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The Impact of COVID-19 Infection on Miscellaneous Inflammatory Disorders of the Gastrointestinal Tract

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KEYWORDS

• COVID-19 • Pandemic • SARS • Gastrointestinal • Inflammation

KEY POINTS

- Clinicians should be aware that numerous inflammatory diseases of the gastroenterology tract may be somewhat modified in patients with active COVID-19 infection
- The clinical presentation of some gastrointestinal inflammatory diorders may be altered by acitve COVID-19 infection
- Management and treatment of some inflammatroy disorders of the gastrointestinal tract may have to be altered in patients with active COVID-19 infection

INTRODUCTION

The novel coronavirus pandemic with COVID-19 has caused immense morbidity and mortality, with more than one million deaths in the United States and more than 6 million deaths globally.[1] Mortality occurs in all groups but is disproportionately higher in the elderly, infirm, male gender, lower socioeconomic classes, and patients having significant comorbidities including those suffering from diabetes mellitus and obesity.[2] Moreover, the pandemic causes considerable morbidity and can persist in a chronic form as reviewed in another chapter in this monograph. Development of relatively effective vaccines, sporadically mandated public health measures such as masks, increasing herd immunity, moderately effective therapy, and perhaps less virulent

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emerging viral strains have significantly diminished COVID-19 infection severity and mortality, but the pandemic endures, with associated morbidity and mortality, especially in the unvaccinated and vulnerable populations. Long (chronic) COVID-19 can relatively frequently cause gastrointestinal (GI) infections or symptoms in some patients who had contracted symptomatic acute COVID-19 infection and is reviewed in another chapter in this monograph.

Organs, including the GI tract, that express angiotensin-converting enzyme 2 (ACE-2) are susceptible to local COVID-19 infection and associated inflammation. COVID-19 can affect the GI tract by direct infection and local inflammation or indirectly from GI ulcerations related to stress, particularly in mechanically ventilated patients or patients administered corticosteroids, and incidentally by deferred screening for GI neoplasms or malignancies such as Barrett's esophagus or colorectal neoplasms due to patient preference or inability of health systems to accommodate endoscopic screenings due to COVID exigencies.

METHODS

The medical and scientific community is generally aware of the nature and importance of systematic reviews. The essence of systematic reviews is that the method and particulars of the literature search are tabulated so that the reader could potentially reconstruct all the data (articles) used in the literature review if needed, including all the articles surveyed by the literature search using the computerized search terms of the literature review and all the articles excluded in the literature search with the listed reasons for every excluded article. The first task is an integral and essential part of a systematic review that requires little documentation, whereas the second task requires extensive documentation by compiling all individual articles excluded from the review article while specifying the reason for each exclusion. It is reasonable to separate these 2 distinct tasks and denote the accomplishment of the first task without the second task by creating a new term "semiquantitative review." By this term a review encompassing the first part of a systematic review, but not the second part, is denoted. This new term is useful because the first task of a systematic review provides one-half or more of the quality of a systematic review, while requiring much less documentation that is entailed in the second task.

This article inaugurates a "semiquantitative review" by declaring all the search terms used in the literature search (with the number of articles reviewed) without detailing the extensive list of excluded articles. This literature review was performed using PubMed and Ovid, independent literature search engines. The literature review was last conducted (and is up to date) as of August 26, 2022, when this article was submitted for publication, and included the following search terms or phrases (with number of identified articles per search term, as derived from PubMed listed in parenthesis): pharynx and COVID-19 (1514); oropharynx and COVID-19 (284); oropharyngeal involvement and COVID-19 (81); anosmia and COVID-19 (1662); dysgeusia and COVID-19 (406); olfactory dysfunction and COVID-19 (886); geographic tongue and COVID-19 (12); COVID tongue (217); gastroesophageal reflux (GERD) and COVID-19 (36); Barrett's epithelium and COVID-19 (13); proton pump inhibitor and COVID-19 (114); intestinal metaplasia and COVID-19 (6); laryngopharyngeal reflux and COVID-19 (3); esophagus, candida, and COVID-19 (1); esophagogastroduodenoscopy (EGD) and COVID-19 (13); nasal endoscopy (EGD) and COVID-19 (134); Barrett's ablation and COVID-19 (1); Barrett's esophagus screening and COVID-19 (7); Cytosponge and COVID-19 (2); high resolution manometry and COVID-19 (7); esophageal varices and COVID-19 (14); achalasia and COVID-19 (6); esophageal necrosis and COVID-19

(5); Boerhaave syndrome and COVID-19 (2); scleroderma and COVID-19 (94); pill esophagitis and COVID-19 (1); corrosive esophagitis and COVID-19 (1); eosinophilic esophagitis and COVID-19 (10); gastropathy and COVID-19 (115); gastroduodenitis and COVID-19; ulcers and COVID-19; *Helicobacter pylori* and COVID-19 (51); *H pylori* antigen and COVID-19 (12); GI hemorrhage and COVID-19 (134); GI bleeding and COVID-19 (262); melena and COVID-19 (35); hematemesis and COVID-19 (23); iron deficiency anemia and COVID-19 (39); fecal occult blood and COVID-19 (82); primary COVID ulcers (69); gastric ulcers and COVID-19 (20); duodenal ulcers and COVID-19 (15); celiac and COVID-19 (133); multisystem inflammatory syndrome and COVID-19 (2132); Crohn disease and COVID-19 (328); ulcerative colitis and COVID-19 (310); mesenteric ischemia and COVID-19 (94); pneumatosis intestinalis and COVID-19 (19); pneumatosis coli and COVID-19 (12); GI perforation and COVID-19 (75); GI obstruction and COVID-19 (110); intussusception and COVID-19 (56); mucormycosis and COVID-19 (747); microscopic colitis and COVID-19 (5); lymphocytic colitis and COVID-19 (3); collagenous colitis and COVID-19 (3); protein-losing enteropathy and COVID-19 (2); cytokine release syndrome and COVID-19 (2045); tocilizumab, perforation, and COVID-19 (19); *Clostridium difficile* and COVID-19 (131); Clostridiodes and COVID-19 (5); appendicitis and COVID-19 (403); diverticulitis and COVID-19 (41); colonic pseudo-obstruction and COVID-19 (5); irritable bowel syndrome (IBS) and COVID-19 (56); colon cancer and COVID-19 (215); colonic polyps and COVID-19 (11); colonoscopy and COVID-19 (218); enteroscopy and COVID-19 (2); capsule endoscopy and COVID-19 (29); balloon endoscopy and COVID-19 (5); computed tomography colonography (CTC) and COVID-19 (10); hemorrhoids and COVID-19 (105); anal fistula and COVID-19 (5); anal abscess and COVID-19 (2); anal fissure and COVID-19 (3); and long (chronic) COVID-19 and GI (77). This work illustrates the utility of a semiquantitative literature review that reviews so many articles, because a systematic review of this literature would encompass so many excluded articles, thereby encumbering such an article with an impractically long list.

PHARYNX

COVID-19 has been detected in oral and nasopharyngeal tissues and secretions, with implications for pathogenesis, transmissibility, and contamination. For example, chewing gum saturated with soluble ACE2 (ACE-2) proteins but lacking the virus may reduce viral transmission by 95%.[3] Oropharyngeal involvement most commonly pathologically produces erosions or ulcers.[4,5] Loss of smell (anosmia) and loss of taste (ageusia) or a taste disorder (dysgeusia) are commonly encountered with COVID-19 infection. For example, in a study of 322 patients with COVID-19 treated at a hospital in India from August through November 2020, 226 patients with COVID-19 (70.2%) experienced olfactory and gustatory disorders, including 165 (51.2%) patients with both olfactory and gustatory disorders, 34 (10.6%) patients with solely olfactory dysfunction, and 27 (8.4%) patients with solely gustatory dysfunction.[6] These symptoms usually present without gross oropharyngeal pathology of nasopharyngitis, nasal obstruction, or glossitis; without the symptom of rhinorrhea; and without zinc deficiency. The true mechanisms remain conjectural and unknown. It has been hypothesized that a decrease in the sensitivity of olfactory neurons and co-expression of ACE-2 and TMPRSS2 in alveolar epithelial cells may cause these olfactory-gustatory disorders.[7] These symptoms often are the first to appear with COVID-19 infection and the last to resolve.[8,9] Corticosteroids have been proposed as a therapy, but their efficacy is unproven.[10] Alternative therapies include nirmatrelvir/ritonavir (Paxlovid) and anticytokine monoclonals.[11] However, efficacy in clinical trials may not apply to the general population.[10]

Geographic tongue manifests as irregular loss of filiform papillae toward the rear of the tongue. This disorder affects about 1% to 2% of patients in the general population and is strongly related to psoriasis and is believed due to genetic and immunologic factors. In a Spanish study of 666 patients with COVID-19 infection, 3.9% had irregular depapillation of the distal lingual dorsum consistent with geographic tongue, also known as COVID tongue.[12] Geographic tongue has been linked with high expression of ACE-2 in epithelial cells at the back of the tongue, possibly leading to injury of infected papillae.[13] Candidiasis of the tongue[14] is reviewed under esophageal candidiasis. Oral manifestations and salivary duct abnormalities from acute COVID infection may persist for months.[15]

ESOPHAGUS

A database incorporating more than 26,000 COVID-19–infected patients reported 19% had symptoms of GERD (gastroesophageal reflux disease).[16] It is unknown whether COVID-19 increases the frequency of GERD symptoms because this study was performed without a control group for comparison. Moreover, GERD symptoms and those directly attributed to COVID-19 infection, such as cough and chest discomfort, may overlap, especially when mild, creating a diagnostic dilemma.[17] However, recent advancements in the rapidity and accuracy of COVID-19 testing generally permits differentiation of these 2 entities.[17] Conversely, patients presenting with predominantly or solely GI symptoms may still have COVID-19 infection in an endemic area.[18] Lastly, these 2 entities commonly coexist in obese subjects who are at high risk of GERD as well as at high risk of severely symptomatic COVID-19 infection. A genetic relationship between GERD and COVID-19 has been proposed, but obesity seems to be the most significant underlying cofactor.[19] Laryngopharyngeal reflux may be disproportionately increased with COVID-19 infection, and melatonin has been proposed as therapy for this condition.[20,21]

The relationship between medications to treat GERD and COVID-19 has been well analyzed. COVID-19 may preferentially infect Barrett's metaplastic epithelium (akin to small bowel epithelium) over normal esophageal columnar mucosa, thereby increasing susceptibility.[22] Proton pump inhibitor (PPI) therapy is associated with increased COVID-19 susceptibility[23] and worse COVID-19 outcomes.[24–26] Other investigators have refuted this association and advocated that other risk factors are more important in patient outcome.[27,28] Famotidine was previously touted as the preferred histamine-2 (H_2) receptor antagonist for hospitalized patients with COVID-19[29] possibly due to decreasing the risk of cytokine storm, but clinical trials unfortunately showed no therapeutic benefits of famotidine compared with other H_2 receptor antagonist therapies.[30,31]

Patients with severe COVID-19 infection are at high risk of developing invasive esophageal candidiasis, especially patients with acute respiratory distress syndrome, chronically receiving corticosteroid therapy, or undergoing prolonged endotracheal intubation.[32] Other proposed clinical risk factors for esophageal candidiasis include prolonged intensive care unit stays, central venous catheters, prolonged broad-spectrum antibiotic therapy, and prior bouts of esophageal candidiasis.[32] Patients with such risk factors are highly susceptible to candida infection because *Candida* species are frequent constituents of the human mycobiome. Deep-seated candida infections are associated with increased mortality. Esophageal candidiasis is associated with the profound immune dysregulation in COVID-19 infection, but the specific underlying immunologic defects are unknown. Esophageal candidiasis typically presents with dysphagia or odynophagia. At EGD esophageal candidiasis

classically presents as a cheesy white superficial exudate. EGD with endoscopic brushings is usually diagnostic. Clinical awareness and screening are needed in the setting of severe COVID-19 infection. Echinocandins and azoles are the primary antifungals used to treat esophageal candidiasis. In patients with advanced COVID-19 infection, *Candida* spp may exhibit resistance to traditional antifungal agents.

The COVID-19 pandemic has greatly disrupted esophageal testing, especially EGD. Diversion of physician resources and endoscopy suite time to the COVID-19 pandemic crisis has decreased the use of screening and other routine endoscopic procedures, but it has spurred use of alternative testing modalities and innovations, especially regarding equipment. For example, one center substituted chest computed tomography (CT) for endoscopy to screen for esophageal varices.[33] A large US database reported that esophageal cancer diagnosis, as well as Barrett's esophagus screening and ablation, decreased during the peak of the pandemic, but the rate of performing esophagectomies did not change.[34] Unsedated nasal endoscopy using topical anesthetic agents such as benzocaine,[35] modified masks for esophageal function testing, and use of the Cytosponge device are notable innovations.[36–38] Fortunately, transmission of COVID-19 in the endoscopy suite to endoscopists, endoscopy staff, and noninfected patients has been exceedingly rare.[39] Practical triage permits optimal utilization of endoscopic resources. As with EGDs, the number of high-resolution manometries (HRMs) decreased by 17.2% from 1587 in 1999 to 1314 in 2020 attributed to the COVID pandemic that peaked in April and May 2020.[40] Notably, the rate of performing HRM hardly decreased in 2020 in areas of Japan relatively affected by the COVID-19 pandemic. One case of endoscopic variceal ligation was successfully performed with cessation of esophageal variceal hemorrhage in an intubated patient with COVID-19 infection.[41] The endoscopy staff successfully applied strict medical precautions to prevent spread of COVID-19 infection to medical personnel participating in the endoscopic procedure.

Uncommon esophageal diseases have been incidentally reported in patients with COVID-19, including achalasia,[42] esophageal necrosis,[43] esophageal rupture/Boerhaave syndrome,[44] and scleroderma esophagus/systemic sclerosis.[45] A patient with pneumonia and respiratory failure from COVID-19 infection had massive upper GI hemorrhage from prolonged nasogastric tube placement.[46] Pill-induced esophagitis was more prevalent in COVID-19–infected patients, partially related to doxycycline antibiotic therapy for treating COVID-19 infection.[47] Mental health issues may underlie the increased corrosive ingestion during the pandemic.[48] In one notable case, esophageal ulceration was detected at the site of COVID-19 virus infection, as detected by electron microscopy.[49]

Eosinophilic Esophagitis

Severity of COVID-19 infection and COVID-19–induced eosinophilic esophagitis (EoE) or eosinophilic GI disorder (EGID) flares was analyzed in a global registry incorporating 94 cases of patients with EoE and EGID who developed acute COVID-19 infection between March and April 2021 (median age, 21 years; range, 1.5–53 years; 73% men).[50] Most patients had a history of atopy (73%) and most had isolated EoE (80%). Before infection with COVID-19, the EoE/EGID activity was reported in clinical remission in 51 (54%) and as moderate in 20 (21%). EoE/EGID treatments at the time of COVID-19 infection included PPI in 49 (52%), swallowed or topical corticosteroids in 48 (51%), and dietary elimination therapy in 34 (36%). COVID-19 symptoms included cough (56%), pyrexia (49%), anosmia (21%), and ageusia (22%). Patients with COVID-19 infection typically had mild infection, with 15% asymptomatic, 70% with mild disease, 12% moderate disease, and only 2% with severe disease. Only 3 patients were

hospitalized. No patients had intensive care unit admissions or deaths. Only one patient experienced an EGID flare during COVID-19 infection. Based on this global registry, patients with EoE do not seem to be at increased risk for severe COVID-19 infection or EoE/EGID flares during acute COVID-19 infection.

In a survey of 102 patients with EoE followed at The University of Salerno and Padua, one patient, a 23-year-old-man with a history of EoE for about 10 years, developed acute COVID-19 infection,[51] while chronically administered therapy with oral viscous budesonide, 15 mL twice daily, and following a legumes-free diet for a suspected dietary history of allergy to legumes. The patient developed acute symptoms of asthenia, headache, anosmia, and ageusia. At diagnosis of acute COVID-19 infection, therapy with budesonide was discontinued, and azithromycin therapy (500 mg/d) was initiated for 5 days. The patient never developed dysphagia, odynophagia, or other esophageal symptoms and never required respiratory assistance or oxygen therapy, findings consistent with moderate COVID-19 infection. He became COVID-19 free by nasal swab several weeks after diagnosis.

STOMACH

Common GI symptoms, such as nausea and vomiting or abdominal pain, may relate to COVID-19 affinity to the abundant ACE2 receptors in the GI tract, including the stomach and duodenum.[52] A large European study of endoscopic findings in COVID-19–infected patients noted common upper GI pathology, including ulcers (25%), erosive/superficial ulcerative gastroduodenitis (16%), and petechial/hemorrhagic gastropathy (9%).[53] A systematic review of EGD in COVID-19–infected patients reported upper GI ulcers in nearly half of subjects.[54] Gastric ulcers in patients with COVID-19 infection were associated with a poor prognosis in one small study.[55] An elderly COVID-19–infected patient died of emphysematous gastritis.[56] Gastric perforation has been reported in patients with COVID-19 infection.[57,58]

In a study conducted from June 1 to July 20, 2020, 108 patients diagnosed with COVID-19 infection underwent antigen screening tests to determine the presence of *H pylori* in stool samples. Thirty-one of the patients were *H pylori*-positive, including 8 women (25.8%), and 77 patients were *H pylori*-negative. The presence of *H pylori* infection was significantly associated with abdominal pain (19.4% vs 2.6%, $P = .007$) and diarrhea (32.3% vs 9.1%, $P = .006$). *H pylori* positivity was not significantly associated with hospital length of stay, severity of the course of COVID-19 infection, or the outcome of COVID-19 infection. This study suggests that *H pylori* does not affect the severity or outcome of COVID-19 infection but does increase the frequency of symptoms of abdominal pain and diarrhea.[59]

Gastrointestinal Hemorrhage

GI hemorrhage is uncommon in hospitalized patients with COVID-19 infection, especially relative to the frequency of other GI complaints. There is a paucity of endoscopic data reflecting prioritization of endoscopic resources and understandable reluctance to perform nonessential, elective endoscopies in COVID-19–infected patients. The spectrum of patient presentation parallels that expected for hospitalized patients with predominant pulmonary or multisystem pathology and prothrombotic tendency. Clinical presentations include progressive anemia, hemoccult-positive stool, hematemesis, melena, abdominal pain, and altered vital signs. Administration of anticoagulants, commonly administered to COVID-19–infected patients to prevent thrombosis, can exacerbate the bleeding. GI hemorrhage was reported in up to 13% of patients hospitalized with COVID-19 infection,

but most studies reported a significantly lower prevalence.[60–63] Another global meta-analysis reported 9% of more than 25,000 COVID-19–infected patients presented with hematemesis.[64] The most common findings in this relatively sparse data set were peptic disease, including gastritis and gastroduodenal erosions/ulcers.[60–63] Pulmonary manifestations usually predominate in patients hospitalized with COVID-19 infection, but occasionally GI hemorrhage may be the presenting symptom.[65] GI hemorrhage can sometimes present with subtle symptoms and signs of GI bleeding and can sometimes present with subtle symptoms and signs of COVID-19 infection.[65] Several patients presented with GI bleeding from esophageal or GI ulcers presumably from primary COVID-19 infection, as evidenced by findings on electron microscopy.[66,67]

GI hemorrhage in COVID-19–infected patients may be self-limited and may be inferred without performing endoscopy, but sometimes the bleeding is severe or even life-threatening, mandating endoscopy.[68–71] Most, but not all, studies suggest a worse prognosis for COVID-19–infected patients with GI bleeding as compared with those without GI bleeding.[70–72] A meta-analysis of 123 patients with GI bleeding noted a reluctance to perform EGD for GI bleeding, with only 40% undergoing EGD and EGD reserved for patients with more severe GI bleeding.[65] This monograph has a chapter dedicated to GI bleeding in COVID-19–infected patients.

Similarly, a survey of 184 general surgeons reported that they operated on 7 or more cases on average per week before the COVID-19 pandemic compared with only 31 (8.5%) respondents reporting the same number of operations during the pandemic ($P < 0.001$). Two-hundred and nine respondents (57.6%) reported that at least 25% of their elective surgeries were canceled or postponed during the COVID-19 pandemic, whereas only 50 (13.8%) reported that at least 25% of their emergent surgeries were canceled or postponed ($P < 0.001$).[73]

SMALL INTESTINE

The vast small intestinal mucosal surface area, with a plethora of lymphatics, constitutes a battleground for host response to foreign antigens, including viruses. Both respiratory alveoli and enterocyte brush borders have abundant ACE-2 receptors, and viral RNA of SARS-CoV-19 has been detected in stool, sometimes persisting for many weeks.[74] Theoretically this can lead to immune-mediated pathology in both organs. Fecal-oral transmission of COVID-19 is likely.[75] There is burgeoning evidence for bidirectional crosstalk between the lungs and gut microbiome that has potential implications for COVID-19 dissemination and disruption of the microbiota by antibiotics.[75,76] Modulation of the gut microbiome by probiotics has a potential role in the prevention of COVID-19 infection and as an adjunctive therapy.[76,77]

Celiac patients do not seem to have increased susceptibility to COVID-19 infection, although one group noted an increased incidence of concomitant celiac disease and type I diabetes during the pandemic.[78,79] There is a concern about increased celiac cases in the future due to the pandemic.[80] Celiac patients do not have a worse outcome with acute COVID-19 infection.[81] One study suggested COVID-19 infection disproportionately disrupted amino acid absorption, with nutritional implications.[82] The mainstay of therapy for celiac disease in COVID-19–infected patients is strict maintenance of a gluten-free diet.[83]

Multisystem inflammatory syndrome, a newly described syndrome in children, mimics regional enteritis and has been found in pediatric patients with COVID-19 associated with viral cytopathic effects coupled with an abnormal immune response.[84] A similar presentation was noted in a young adult man,[85] who recovered

from COVID-19 infection but presented later with small bowel obstruction, fistula, and contained perforation, deemed secondary to prior enteritis. COVID-19 may be associated with acute exacerbations of Crohn disease.[85,86]

The most severe small intestinal manifestations of COVID-19 infection are enteritis, hemorrhage, infarction, and perforation likely secondary to microcirculatory and sometimes large vessel thromboses. Histologic examination of intestinal ischemia in COVID-19–infected patients noted small vessel fibrin thrombi, submucosal vessels with fibrinous degeneration, and perivascular neutrophils.[87] Acute mesenteric ischemia in patients with COVID-19 may result from acute emboli, thrombi, and nonocclusive mesenteric ischemia, or combinations thereof.[88] A database of almost 3000 Italian patients hospitalized with COVID-19 infection noted 0.7% had mesenteric ischemia either at presentation or during the hospitalization, with almost 40% mortality reported in patients with mesenteric ischemia.[89] In a pooled database, 24% of patients with COVID-19 with mesenteric ischemia had small intestinal involvement.[90] Small series note small intestinal infarction.[91] Symptoms of early mesenteric ischemia are nonspecific, and CT findings are often only moderately specific, leading to frequent delayed diagnosis and delayed intervention, especially during the pandemic.[92] Large vessel thromboses have been reported in COVID-19–infected patients, including involvement of the superior mesenteric artery or the portal/mesenteric veins.[92–94]

Twenty-two percent of a series of COVID-19–infected patients with pneumatosis had isolated small intestinal involvement.[95] A child with multisystem inflammatory syndrome developed pneumatosis and small intestinal perforation but survived after undergoing surgery.[96] A Mexican series of COVID-19–infected patients included 10 patients with intestinal perforations, of whom 4 had perforations located in the proximal jejunum.[97] A case report described a child with both pneumatosis and protein losing enteropathy.[98] Two cases of severe enteritis necessitating small bowel resections were reported, including one COVID-19–infected patient without respiratory symptoms.[99,100]

COVID-19 infection may be associated with intussusception in infants or children due to bowel wall inflammation.[101,102] Two children had intussusception with COVID-19 infection with evidence of the virus causing inflammation in mesenteric and intestinal tissue.[103]

COVID-19–infected patients with underlying risk factors including uncontrolled diabetes, high-dose corticosteroid therapy, and exposure to mechanical ventilation have increasingly developed mucormycosis, sometimes with GI involvement.[104] Clinicians must by vigilant for invasive mucormycosis, complicating the therapy for advanced COVID-19 infection.[105]

COLON

A large study surveilling the incidence and severity of COVID-19 infection from February 1 through July 31, 2020 in 10,552 patients with microscopic colitis (MC), including 3237 with the MC type denoted collagenous colitis (CC) and 7315 with the MC type denoted lymphocytic colitis (LC), versus 52,624 matched controls without MC, as diagnosed by colonic biopsies in Sweden from 1989 through 2016 (using the Epidemiology Strengthened by histoPathology Reports in Sweden [ESPRESSO study]), reported that patients with the CC type had a significantly higher risk of developing COVID-19 infection (hazard ratio [HR] = 1.72; 95% confidence interval [CI], 1.29–2.28), a significantly higher risk of hospitalization for COVID-19 infection (HR = 3.40; 95% CI, 2.03–5.70), and a significantly higher risk of developing severe

COVID-19 infection (HR, 2.48; 95% CI, 1.33–4.63) compared with controls.[106] Severe COVID-19 infection was defined by hospitalization with laboratory-confirmed COVID-19 as the primary diagnosis or by intensive care unit admission or death within 30 days of hospital admission with COVID-19 infection regardless of whether COVID-19 was the primary diagnosis on admission. Individuals suffering from severe COVID-19 infection or death before July 31, 2020, were censured to further follow-up. These results were not due to potential confounders of immunosuppression from oral corticosteroid therapy (used to treat MC) or PPI use (associated with MC). Contrariwise, there were no associations between the LC type of MC and severe COVID-19 outcomes. This work strongly suggests an association between CC and COVID-19 infection and severe COVID-19 infection/poor patient outcome, but no such association between LC and these parameters of severe COVID-19 infection were observed. Although the precise biological mechanism for the observed association between CC and severe COVID-19 outcomes is unknown, the increased risk may relate to genetic factors that modify immune responses to viral pathogens, such as an extended HLA haplotype associated with CC (but unassociated with LC) that is associated with impaired immune responses to microbial and viral pathogens with CC. Interestingly, this study demonstrated an increased prevalence of the rs13071258 A variant on the genetic locus 3p21.31 in individuals with CC but not with LC. This locus harbors 6 genes potentially affecting immunologic defense to viral infections. This study provides important insight into the divergent response of CC versus LC to acute COVID-19 infection, but this study requires further confirmation of the postulated biological mechanisms.

Interestingly, this locus would be subject to chromosomal amplification in trisomy-21 (Down syndrome) because of the extra copy of this allele in this syndrome. This phenomenon may underlie the worse GI or other organ outcomes in patients with COVID-19 infection who have Down syndrome.[107] For example, patients with Down syndrome and COVID-19 infection have worse outcomes from chronic GERD than controls with COVID-19 infection without Down syndrome.[108]

In a case report, one patient with severe, chronic, CC had severe acute COVID-19 infection manifested by prolonged hospitalization.[109] Notably, this patient exhibited protein-losing enteropathy (PLE), attributed to collagenous duodenitis (CD) coexistent with advanced collagenous colitis from a pathologically thick microscopic collagen layer in the duodenum that likely prevented normal absorption of individual amino acids and small chains of amino acids in the small bowel. The reported novel association of CD (and CC) with PLE and their association with severe COVID-19 infection was potentially attributed to relative immunosuppression from hypoproteinemia, hypoalbuminemia, hypogammaglobulinemia, and severe malnutrition from PLE. This patient,[109] however, was not analyzed for the presence of the rs13071258 A variant on the genetic locus 3p21.31, which is potentially associated with severe COVID-19 infection in individuals with CC.[106]

A 62-year-old woman, with chronic GERD, but no administration of PPI or nonsteroidal antiinflammatory drugs (NSAIDs) for several years and no other GI symptoms or disorders, developed acute COVID-19 infection manifesting as acute onset of cough, severe headache, and low-grade pyrexia.[110] After 10 days of gradual improvement after instituting symptomatic therapy, the patient developed watery, nonbloody diarrhea, with up to 6 bowel movements daily, and rectal urgency, which persisted for 3 months despite symptomatic treatment with acetaminophen and loperamide. Stool microscopy and cultures were negative for standard enteric pathogens. Complete blood count, liver function tests, kidney function tests, thyroid function tests, and C-reactive protein levels were within normal limits. Tissue transglutaminase immunoglobulin A test was negative. Colonoscopy, performed for persistent diarrhea,

revealed only scattered uncomplicated sigmoid diverticula. Histopathological analysis of sigmoid and descending colonic biopsies revealed increased chronic inflammatory cell infiltration of the lamina propria, lymphocytes extending into the surface epithelium and the epithelium lining the crypts, and findings typical for lymphocytic colitis without findings of collagenous colitis or inflammatory bowel disease. This case report suggests that lymphocytic colitis should be considered in the differential of chronic persistent watery diarrhea after acute COVID-19 infection, before diagnosing longCOVID, even though COVID-19 likely does not increase the risks of lymphocytic colitis.[106]

A 43-year-old man developed GI bleeding after treatment with tocilizumab, a monoclonal antibody against interleukon-6 (IL-6), for severe acute COVID-19 infection complicated by acute respiratory distress syndrome believed due to cytokine release syndrome (CRS).[111] Supportive investigations for CRS included highly elevated levels of IL-6, ferritin, and lactate dehydrogenase. Colonoscopy performed for GI bleeding revealed terminal ileal and cecal ulcers. The patient required surgical resection of the diseased terminal ileum and cecum because of cecal perforation. This patient had a history of potential confounders including lupus anticoagulant without receiving chronic anticoagulation therapy, chronic renal insufficiency, and the cytokine release syndrome itself, all of which could promote enteric ulcerations. Tocilizumab has been previously associated with lower GI perforation and colonic diverticular perforation during treatment of rheumatoid arthritis[112] but has not been previously associated with GI perforation during treatment of the cytokine release syndrome from severe COVID-19 infection.

In a study of 11 hospitals in New York City, the rate of Clostridiodes (Clostridium) difficile infection increased from the spring of 2019 to the spring of 2020 associated with the onset of the COVID-19 pandemic crisis in spring 2020.[113] Approximately one-third of cases of *C difficile* in spring of 2020 were in patients with COVID-19 infection, but two-thirds of cases were unassociated with COVID-19 infection. The increase in *C difficile* during the spring of 2020 correlated with a 20% increase in antibiotic usage in spring 2020 from the year earlier that was correlated with increased cephalosporin therapy to treat infections but was uncorrelated with increased use of other antibiotics. Cephalosporins are a known significant risk factor for *C difficile* infection. This correlation occurred in each of the 11 study hospitals, which used independent antibiotic protocols.

In a retrospective study of 6002 abdominal CT examinations conducted at 5 hospitals by investigators at the Massachusetts General Hospital, the rates of positive diagnoses of acute appendicitis and/or diverticulitis over the 6 weeks just before versus the 6 weeks just after the onset of the COVID-19 pandemic in March 2022 were 4% (144) versus 4%[100] for appendicitis and 8% versus 7% for diverticulitis ($P > 0.2$ for both).[114] For positive CT examinations, the rates of perforation, hospitalization, surgery, and catheter drainage changed minimally from before to after the pandemic onset by −2%, −3%, −2%, and −3%, respectively, for appendicitis (n = 244, $P > 0.3$ for all) and by +6% ($P = 0.2$), +9% ($P = 0.06$), +4% ($P = 0.01$), and +1% ($P = 0.6$), respectively, for diverticulitis (n = 443). CT examinations performed for suspected appendicitis or diverticulitis declined slightly after the pandemic onset most likely reflecting patients leaving urban centers due to the pandemic and altered triage of patients without COVID-19. However, the diagnostic rates, disease severity at presentation, and treatment approach otherwise remained mostly unchanged during the first 6 weeks of the COVID pandemic compared with the previous 6 weeks.

Several cases of acute colonic pseudoobstruction have been reported in patients with severe COVID-19–associated pneumonia.[115] Patients typically are elderly and

Table 1
Effect of COVID-19 infection on gastrointestinal disorders and diseases

Disease or Disorder	Clinical Characteristics	Mechanism
Anosmia & ageusia/ dysgeusia	Very common. Often the first symptom to manifest with COVID-19 infection and the last symptom to resolve. Bothersome symptoms but not life-threatening. Proposed, unproven therapies include corticosteroids and Paxlovid.	Not associated with nasopharyngitis, nasal obstruction, glossitis, zinc deficiency, or rhinorrhea. Postulated decreased sensitivity of olfactory neurons associated with expression of ACE-2 in alveolar epithelial cells.
Geographic (COVID) tongue	Affects about 4% of infected patients. Associated with minor symptoms.	Loss of filiform papillae in rear of tongue from damage caused by high expression of ACE-2 in epithelial cells.
GERD (gastroesophageal reflux disease)	Very common with COVID-19 infection but also very common without COVID-19 infection. GERD likely does not arise from acute COVID-19 infection but likely arises from shared risk factors, such as obesity.	COVID-19 may preferentially infect Barrett's epithelium over normal esophageal mucosa, and PPI therapy may be associated with increased COVID-19 susceptibility.
Esophageal candidiasis	Risk factors include acute respiratory distress syndrome, chronic corticosteroid therapy, and prolonged endotracheal intubation. Often associated with severe COVID-19 infection and has a high mortality due to this association. Typical symptoms are dysphagia and odynophagia. EGD classically demonstrates a cheesy exudate in esophagus. Endoscopic brushings are usually diagnostic. Primary therapies are echinocandins and azoles.	Associated with profound immune dysregulation with COVID-19 infection, but the specific underlying immunologic defects are unknown.
Pill-induced esophagitis	More prevalent in COVID-19 infected patients.	Partly related to increased use of doxycycline antibiotics to treat COVID-19 infection and increased corrosive ingestion due to COVID-19 pandemic–related stress.
Eosinophilic esophagitis	Apparently eosinophilic esophagitis does not increase the frequency or severity of COVID-19 infection. Acute COVID-19 infection does not apparently cause flares of eosinophilic esophagitis.	Patients with eosinophilic esophagitis typically have mild COVID-19 infection. COVID-19 esophageal infection might be related to oral corticosteroid therapy for eosinophilic esophagitis.

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Disease or Disorder	Clinical Characteristics	Mechanism
Gastric ulcers	Gastric ulcers very common in patients with COVID-19 infection who are undergoing EGD.	*H pylori* does not apparently affect the severity of COVID-19 infection. Several patients had esophageal or gastric ulcers from primary COVID-19 infection, as demonstrated by electron microscopy.
GI hemorrhage	Occurs in about 9% or less of hospitalized COVID-19–infected patients. Often the GI bleeding is mild and does not mandate endoscopy. Patients with GI bleeding often have a worse prognosis from COVID-19 infection than nonbleeding COVID-19–infected patients. GI hemorrhage in patients with COVID-19 is often from gastric ulcers. GI bleeding may sometimes arise from anticoagulation used to treat a hypercoagulopathy associated with COVID-19 infection.	GI bleeding rarely due to ulcers associated with primary COVID-19 infection.
Celiac disease	Celiac patients do not have increased susceptibility to COVID-19 infection and do not have a worse outcome from COVID-19 infection. The mainstay of therapy in COVID-19–infected patients is maintenance of a gluten-free diet.	The 2 different diseases do not seem to significantly interact.
Multisystem inflammatory syndrome	Rare syndrome that occurs in children. Clinically can resemble regional enteritis. Can cause GI obstruction, fistula, or contained GI perforation.	Syndrome associated with an abnormal immune response due to viral cytopathic effects.
Mesenteric ischemia	COVID-19 infection likely increases the risk of mesenteric ischemia. Mesenteric ischemia has a high mortality in COVID-19–infected patients.	Most likely increased frequency of mesenteric ischemia due to microcirculatory thrombosis, but sometimes can occur from large vessel thrombosis. COVID-19 can produce a hypercoagulopathy. High mortality from mesenteric ischemia attributed to delayed diagnosis because symptoms can be confused with acute COVID-19 infection.

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Disease or Disorder	Clinical Characteristics	Mechanism
Small bowel intussusception	Frequency may increase with COVID-19 infection.	Attributed to bowel wall or mesenteric lymph node inflammation, edema and thickening from local viral infection that forms a lead point for the intussusception.
GI infection with mucormycosis	Increased risk with advanced COVID-19 infection due to immunosuppression. Associated with high mortality.	Increased risk attributed to high-dose corticosteroid therapy, exposure to mechanical ventilation, and advanced COVID-19 infection.
Collagenous colitis	Significantly higher rate of contracting COVID-19 infection, having severe COVID-19 infection, and of being hospitalized for COVID-19 infection than patients with lymphocytic colitis or controls.	May relate to genetic factors associated with predisposition to developing collagenous colitis such as an extended HLA haplotype or the rs13071258 A variant on genetic locus 3p21.31 associated with collagenous colitis. This genetic locus harbors 6 genes potentially affecting the immune defense against viral infections.
Lymphocytic colitis	Has similar rate of contracting COVID-19 infection and developing severe infection as controls. Lymphocytic colitis should be considered in the differential of watery diarrhea after contracting acute COVID-19 infection.	Unlike collagenous colitis, lymphocytic colitis is not associated with genetic abnormalities affecting host defenses against viruses.
Tocilizumab-associated colonic perforation	Case report of developing terminal ileal and cecal ulcers that caused colonic perforation after initiating tocilizumab therapy for suspected cytokine release syndrome in a patient with COVID-19 infection.	Tocilizumab has previously been associated with lower GI perforation and colonic diverticular perforation after its use to treat rheumatoid arthritis.
Acute appendicitis and acute diverticulitis	COVID-19 infection does not affect the frequency of hospitalization, colonic perforation, or surgery from these 2 diseases.	COVID-19 infection does not seem to affect the natural history of these 2 diseases.
Irritable bowel syndrome	During pandemic patients with irritable bowel syndrome experienced more severe GI symptoms, more severe extraintestinal symptoms, and more sleep difficulties than	Patients likely experience more severe symptoms of irritable bowel syndrome due to anxiety related to the pandemic.

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Table 1
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Disease or Disorder	Clinical Characteristics	Mechanism
	before the COVID-19 pandemic.	
Inflammatory bowel disease	COVID-19–infected patients have a worse outcome from inflammatory bowel disease when treated with corticosteroids but not when treated with tumor necrosis factor antagonists.	Corticosteroids may decrease immunologic defenses against COVID-19 infection. Another chapter in this monograph is devoted to COVID-19 infection in patients with inflammatory bowel disease.

have normal serum lactate levels, clinically obscure hypoxia, abdominal distension, sluggish bowel sounds, and colonic dilatation supported by radiographic findings at abdominal flat plate or abdominal CT. Acute colonic pseudoobstruction in patients admitted with COVID-19 pneumonia requires a high index of suspicion, as it warrants early mitigation by discontinuing offending agents, optimizing electrolytes, and therapeutic colonic decompression to decrease morbidity and mortality.

The COVID-19 pandemic has affected colonoscopy for screening or surveillance of colon cancer or colonic polyps. The COVID-19 pandemic has created a backlog of colonoscopy for such indications with attendant stricter application of colonoscopy indications due to potential risks to patients or endoscopy personnel from exposure to COVID-19 infection.[116] One approach to decrease exposure to COVID-19 infection is to offer some patients CTC. Indications for CTC in a study of 224 patients at 4 academic British hospitals included the following: change in bowel habits (116/224; 48%), positive fecal immunochemical test (69/224; 31%), iron deficiency anemia (50/224; 23%), weight loss (27/224; 7.6%), bleeding per rectum (27/224; 12%), polyp surveillance (25/224; 11%), and abdominal pain (20/224; 9%). Of 224 patients undergoing CT colonography in May to July 2020 at 4 British hospitals, 55 patients (24.6%), had a greater than or equal to 6 mm colonic polyp detected by CTC.[117] Of 169 patients contacted by telephone for follow-up, none reported any new symptoms of COVID-19 infection (cough, pyrexia, anosmia, ageusia) within 14 days of the CTC. None of the 86 staff performing CT colonography who were contacted developed COVID-19 infection after the procedure. These findings suggest that CT colonography can be performed relatively safely during the COVID-19 pandemic, with a relatively high yield of colonic polyps by expert GI radiologists. The risks of developing COVID-19 infection from CTC are low in patients and in the radiology staff.

In a study of 190 consecutive tertiary referrals for IBS, patients seen during the COVID-19 pandemic had greater IBS severity (IBS-SSS: 352 vs 318, $P = 0.03$), more severe extraintestinal symptoms (noncolonic score: 269 vs 225, $P = 0.03$), more frequent sleep difficulties ($P = 0.03$), and feelings of helplessness and loss of control ($P = 0.02$) compared with baseline patients before the pandemic.[118] However, patients during the pandemic had similar HAD-Anxiety ($P = 0.96$) and HAD-Depression ($P = 0.84$) scores (the HAD, or Hospital Anxiety and Depression score, is a 14-item self-administered anxiety and depression scale specifically designed for use in non-psychiatric settings to semiquantify feelings of anxiety and depression). During the pandemic, unmarried patients ($P = 0.03$) and workers in stressful jobs ($P = 0.0038$) had greater IBS severity. This study demonstrated that patients seen in tertiary care with refractory IBS during the COVID-19 pandemic had a

Table 2
Frequency of performing diagnostic and therapeutic GI tests during the COVID-19 pandemic (extensively reviewed in another chapter in this monograph on gastrointestinal endoscopy during the COVID-19 pandemic)

Test or Procedure	Effects Associated with COVID-19 Pandemic	Postulated Mechanism
EGD	The frequency of performing EGD during the acute pandemic peak (in March–April 2000) fell dramatically to just a few percentage of its baseline rate before the pandemic. The rate has recovered vigorously after March–April 2020 but still is lower than the baseline rate before the pandemic.	EGD is often deferred in patients with mild GI bleeding or other mild symptoms because of patient preference or concerns about transmission of COVID-19 infection to endoscopy suite personnel. EGD should be performed for urgent or emergent indications.
EGD for screening/ surveillance of Barrett's esophagus and esophageal adenocarcinoma	Markedly decreased performance of EGDs for these indications during the pandemic	EGD often deferred or postponed due to these indications becauser EGD is considered a lower priority during pandemic compared with urgent indications for EGD. EGD should be performed urgently or emergently for suspected esophageal cancer.
CT of chest	Has been used as an alternative diagnostic test for EGD (eg, to detect esophageal varices)	CT, however, has limited applicability because it is rarely therapeutic. For example, CT, unlike EGD, cannot be used to band esophageal varices.
Cytosponge device	Recent innovation that permits acquiring esophageal tissue with less procedure time and at lower cost than EGD.	Experimental procedure that may soon provide a substitute for EGD that is less costly and less labor-intensive.
Unsedated nasal endoscopy	Can be used as an alternative to EGD. Does not require a nurse anesthetist.	Less costly than EGD. Requires less endoscopic resources, less endoscopic personnel, and less procedure time.
Screening and surveillance colonoscopy	Screening colonoscopy declined dramatically during the acute COVID-19 pandemic peak but has gradually recovered somewhat.	Screening colonoscopy is generally contraindicated in patients with acute COVID-19 infection. Screening colonoscopy is often deferred or postponed in favor of more urgent colonoscopy indications even in patients who are not positive for COVID-19 infection.

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Table 2
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Test or Procedure	Effects Associated with COVID-19 Pandemic	Postulated Mechanism
Other colonoscopy indications	Colonoscopy for emergent or urgent indications usually performed. Colonoscopy may be deferred for elective indications depending on the indication and local practice patterns.	Colonoscopy may sometimes be deferred for elective indications due to perceived risk of contracting COVID-19 infection during colonoscopy to endoscopy staff or patients.
High-resolution manometry (HRM)	Number performed markedly decreased during pandemic.	Decrease attributed to risks of contracting or transmitting COVID-19 infection during the procedure. Also attributed to patient preference and strict endoscopy suite guidelines for performing procedures during the pandemic.

significantly higher symptom burden. These findings suggest the importance of the gut-brain axis in IBS and that lack of support and perceived loss of patient control during the COVID-19 pandemic may exacerbate the symptoms of IBS.

COVID-19–infected patients with inflammatory bowel disease as compared with patients without COVID-19 infection have a worse prognosis when treated with corticosteroids but not with tumor necrosis factor antagonists.[119,120] The management of patients with cancer receiving immune checkpoint inhibitor therapy may be affected by COVID-19 infection due to the occurrence of immune checkpoint inhibitor colitis.[121]

ANUS

Hemorrhoids are very common in both the general population and COVID-19–infected patients. Surgery for hemorrhoids should be prioritized according to symptoms and signs, with deferral of elective surgery. An e-consult may help in prioritizing patients for surgery.[122]

Anal fissures are very common during the pandemic and may be increased by COVID-19 infection, with a reported rate of 30% in patients with chronic COVID-19 attributed to sitting on a chair in front of a computer while working at home, and shared risk factors, especially obesity.[123]

In a survey of 45 office procedures performed by proctologists during the pandemic, the most common indication for surgery was anal abscesses and/or fistula (48.9%).[124]

SUMMARY

Although most of the morbidity and mortality of the COVID-19 pandemic involves the respiratory system, the virus also prominently affects the GI system in which it produces considerable symptoms and contributes to patient morbidity and occasionally mortality. The COVID-19 virus can directly infect GI mucosa due to the abundant ACE-2 receptors within these organs. This work describes the effect of COVID-19 on miscellaneous GI disorders (**Table 1**), thereby supplementing other chapters in this monograph reviewing individual GI symptoms or disorders in patients with COVID-

19 infection, inflammatory bowel disease, GI bleeding, GI endoscopy, surgical considerations with GI disorders, diagnostic and therapeutic GI radiology (Table 2), GI pathology, and chronic (long) COVID infection. Other chapters in this monograph review pancreatic and hepatic symptoms and disorders associated with COVID-19 infection.

CLINICS CARE POINTS

- It is important to consider gastrointestiunal inflammastory diseases because they may influence the inflammatory reactions to COVID-19 infection or in turn be influnced by inflammatory changes induced by the COVID-19 infection.
- The gastrointestinal tract, especially the stomach and small intestine, has as many ACE-2 (angiotensin converting enzyme-2) receptors to the COVID-19 virus as the respiratory tract, allowing for frequent local gastrointestinal mucosal infection, disruption, and inflammation by the virus.
- Clinicians must be aware of how the COVID-19 virus affects many gastrointestinal disorders to manage these disorders in patients with simultaneous COVID-19 infection.

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