly susceptible target for SARS-CoV-2 infection [17].

SARS-CoV-2 entry into host cells is also dependent on the Transmembrane Serine Protease (TMPRSS2), which cleaves the S protein of human coronaviruses on the cell membrane to allow the virus to fuse the cell membrane and thus enter the host cell [18,19]. Recent studies revealed that both ACE2 and TMPRSS2 were highly expressed in absorptive enterocytes in both the ileum and colon, thus providing evidence of the potential mechanisms by which SARS-CoV-2 invades the digestive system [20]. This same mechanism has been identified as the potential route that SARS-CoV-2 invades the respiratory tract and may provide a potential target for COVID-19 pharmacotherapies [19,20].

Current evidence links severe cases of COVID-19 with higher concentrations of cytokines and numerous studies suggest that this "cytokine storm" may contribute to the mortality of COVID-19 [21-23]. Researchers have hypothesized that SARS-CoV-2 may induce a similar increase in these inflammatory cytokines in the gastrointestinal tract, thus damaging the mucous membrane barrier of these digestive organs causing the now cardinal GI symptoms associated with COVID-19 [17]. Current studies are already beginning to strengthen this hypothesis, as these studies revealed cytokine genes that were induced by SARS-CoV-2 [24,25]. Investigators have also begun to speculate if SARS-CoV-2 affects the enteric nervous system by either direct viral infection or through these inflammatory cytokines, which could exacerbate gastrointestinal symptoms. For example, the interconnected gut-brain axis may allow SARS-CoV-2 and its elicited immune response to stimulate the vagus nerve to induce vomiting [26].

Fecal transmission

While it has been known that COVID-19 can spread via respiratory droplets through person-to-person contact, there have been new reports regarding fecal transmission of COVID-19. Clinicians have begun using a viral RNA qPCR test to measure the levels of SARS-CoV-2 in patients' stool, especially since asymptomatic carriers may show elevated SARS-CoV-2 in their stool [27]. In a recent study that utilized this testing procedure, researchers were surprised to find a longer disease course in patients with digestive symptoms. They found that compared to patients with only respiratory symptoms, patients who experience gastrointestinal symptoms are more likely to have a positive fecal viral test and take significantly longer to clear the virus (i.e., 44.2 vs 33.7 days) [7]. Further studies revealed that approximately 23% to 82% of patients continue to have positive fecal results after having negative respiratory results [28]. This data suggests the potential for patients to continue to transmit SARS-CoV-2 via the fecal-to-oral route up to seven days after respiratory test results may suggest they are no longer contagious.

Probiotics

Further studies have shown an abundance of certain bacteria such as *Coprobacillus*, a bacterium known to strongly upregulate ACE2 in the gut, to be associated with higher COVID-19 severity while an abundance of *Faecalibacterium prausnitzii*, a

bacterium known for its anti-inflammatory properties, has been associated with a decrease in disease severity [29,30]. Other *Bacteroide* strains have been shown to downregulate ACE2 in the gut, leading to a decreased viral load in fecal samples. These correlations between gut microbiome alterations and disease severity suggest a new potential treatment approach to patients diagnosed with COVID-19. In fact, studies have suggested that prebiotics and probiotics may prevent and/or treat COVID-19 [31].

Probiotic strains, such as *bifidobacterial* and *lactobacilli*, have regulated the immune response to allow for influenza virus clearance from the respiratory tract [32,33]. Similarly, probiotic strains may alter proinflammatory cytokines to minimize the COVID-19 immune-response mediated damage to the lungs [34]. This is especially important since probiotics could serve to reduce both gastrointestinal and respiratory symptoms associated with COVID-19. The ability of probiotic administration to reduce these respiratory symptoms is not surprising, as prior studies have reinforced the existence of a gut-lung axis, which allows the gut microbiota to modulate the severity of lung infections, including influenza and *Mycobacterium tuberculosis* infections and potentially including SARS-CoV-2 infections [35,36]. This is not surprising since prior studies have indicated that human gut microbiota is closely connected to the immune system [37,38]. These studies found that a diverse microbiome enhances the immune defense response whereas a dysbiotic microbiome has a strong association with immune system dysfunction, autoimmune diseases and poor patient outcomes during critical illnesses.

Conclusion

Understanding the symptoms, especially the less obvious mild symptoms, of a COVID-19 infection are particularly important to allow for early diagnosis and prevention of disease transmission. Therefore, it is important for both clinicians and the general population to recognize the gastrointestinal symptoms associated with COVID-19 infections. Per the recommendation of the CDC, patients experiencing diarrhea, anorexia, nausea and/or vomiting should self-quarantine for a minimum of 14 days and/or until COVID-19 can be ruled out via negative respiratory tests. Individuals who are under self-quarantine should stay home and separate themselves from others [39].

Future studies should continue to identify the prevalence, onset and duration of these gastrointestinal symptoms so that early detection and diagnosis is possible. Furthermore, a more comprehensive analysis is required to understand the potential of fecal-to-oral transmission of the SARS-CoV-2 virus as this could greatly impact pandemic control strategies [40]. Specifically, it is important we elucidate the underlying mechanisms responsible for the longer disease course in patients with digestive symptoms and the potential that the SARS-CoV-2 virus may increase the permeability and diminish the intestinal wall barrier function, allowing for easier invasion of pathogens across the intestinal surface area and inducing nutrient malabsorption. Efforts should also be made to examine whether SARS-CoV-2 alters the concentration of inflammatory cytokines within the digestive tract and the short- and long-term consequences of these potential alterations. Finally, additional research is needed to assess the ability of prebiotics and probiotics to combat COVID-19.

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