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Diarrhea and COVID-19 Infection

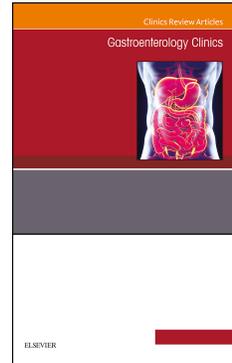
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## Diarrhea and COVID-19 Infection

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## ABSTRACT

The global COVID-19 pandemic has caused significant morbidity and mortality, thoroughly affected daily living, and caused severe economic disruption throughout the world. Pulmonary symptoms predominate and account for most of the associated morbidity and mortality. However, extrapulmonary manifestations are common in COVID-19 infections, including gastrointestinal symptoms, such as diarrhea. Diarrhea affects about 10% to 20% of COVID-19 patients. Diarrhea can occasionally be the presenting and only COVID-19 symptom. Diarrhea in COVID-19 subjects is usually acute but is occasionally chronic. It is typically mild-to-moderate and nonbloody. It is usually much less clinically important than pulmonary or potential thrombotic disorders. Occasionally the diarrhea can be profuse and life-threatening. The entry receptor for COVID-19, ACE-2 (angiotensin converting enzyme-2), is found throughout the GI tract, especially in the stomach and small intestine, which provides a pathophysiologic basis for local GI infection. COVID-19 virus has been documented in feces and in GI mucosa. Patients with preexisting diarrhea before contracting COVID-19 infection may have diarrhea exacerbation with COVID-19 infection, or alternatively the diarrhea may be incidental to COVID-19 infection. Treatment for COVID-19 infection, especially antibiotic therapy, is a common culprit. but secondary infections including bacteria, especially C. difficile, are sometimes implicated. Workup for diarrhea in hospitalized patients usually includes routine chemistries; basic metabolic panel; and a complete hemogram; sometimes stool studies, possibly including calprotectin or lactoferrin; and occasionally abdominal CT scan or colonoscopy. Treatment for the diarrhea is intravenous fluid infusion and electrolyte supplementation as necessary, and symptomatic antidiarrheal therapy, including Loperamide, kaolin-pectin, or possible alternatives. Superinfection with C. difficile should be treated expeditiously. Diarrhea is prominent in post-COVID-19 (long COVID-19), and is occasionally noted after COVID-19 vaccination. The spectrum of diarrhea in COVID-19 patients is presently reviewed including the pathophysiology, clinical presentation, evaluation, and treatment.

## INTRODUCTION

COVID-19 (coronavirus disease of 2019), caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), is estimated to have infected more than 40% of the global population (>3 billion people) with more than 600 million documented infections and has claimed more than 6.5 million lives including more than one million Americans (1). Pneumonia and respiratory complications account for most of the morbidity and mortality from COVID-19. However, ACE-2 (angiotensin converting enzyme-2), the entry receptor for the coronavirus SARS-CoV-2, is expressed in many extrapulmonary tissues and viral invasion and disruption occurs throughout the body. Extrapulmonary manifestations of COVID-19 infection include hemostatic abnormalities and thrombotic complications, cardiac dysfunction and arrhythmias, liver dysfunction and hepatitis, central nervous system/peripheral nervous system complications, acute kidney injury (AKI), and various skin rashes and eruptions (2). Pyrexia, cough, dyspnea, pharyngitis, rhinorrhea, and malaise are the most common COVID-19 symptoms. ACE-2 receptors are more highly expressed in gastrointestinal (GI) mucosa than in respiratory mucosa, especially in the stomach and small intestine (3). GI symptoms are relatively common, including prominently diarrhea, as well as nausea, emesis, anorexia, abdominal pain, and heartburn (4).

The relationship between diarrhea and respiratory symptoms and between diarrhea and patient prognosis are variable. GI symptoms, including diarrhea, are sometimes the presenting symptoms with variable development of respiratory and hemostatic derangements. Diarrhea in the COVID-19-infected patient is typically mild-to-moderate but can occasionally be severe and life-threatening (5,6).

## METHODS

The relevant literature was reviewed using two independent computer search engines, PubMed and Ovid. The literature review was continuously updated until nearly submitting this review to the Journal on October 21, 2022. This work constitutes a semiquantitative review as defined in “The impact of COVID-19 infection on miscellaneous inflammatory disorders in the gastrointestinal tract” which is another chapter in this monograph. This semiquantitative review differs from a systematic review only by not listing articles identified by the computerized search which were excluded from this review and by not compiling the reason(s) for their exclusion.

This computerized literature review included the following search terms, key words, or phrases [with listing in brackets identifying the number of articles identified by PubMed per search term]: diarrhea and COVID [1805]; bloody diarrhea and COVID [19]; chronic diarrhea and COVID [181]; long COVID and diarrhea [34]; dehydration and diarrhea and COVID [12]; acute renal failure and diarrhea and COVID [79]; acute kidney injury and diarrhea and COVID [59]; fecal shedding of COVID [192]; fecal-oral transmission and COVID [29,593]; enterocytes and COVID [128]; colonocytes and COVID [3]; angiotensin converting enzyme-2 (ACE-2) receptor and intestines [214]; C difficile and COVID [63]; secretory diarrhea and COVID [3]; diarrhea therapy and COVID [711]; anti-diarrheals and COVID [9]; Loperamide and COVID [2]; kaolin pectin and COVID [0]; cholestyramine and COVID [1]; flavonoids and COVID [624]; intestinal ova and parasites and COVID [1]; amebiasis and COVID [14]; cytomegalovirus and COVID [297]; microscopic colitis and COVID [6]; bacterial infections and diarrhea and COVID [61]; colonoscopy and COVID [233], flexible sigmoidoscopy and COVID [11], enteroscopy and COVID [3], capsule colonoscopy and COVID [16], balloon enteroscopy (endoscopy) and COVID [0]; disposable endoscopes and COVID [39]; CT colonography and COVID [10]; fecal occult blood and COVID [88]; fecal immunological testing (FIT) and COVID [13]; iron deficiency anemia and COVID [42]; colonoscopy screening and COVID [168]; colon and adenomas and COVID [13]; colon cancer screening and COVID [119]; colonoscopy surveillance and COVID [109]; colonic pseudo-obstruction and COVID [5]; long COVID and GI endoscopy [8]; GI endoscopy complications and COVID [36]; GI endoscopy guidelines and COVID [34]; gastrointestinal endoscopy and COVID transmission [195]; radiation proctitis and COVID [0]; rectal ulcer and COVID [12]; hemorrhoids and COVID [108]; rectal fissure and COVID [0]; SARS-CoV-2 viral RNA particles in stool [21]; diabetic diarrhea and COVID [156]; Diosmectite and COVID [2]; probiotics and COVID [353]; and microbiota and COVID [925].

**INSTRUCTIVE CASE REPORT (moderately severe diarrhea from COVID-19 directly contributing to mortality (via acute renal failure from dehydration))**

A 41-year-old female with multiple mild-to-moderate (asymptomatic) chronic health disorders and risk factors for COVID-19, all likely from the metabolic syndrome, including severe obesity (BMI=37 Kg/m<sup>2</sup>), mild diabetes mellitus treated with metformin, hypertension treated

with metoprolol, hypertriglyceridemia, and hypercholesterolemia, who worked as a nurse's aide, presented with moderately severe diarrhea with 7 to 10 moderately profuse watery bowel movements per day and minor upper respiratory symptoms of minimal cough, rhinorrhea, and low grade pyrexia (5). Physical examination revealed signs of dehydration and hypovolemia: decreased skin turgor, mild tachycardia at rest, orthostasis, and absent axillary sweat. There were no signs of respiratory distress: respiratory rate was 20 rpm, O<sub>2</sub> saturation was 97% on room air, lung fields were clear on auscultation and percussion, and lung fields were clear on chest roentgenogram.

Routine laboratory chemistries revealed multiple electrolyte derangements (hypokalemia, hyponatremia, and hypochloremia); mild prerenal azotemia, and an increased creatinine level; all of which were acutely abnormal from their previously normal baseline. The urine specific gravity was 1.029 (level highly consistent with severe dehydration). Stool workup revealed negative tests for C. difficile toxins A and B, negative stool examinations for ova and parasites, negative stool cultures for enteric bacterial pathogens, and normal levels of fecal calprotectin and lactoferrin.

She received aggressive intravenous hydration, intravenous electrolyte repletion, and emergency dialysis while monitored in an intensive care unit (ICU) bed. She rapidly succumbed from acute renal failure associated with dehydration, electrolyte derangements, and prerenal azotemia, all attributed to the moderately severe COVID-19-associated diarrhea. The proximate cause of death was acute renal failure from the underlying cause of severe dehydration and electrolyte derangements attributed to the moderately severe diarrhea from acute COVID-19 infection (without her initially presenting with COVID-19 pneumonia): This patient presented in mid-March 2020 as one of the first ten patients with COVID-19 infection diagnosed in Michigan and the case report was published in April 2020, as one of the first 40 publications in the world on the COVID-19 pandemic (5).

## DISCUSSION

### Pathophysiology

SARS-CoV-2 viral RNA particles are detected in stool in about half of acutely infected subjects (7) (Box 1). Only a modest proportion of those with fecal shedding have GI symptoms,

but viral RNA is still detectable in stool after pharyngeal clearance (8,9). Fecal-oral transmission of COVID-19 is strongly implicated in infection but awaits further confirmation (10-12). Fecal shedding often precedes COVID-19 symptoms and may continue after symptoms resolve (13). The clinical utility of fecal testing for COVID-19 is currently limited because it is costly and has limited availability, but it may be useful in patients with evident GI symptoms with delayed viral testing and in patients with unremitting diarrhea (13).

The pathophysiology of acute diarrhea presenting during COVID-19 infection is multifactorial and variable. Putative mechanisms include viral entry through the abundant GI ACE-2 receptors with disruption of the absorptive surface of enterocytes and colonocytes; increased intracellular mucosal permeability; change of bowel flora; and gut ischemia, and possibly a calcium-dependent secretory diarrhea (14-17). Endoscopic data are sparse, but GI mucosal inflammation appears mild to moderate, with bloody diarrhea decidedly unusual in COVID-19 infection (3,14).

Antibiotic therapy for pulmonary and other local infections can induce diarrhea, especially from *C. difficile* infection. Other medications or interventions, such as tube feeding, can also cause diarrhea. Diarrhea commonly occurs in post-COVID or "long" COVID states. Diarrhea can begin after COVID-19 vaccination.

### Epidemiology

GI symptoms, including anorexia, nausea/emesis, abdominal pain, and diarrhea, are common in patients with COVID-19 infection. Diarrhea is the most common or second most common GI complaint in most patient surveys, with a reported incidence ranging from 10% to 20% (18). A meta-analysis of 60 studies noted about 18% had GI complaints, excluding the extremely common symptom of ageusia. In one survey of GI symptoms, 13% had diarrhea, 10% had nausea/emesis, and 9% had abdominal pain (19). A systematic analysis of >18,000 patients reported diarrhea in 11.5%, nausea/emesis in 6.3%, and abdominal pain in 2.3% (20). Various studies note a wide range of diarrhea prevalence, ranging from 2% to 49.5% (21-24), and a meta-analysis of >132,000 COVID-19 subjects noted a diarrhea prevalence of 12%, and of anorexia of 22% (25). An early meta-analysis noted the wide range of diarrhea prevalence among studies and reported a pooled prevalence of 10.4% (26). Another meta-analysis of about 79,000 patients

reported a 16.5% diarrhea prevalence (27). A meta-analysis of >25000 COVID-19 subjects had a prevalence of anorexia in 20% and of diarrhea in 13% (28).

Diarrhea is also common in the pediatric population. A meta-analysis of 2855 children or adolescents with COVID-19 reported a 4% diarrhea prevalence (29). A systematic review of 2914 pediatric patients reported a 10.1% diarrhea prevalence (30). A meta-analysis of 32 pediatric studies noted a 19% prevalence of diarrhea (31), while another meta-analysis noted a pooled prevalence of 10% (32). Children typically have a mild COVID-19 viral syndrome, with mild and self-limited diarrhea that is sometimes not even self-reported. However, 27% of pediatric COVID-19 patients with the dreaded Multisystem Inflammatory Syndrome in Children (MIS-C) had diarrhea in one meta-analysis (33).

#### Diarrhea characteristics

Diarrhea may be the first and occasionally the only COVID-19 symptom (34,35). A systematic review noted 4.3% presented with diarrhea (35). Diarrhea usually starts within 5 days of presentation and usually lasts for 2-6 days (34,35). COVID-19 subjects with diarrhea as their only symptom are diagnosed later than those presenting with respiratory symptoms (5). COVID-19 diarrhea is usually mild and self-limited, with less than six loose or watery bowel movements daily with each bowel movement typically consisting of modest volume (5,9,12,33,35)(Box 1). Stool is usually hemocult negative, but occasionally hemorrhagic colitis is described (36,39). One two-year-old child with COVID-19 had bloody dysentery as her only symptom of COVID-19 infection and recovered (36,37). Severe diarrhea with up to 30 bowel movements rarely occurs (8,38).

#### Clinical Correlations

Generally, GI symptoms of COVID-19, including diarrhea, are not correlated with demographic or clinical parameters (18). One recent study suggested that age <80 years, immunosuppression, and a history of irritable bowel syndrome (IBS) may correlate with GI symptoms (39). The presence of diarrhea is not clearly correlated with poor clinical outcomes, including death (8,18,40). However, one American study correlated severe outcomes with diarrhea (41). Another study correlated COVID-19 diarrhea with poor outcomes but noted that the correlation was stronger between abdominal pain and poor outcomes (42). A meta-analysis

suggested abdominal pain, but not diarrhea, was correlated with severe outcomes (43). Contrariwise, three COVID-19 studies noted that diarrhea was correlated with improved clinical outcomes (44-46). Overall, diarrhea in COVID-19 subjects does not clearly portend a bad prognosis. COVID-19 outcomes in children and adolescents are generally excellent in patients with or without diarrhea, except for patients with MIS-C (30,31,32,34).

A comprehensive drug history must be obtained because medications that are used off-label as prophylaxis or treatment of COVID-19 infection may cause diarrhea (47-49). The patient should be asked about non-prescription (over-the-counter) supplements because such drugs may cause diarrhea. This diagnosis should be strongly considered if the diarrhea correlates temporally with drug initiation. Drug discontinuation or substitution should be considered if clinically feasible.

#### Laboratory tests

Blood tests for stable outpatient COVID-19 individuals are not required, except for those with abdominal pain or bloody diarrhea. In hospital infected patients should undergo routine blood tests including a complete hemogram with leukocyte differential, serum electrolytes, and a basic metabolic panel (Box 2). A healthy outpatient with COVID-19 and diarrhea, but without recent antibiotic exposure, may be a candidate for expectant treatment without undergoing stool tests. However, patients who are elderly, present to the emergency department, are chronic residents in a healthcare facility, have fever, or have significant abdominal pain should have stool tests for C. difficile. Stool testing for other bacterial pathogens has a modest yield while stool tests for ova and parasites have a low yield except for patients with immunosuppression, with a prior history of such infections, or with a recent travel history. Hospitalized patients and patients with bloody diarrhea should undergo stool testing.

Stool determination for fecal leukocytes or for the more modern stool tests of calprotectin or lactoferrin should be performed to check for intestinal inflammation. Fecal COVID-19 patients with bloody, profuse, or unremitting diarrhea should be considered for colonoscopy. Cytomegalovirus colitis is an important consideration in immunocompromised subjects, including those receiving immunosuppressive therapy after organ transplantation. Conceivably, inflammatory bowel disease (IBD) may first present during COVID-19 infection. Scant data exist concerning endoscopy in COVID-19 subjects (see accompanying chapters on gastrointestinal bleeding by Cappell and Friedel and on GI endoscopy by Sultan and coauthors). Physicians are now less reluctant to perform colonoscopy in patients with COVID-19 infection due to the advent of moderately effective vaccines, herd immunity, lower mortality with newer genetic variants, improved infection control in GI endoscopy units, and improved COVID-19 therapies. The sparse data on colonoscopy in COVID-19 infected patients usually relate to colonoscopy

indications of GI hemorrhage or occasionally abdominal pain rather than diarrhea. A small COVID-19 cohort reported inflammatory and erosive abnormalities throughout the GI tract with COVID-19 infection (50), a finding supported by other studies (51-53).

Computerized tomography (CT) imaging is preferable to magnetic resonance imaging (MRI) to evaluate diarrhea in potentially unstable patients infected with COVID-19 because of its rapid turnaround time and lower cost. CT imaging should be considered for COVID-19 patients, once stabilized, if they present with diarrhea that is bloody, associated with abdominal pain, or significant laboratory abnormalities, including leukocytosis, acidosis, or prerenal azotemia (Box 2). Colitis and other abdominal abnormalities may occur in patients without apparent respiratory symptoms, but thoracic CT windows should be obtained during abdominal CT because COVID-19 frequently causes pneumonia (8,54). CT findings in COVID-19 patients with diarrhea include colonic wall thickening and edema. CT Imaging can also diagnose GI perforation, pneumatosis coli, diverticulitis, or appendicitis (55,56). The differential diagnosis for diffuse or segmental colitis in such patients includes COVID-19 itself, other pathogens such as *C. difficile* or CMV, and bowel ischemia.

Chronic diarrhea including episodic diarrhea that becomes more manifest coincident with COVID-19 infection may arise from prior disorders exacerbated by COVID-19 infection, a new entity initiated by the infection, or incidental emergence of another disorder. Antecedent (possibly undiagnosed) disease may become more manifest during the pandemic, including irritable bowel syndrome (IBS), small intestinal bacterial overgrowth, pancreatic insufficiency, microscopic colitis, and ulcerative proctitis (57). Chronic diarrhea has a broad differential including diseases classified as inflammatory, bloody, fatty, or dysenteric. Additional testing can include stool electrolytes (to differentiate secretory from non-secretory diarrhea), qualitative or quantitative fat (to detect steatorrhea), stool elastase (to diagnose chronic pancreatitis), stool for calprotectin or lactoferrin (to diagnose severe inflammatory diarrhea/colitis), and plasma serotonin and chromogranin A (to help diagnose neurosecretory diarrhea). Colonoscopy and CT imaging are often helpful to diagnose pancreatic diseases, IBD, or neuroendocrine tumors. The diagnosis of COVID-19 primary diarrhea is largely one of exclusion (58).

### Management

COVID-19 research is generally highly active and intense but is not focused on GI manifestations because these are usually not life-threatening. Specific novel treatments exist for COVID-19 infection, but none are designed to treat diarrhea per se (26). Treatment for diarrhea is largely symptomatic and supportive. Judicious use of antidiarrheals, such as Loperamide (diphenoxylate-atropine), may be considered if the diarrhea is unremitting with negative stool tests for *C. difficile* and no evidence of ileus,

intestinal obstruction, or GI perforation (Box 3). Kaolin-pectin may be an effective and safe symptomatic therapy (59). A bile acid sequestrant was used for COVID-19 diarrhea in a patient whose colonoscopy demonstrated ileocolonic ulcers (60). Antiparasitic drugs and flavonoids have been proposed as treatment for COVID-19 diarrhea (61-63). Diosmectite, an adsorbent clay with anti-inflammatory properties, may be effective therapy for COVID-19 diarrhea (64). Traditional Chinese herbal medications may have a potential role in treating GI symptoms (65). A Chinese group has examined massage therapy for COVID-19 diarrhea (66).

Intravenous fluid is administered as necessary as guided by hypovolemia and prerenal azotemia, and serum electrolytes are supplemented as necessary as guided by the serum chemistries in hospitalized COVID-19 patients with diarrhea. Patients with hemodynamic compromise from severe dehydration from severe diarrhea may require aggressive intravenous hydration while monitored in an ICU and may require emergency dialysis. Intravenous fluids should be administered cautiously in patients with hypoxemia or cardiac failure associated with severe COVID-19 infection. Infants and young children may require specific rehydration solutions.

Probiotics have been considered for COVID-19 infection and specifically for associated diarrhea, with so far unsubstantiated benefits (67,69). Moreover, probiotics are a heterogeneous group that should be administered cautiously in patients with multiorgan dysfunction and a potential leaky gut (69). China's National Health Commission supports probiotics for severe COVID-19 patients (70). One Italian study noted a positive effect of "bacteriotherapy" on both diarrhea and respiratory status of COVID-19 infected patients (71).

#### Diarrhea with severe COVID-19

Patients with severe COVID-19 infection are monitored in the ICU where they are exposed to hospital flora with risks of superinfection. Acute viral respiratory infections alter immune response and the ecology of respiratory and GI tract infections. Secondary, viral, bacterial, and fungal infections, can occur, including *Candida* species, CMV, *Aspergillus*, *Klebsiella*, *Mucormycosis*, and *Acinetobacter* (72). *C. difficile* is the most prevalent superinfection that causes diarrhea (73). A patient with severe COVID-19 and CMV hemorrhagic enterocolitis survived with specific therapy (74). Enteral feedings in COVID-19-infected patients (often via gastrostomy) are generally well tolerated, but the rate and feeding solution may have to be adjusted if diarrhea occurs (75). MIS-C usually occurs in children and is often treated with parenteral immunoglobulin and corticosteroids (34,76).

#### *Clostridioides difficile*

*Clostridioides* (formerly *Clostridium*) *difficile* is the most common secondary GI infection in COVID-19 subjects (72,73). Stool tests for *C. difficile* should be performed in all hospitalized patients with COVID-19 infection and diarrhea and in all COVID-19 infected outpatients with abdominal pain, fever, bloody diarrhea, or chronic diarrhea. This test should be repeated, even if negative, if the diarrhea persists. Treatment should be initiated expeditiously for a positive test. Some centers noted a decrease in *C. difficile* stool testing during the early pandemic and the incidence of *C. difficile* did not increase during the pandemic (77-79). The unchanged rate may relate to judicious antibiotic stewardship and increased infectious precautions during the pandemic. In a small cohort of COVID-19 subjects, only 19% of co-infected patients had positive stool tests for *C. difficile* on admission, and the rest developed *C. difficile* infection after the COVID-19 diagnosis. Outcome data on co-infection is preliminary (80). Theoretically, COVID-19 and *C. difficile* may interact with each other to increase the virulence, transmissibility, and duration of each infection (77). In one series, co-infection was associated with more severe and prolonged diarrhea and increased mortality as compared to those with COVID-19 without *C. difficile* infection (81). COVID-19 subjects generally initially had diarrhea attributable to the virus and some of these subjects developed diarrhea exacerbation from *C. difficile* superinfection; the latter group had increased mortality (82,83). Fecal microbiota transplantation (FMT) has continued during the pandemic and remains a viable therapeutic option for *C. difficile* treatment though comprehensive donor testing is essential (84).

#### Inflammatory bowel disease/miscellaneous inflammatory disorders

Treatment of patients with ulcerative colitis and regional enteritis becomes more complex in patients with COVID-19 infection (see accompanying chapter on inflammatory bowel disease by Summa and Hanauer). Two patients developed ulcerative colitis de novo simultaneous with COVID-19 infection, but the concurrence may have simply been coincidental (85). COVID-19 enteritis may mimic regional enteritis, including one patient with multiple fistulae and a jejunal perforation (86,87). COVID-19 symptoms are similar in IBD patients as compared to those in the general population, with 27% of IBD patients presenting with diarrhea in one meta-analysis (88). Five out of twelve IBD patients noted diarrhea as their first COVID-19 symptom and two had diarrhea as their only symptom (89). IBD patients do not seem to be more susceptible to COVID-19 infection, nor do they have more severe COVID-19 outcomes or higher mortality than patients without IBD (88,90). Guidelines suggest using standard treatment for IBD during the pandemic, while avoiding diarrhea exacerbation through recognition of immunosuppression inducing greater susceptibility to *C. difficile* colitis (91).

Analysis of a large Swedish cohort, demonstrated microscopic colitis (MC) subjects were more prone to contract COVID-19 infection and those with the subtype of collagenous colitis but not the

subtype of lymphocytic colitis, had more severe COVID-19 disease and higher mortality (92). Case reports documented new lymphocytic colitis or collagenous colitis with COVID-19 infection (93,94). Colonoscopy with biopsies to exclude MC is a consideration in all patients who have apparently recovered from COVID-19 infection but have persistent diarrhea. The treatment of immune-checkpoint inhibitor colitis is challenging during the pandemic due to the need to maintain immunomodulatory therapy. Moderate dose corticosteroids are a consideration in patients with less severe COVID-19 infection, but tocilizumab should be avoided because of the risk of intestinal perforation (95).

### Long COVID

Most COVID-infected subjects recover without sequelae, but a proportion have some symptoms that persist or reappear weeks to months after the original infection in a post-COVID-19 syndrome, also called Long COVID (see accompanying chapter on Long COVID by Trindade et al.). About 40% of subjects in one Long COVID cohort manifested diarrhea (96) and about 13% of subjects in another Long COVID cohort manifested diarrhea (97). A systematic review noted that abdominal pain, nausea, and anorexia were more common than diarrhea in Long COVID (98). A Chinese group noted that at 90 days post discharge from the hospital for COVID-19 infection, 15% had diarrhea with higher rates of anorexia or nausea (99). In another long COVID-19 cohort about 18% had diarrhea five months after acute infection (100). Diarrhea during the initial acute COVID-19 infection was correlated with the presence of diarrhea in Long COVID-19 (101). Long COVID-19 can evolve into irritable bowel syndrome, as occurs in other post-infectious diarrheal states (102). Antidiarrheals and antispasmodics may be utilized after negative stool studies, including studies for *C. difficile*. However, other causes of chronic diarrhea should be considered with performance of colonoscopy, if not already performed. Chronic symptoms after acute COVID-19 infection are uncommon in children (103).

### Vaccine

About 3% of subjects in a large COVID-19 vaccine database reported diarrhea but prolonged diarrhea is unusual (104). The Pfizer vaccine informational site reported 11% of adults had diarrhea, with almost 90% of these cases being mild (105). Diarrhea is more common after the adenovirus vector vaccine than mRNA vaccines, and the frequency of the incidence of diarrhea increased with increased adjuvant concentration in the vaccine preparation (106). Multisystem inflammatory syndrome was reported in one adult after COVID-19 vaccination (107).

### Clinical implications & Emerging trends

The COVID pandemic is a rapidly evolving pandemic due to rapidly emerging new viral strains with greater contagiousness but apparently lower mortality; vaccines that prevent and protect against

infection; the development of herd immunity; development of moderately effective antibiotic therapy; and implementation of infection controls to reduce population exposure. Diarrhea is a minor symptom in the overwhelming majority of COVID-19 patients that typically requires only symptomatic therapy and exclusion of more specific causes of diarrhea exacerbation, such as C. difficile superinfection. However, given the huge magnitude of the pandemic with pandemic mortality numbering in the many millions, even the mostly minor symptom and disorder of diarrhea can contribute to pandemic mortality due to the huge number of infected patients. It is critical to recognize life-threatening dehydration and electrolyte depletion early to expeditiously initiate intravenous hydration and electrolyte repletion, and even perform emergency dialysis as necessary in an ICU setting.

This review is best considered as a snapshot of the current state of diarrhea with COVID, with likely future advancements and improvements in clinical therapy, management, and prognosis over time.

## CONCLUSION

COVID-19 morbidity and mortality largely results from respiratory disease and sometimes from the development of a hypercoagulable state. However, extrapulmonary disorders are common including GI complaints of anorexia, nausea/emesis, abdominal pain, or diarrhea. The GI pathophysiology is largely due to the abundant ACE-2 receptors within GI mucosa promoting SARS-CoV-2 viral entry. Diarrhea is the most common or second most common GI symptom in most COVID-19 patient surveys. COVID-19 diarrhea is usually non-bloody and moderate. It can be the presenting symptom of COVID-19 infection, but most commonly occurs within several days after the onset of other COVID-19 symptoms. It usually lasts for only several days but can be prolonged. Fecal–oral transmission of the virus is likely but requires further substantiation. Stool analysis for COVID-19 currently has limited clinical utility. Mortality is increased in some studies of COVID-19 cohorts with diarrhea, but this is not reported in most studies. Diarrhea presenting later in the hospitalization for COVID-19 infection is often related to C. difficile infection. Late–presenting diarrhea is usually associated with a worse prognosis. Mild diarrhea from COVID-19 infection is usually treated symptomatically with anti-diarrheal medications while severe diarrhea may require intravenous fluid infusion and electrolyte replacement therapy as necessary. The differential diagnosis for diarrhea includes potential medicine side-effects, such

as from antibiotics, and C. difficile infection. Diarrhea is an increasingly common complaint in subjects who have Long COVID.

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#### CLINICAL-CARE POINTS

- The COVID pandemic has infected more than 600,000,000 patients worldwide and has killed more than 6,000,000 patients. Most of the mortality from COVID-19 arises from COVID-19 pneumonia and pulmonary complications.
- Diarrhea is common with COVID-19 infection. It is reported in about 10%-20% of cases. It is recognized as one of the presenting symptoms of this infection.
- The diarrhea is typically mild-to-moderate, watery, and non-bloody; it typically lasts 2 to 6 days, with somewhat variable duration.
- The diarrhea is believed to be due to local invasion of the virus via the angiotensin converting enzyme-2 (ACE-2) receptor, which is highly expressed in gastrointestinal mucosa, especially in the stomach and small intestine. The virus is often shed in stool.
- Rarely the diarrhea can be severe and cause dehydration and electrolyte abnormalities that require intravenous hydration and electrolyte repletion. In extreme instances, the diarrhea can contribute to acute renal failure from hypovolemia associated with COVID-19 infection.
- The diarrhea when mild is typically treated symptomatically with antidiarrheals such as Loperamide.
- Work-up for severe diarrhea in hospitalized adults with COVID-19 infection includes routine serum electrolytes, liver function tests, and a basic metabolic panel; a hemogram

and leukocyte differential; sometimes routine stool tests including a test for C. difficile; and very occasionally abdominal computerized tomography or colonoscopy.

- The differential diagnosis of persistent diarrhea with COVID-19 infection includes, in addition to primary COVID-19 diarrhea, medication-associated diarrhea especially from antibiotics; hyperalimentation via percutaneous endoscopic gastrostomy or other tube feedings; C. difficile infection; and, occasionally, irritable bowel syndrome; lymphocytic colitis; or other diarrheal disorders.
- The diarrhea typically has a favorable prognosis in the absence of COVID-19 pneumonia. However, it is variably reported that diarrhea associated with COVID-19 infection may have a worse prognosis.
- Diarrhea is increasingly reported persisting for more than four weeks after acute COVID-19 infection, as part of Long COVID-19. Although inadequately characterized, Long COVID diarrhea appears to have a good prognosis.

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**Box 1. Diarrhea associated with COVID-19 infection**Pathophysiology

Believed related to local infection of gastrointestinal mucosa mediated by local angiotensin converting enzyme-2 (ACE-2) receptor

About 50% of patients with COVID-19 infection have fecal shedding of SARS-2CoV-2 (severe acute respiratory syndrome coronavirus-2)

Clinical characteristics

About 10%-20% of patients with COVID-19 infection have diarrhea, with some variability reported among studies

Diarrhea is typically moderate with  $\leq 6$  watery and non-bloody bowel movements per day

Occasionally diarrhea is severe with  $>6$  bowel movements per day. Such severe diarrhea is often accompanied by patient dehydration and serum electrolyte abnormalities

Duration of diarrhea is typically 2-6 days, with some variability among studies

**Box 2. Laboratory workup of diarrhea associated with COVID-19 infection in hospitalized patients**Blood tests

Hemogram with leukocyte differential

Serum electrolytes, glucose, blood urea nitrogen and creatinine

Basic metabolic panel, including routine liver function tests

Blood cultures

Stool tests

Stool for bacterial culture and sensitivity

Stool for ova and parasites

Stool for *C. difficile* (confirm positive test by PCR)

Fecal leukocytes (or more modern alternatives of stool for calprotectin or lactoferrin) to diagnose severe inflammatory diarrhea/colitis

Further tests

KUB (kidneys ureter, bladder) or consider CT computerized tomography scan of abdomen for: notable abdominal pain, leukocytosis, or positive blood cultures

Colonoscopy if patient relatively stable and concern for cytomegalovirus colitis

Unusual tests

Spot stool with Sudan-4 stain (to evaluate qualitatively for steatorrhea)

Stool electrolytes (to evaluate for secretory diarrhea)

Neuroendocrine workup for diarrhea (plasma serotonin and chromogranin A)

Stool elastase (to evaluate for chronic pancreatitis)

*PCR – polymerase chain reaction*

**Box 3. Treatment of diarrhea associated with COVID-19 infection**Antidiarrheal therapy

Antidiarrheals as symptomatic therapy after excluding specific causes (such as C. difficile infection): Loperamide (diphenoxylate-atropine), Kaolin-pectin, and possibly flavonoids, Diosmectite, an adsorbent clay, or probiotics

Intravenous therapy

Intravenous hydration and repletion of serum electrolytes for severe diarrhea accompanied by dehydration, serum electrolyte abnormalities, and possibly prerenal azotemia. Infants and young children may require special rehydration solutions.

Special treatments & monitoring in selected circumstances

Monitor patient in an intensive care unit if patient exhibits hemodynamic compromise from hypovolemia

Acute hemodialysis if necessary for severe electrolyte abnormalities and acute renal failure

Special therapies for diarrhea from C. difficile colitis, cytomegalovirus colitis, microcytic colitis, chronic pancreatitis, and neuroendocrine causes of diarrhea