Coronavirus disease 2019 (COVID-19): Issues related to gastrointestinal disease in adults

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INTRODUCTION

At the end of 2019, SARS-CoV-2, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. Coronavirus disease 2019 (COVID-19) primarily manifests as a lung infection with symptoms ranging from those of a mild upper respiratory infection to severe pneumonia, acute respiratory distress syndrome, and death. COVID-19 disproportionately affects patients with pre-existing comorbidities and/or older adults. All medical professionals, including gastroenterology and hepatology clinicians, are tasked with rapidly adjusting their practice to curtail the spread of COVID-19, while providing care to their patients.

This topic will discuss COVID-19-related issues for patients with gastrointestinal and liver disease. As understanding of COVID-19 illness continues to evolve, the approach to diagnosis and management may require modification as well.

Other important aspects of COVID-19 infection are discussed in detail separately:

- (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention".)
- (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings".)
- (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults".)
- (See "Coronavirus disease 2019 (COVID-19): Outpatient management in adults".)

POSSIBLE RISK FACTORS FOR COVID-19

Some patients with chronic gastrointestinal (GI) or liver disease may be at increased risk for COVID-19 and for more severe illness. Potential risk factors in these patients include their chronic inflammatory disease, comorbidities (eg, diabetes mellitus), immune-modifying therapies, and the need for regular office, endoscopy center, or laboratory visits. These patient groups include [1]:

- Patients with cirrhosis
- Patients with chronic cholestatic liver disease (eg, primary sclerosing cholangitis, primary biliary cholangitis)
- Liver transplantation recipients [2] (see "Coronavirus disease 2019 (COVID-19): Issues related to solid organ transplantation")

For patients with inflammatory bowel disease (IBD), preliminary data have suggested that the prevalence of COVID-19 is not higher than that of the general population [3-6].

The risk of COVID-19 for patients on biologic therapy for chronic inflammatory diseases (eg, IBD, rheumatoid arthritis, psoriasis) is uncertain [5]. (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults", section on 'COVID-19-specific therapy'.)

The gastrointestinal tract may be susceptible to SARS-CoV-2 infection because of widely expressed angiotensin-converting enzyme 2 (ACE2) receptors in the intestine [7]. ACE2 is a receptor for SARS-CoV-2 virus, and digestive symptoms associated with SARS-CoV-2 infection may be caused by direct viral attack as well as tissue and organ damage due to the immune response [8,9]. Staining of tissue specimens from patients with COVID-19 demonstrated that the positive areas were mainly distributed in the cytoplasm of gastric and intestinal epithelial cells and the cilia of glandular epithelial cells [8]. In addition, viral nucleocapsid protein was detected in the cytoplasm of gastric, duodenal, and rectal glandular epithelial cells. However, understanding of the pathogenesis of digestive disease associated with SARS-CoV-2 virus is evolving, and its effects on existing chronic GI disorders remains uncertain [10].

CLINICAL MANIFESTATIONS AND DIAGNOSTIC TESTING

Symptoms of disease flare that can mimic COVID-19 — The clinical presentation of several gastrointestinal (GI) and liver diseases (eg, Crohn disease, ulcerative colitis, autoimmune hepatitis) can mimic COVID-19 infection [11]. Examples include diseases that manifest with diarrhea, anorexia, and acute hepatitis and/or abnormal liver biochemical and function tests [12]. Thus, for patients with

an existing diagnosis of chronic GI or liver disease, the clinician will need to assess whether symptoms are related to a disease flare or COVID-19. The approach to testing for COVID-19 is discussed separately. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Diagnosis'.)

Digestive symptoms — Patients with COVID-19 typically present with fever and respiratory symptoms; however, gastrointestinal symptoms have been commonly reported in patients diagnosed with COVID-19 [7,12-15]. For example, in a study including 318 adult patients who were hospitalized with COVID-19, 195 patients (61 percent) reported at least one digestive symptom, and the most frequently reported symptoms were anorexia in 110 patients (35 percent), diarrhea in 107 patients (34 percent), and nausea in 84 patients (26 percent) [13]. Similarly, in another study of 204 patients with COVID-19, 103 patients (51 percent) reported at least one digestive symptom, and the most commonly reported symptoms were anorexia and diarrhea [12].

Some patients with COVID-19 have presented with isolated GI symptoms that may precede the development of respiratory symptoms [16,17]. As an example, in a study of 1141 patients with COVID-19, 183 patients (16 percent) presented with GI symptoms (eg, diarrhea, nausea, vomiting) in the absence of respiratory complaints [16].

Limited data have suggested that diarrheal symptoms in patients with COVID-19 have been associated with virus RNA in stool [14,18,19]. In a study of 84 patients with SARS-CoV-2 pneumonia, stool samples from patients with diarrhea had higher rates for detecting SARS-CoV-2 virus RNA by real time polymerase chain reaction compared with patients without diarrhea (69 versus 17 percent) [18].

Hepatic manifestations — The clinical presentation of COVID-19 may include hepatic manifestations such as acute hepatitis and abnormal liver biochemical and function tests [20].

When to test for COVID-19 in patients with GI symptoms — The diagnosis of COVID-19 is suspected primarily in patients with the new onset of fever and/or respiratory tract symptoms (eg, cough, dyspnea), while other consistent symptoms include myalgias, diarrhea, and aberrancy in sense of smell or taste.

For patients with GI symptoms, we favor testing for COVID-19 in the following cases [21]:

- Hospitalized patients with the new onset of GI symptoms
- Outpatients with the new onset of GI symptoms for over 48 hours
- Patients with established GI disease (eg, Crohn disease) with symptoms suggestive of a disease flare (eg, diarrhea, vomiting)

In a minority of patients, GI symptoms such as diarrhea may be the presenting symptom or may precede the development of respiratory symptoms [16,17,21]. While the diagnosis of COVID-19 may be suspected based on presenting symptoms, additional factors that inform the decision to perform testing include the patient's geographic location, risk of exposure, rate of community transmission, and the availability of testing. The epidemiology and diagnosis of COVID-19 are discussed in more detail separately. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Diagnosis'.)

Additionally, stool testing to exclude *Clostridioides* (*C*., formerly *Clostridium*) *difficile* infection is obtained for patients with diarrhea who are at risk for *C. difficile* infection (eg, recent antibiotic use) or who may require therapy (eg, antidiarrheal agents) to control symptoms. (See 'Managing symptoms related to viral infection' below.)

Managing symptoms related to viral infection — For symptomatic therapy for infectious diarrhea, the antidiarrheal agent loperamide can be used in an initial dose of 4 mg and with a maximum daily dose of 16 mg in patients without fever, bloody stools, or risk factors for *C. difficile* infection. Use of loperamide for patients with acute diarrhea is discussed separately. (See "Approach to the adult with acute diarrhea in resource-rich settings", section on 'Management'.)

For patients with symptoms of gastroenteritis (eg, nausea, vomiting), antiemetic drugs can often help relieve symptoms, in addition to supportive measures including oral or intravenous hydration. Management of patients with gastroenteritis and use of antiemetics are discussed separately. (See "Acute viral gastroenteritis in adults", section on 'Treatment' and "Characteristics of antiemetic drugs".)

Symptomatic therapy for digestive symptoms may reduce the risk of complications such as electrolyte disturbances (eg, hypokalemia) or colonic ischemia related to volume depletion. (See "Colonic ischemia".)

Specific management for COVID-19 is discussed in more detail separately. (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults" and "Coronavirus disease 2019 (COVID-19): Outpatient management in adults".).

MANAGEMENT PRINCIPLES

General strategies to reduce risk of infection — If community transmission of SARS-CoV-2 virus is present, preventive measures to reduce exposure to the virus include (see "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Prevention'):

- General preventive measures such as hand hygiene and social distancing.
- Use of telemedicine visits for ongoing disease management.
- Decreased frequency of routine laboratory and imaging surveillance when the associated risk is deemed to be low.
- Delay nonurgent endoscopic procedures (eg, colorectal cancer screening) (see 'Implications for endoscopy' below).
- Use of lower-volume laboratories off-site from larger healthcare facilities.
- For patients with stable disease and without known or suspected COVID-19, continuing the established medication regimen to avoid a disease flare that may result in the need for diagnostic testing and/or inpatient hospitalization.
- For patients on glucocorticoids, therapy should not be abruptly discontinued, but should be used at the lowest dose possible to control the underlying disease, regardless of COVID-19 exposure or infection status.

Inflammatory bowel disease

Diagnostic considerations during pandemic — For patients with symptoms of active inflammatory bowel disease (IBD) (eg, diarrhea) who are also at risk for COVID-19 (eg, recent exposure, high rate of community transmission), evaluation includes COVID-19 testing, stool studies to exclude enteric infections (eg, *C. difficile* infection), noninvasive inflammatory markers (eg, C-reactive protein, fecal calprotectin), and serum drug trough levels (for patients on biologic therapy). (See "Treatment of Crohn disease in adults: Dosing and monitoring of tumor necrosis factor-alpha inhibitors", section on 'Monitoring' and "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults".)

However, in patients with SARS-CoV-2 virus, nonspecific markers of inflammation (eg, C-reactive protein) may be elevated due to COVID-19 rather than IBD. (See "Clinical manifestations, diagnosis, and prognosis of Crohn's disease in adults" and "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults".)

If fecal markers (eg, fecal calprotectin, lactoferrin) are not elevated, endoscopic evaluation is not necessary, as negative test results indicate the absence of active bowel inflammation. For most patients with an established diagnosis of IBD, elevated fecal inflammatory marker levels along with typical symptoms of active disease (eg, diarrhea) in the absence of infection are sufficient to initiate IBD treatment. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Pretreatment evaluation'.)

Urgent endoscopic evaluation is reserved for patients in whom the results will change management [6]. For example, patients with suspected severe acute ulcerative colitis are typically started on glucocorticoids intravenously but still require at least a limited lower endoscopy with biopsies to confirm the diagnosis and exclude other conditions (eg, viral infection). (See "Management of the hospitalized adult patient with severe ulcerative colitis", section on 'Pretreatment evaluation'.)

Patients without COVID-19

Patients with IBD in remission — Available data have suggested that patients with IBD in remission are not at higher risk for SARS-CoV-2 virus infection and that such patients should continue maintenance therapy to sustain remission [3,4,6]. Discontinuing maintenance therapy has been associated with disease relapse that may require hospitalization and/or glucocorticoid therapy, and thus, increase the risk of COVID-19 [3,22].

Therapies for maintaining remission in patients with Crohn disease are discussed separately. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Maintenance of remission' and "Overview of medical management of high-risk, adult patients with moderate to severe Crohn disease", section on 'Maintenance therapy'.)

Therapies for maintaining remission in patients with ulcerative colitis are discussed separately. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Maintenance of remission' and "Management of moderate to severe ulcerative colitis in adults", section on 'Maintenance of remission'.)

Patients with active IBD — For patients with a flare of Crohn disease or ulcerative colitis in the absence of COVID-19, adding or escalating anti-inflammatory or biologic therapy may be required for symptomatic improvement and inducing remission. (See 'Diagnostic considerations during pandemic' above.) For example, therapeutic options for mild IBD include oral budesonide, aminosalicylates, and topical (rectal) therapy, while options for moderately to severely active IBD include biologic therapies (eg, anti-tumor necrosis factor [TNF] agents, anti-integrin agents, and anti-interleukin agents) [6]. The approach to using these therapies has not changed during the pandemic.

However, if systemic glucocorticoids are deemed necessary for patients with active IBD during the pandemic, the lowest dose of glucocorticoid that will result in clinical response is used for a short duration before transitioning to another therapy that is glucocorticoid-sparing [6]. For example, management of a patient who is hospitalized with severe ulcerative colitis in the absence of COVID-19 may include treatment with a glucocorticoid (eg, methylprednisolone 16 to 20 mg intravenously every eight hours) for three days, and if there is no clinical response, medical therapy is escalated to infliximab [6,23]. Surgery is an alternative option for patients who do not improve with medical therapy. Additionally, in the COVID-19 era, the initial use of infliximab at a dose of 5 mg/kg rather than

glucocorticoid therapy is a reasonable approach. Management of hospitalized patients with ulcerative colitis including escalating medical therapy is discussed in more detail separately. (See "Management of the hospitalized adult patient with severe ulcerative colitis".)

Diagnosis, pretreatment assessment, and medical management of Crohn disease are discussed separately:

- (See "Clinical manifestations, diagnosis, and prognosis of Crohn's disease in adults".)
- (See "Overview of the medical management of mild (low risk) Crohn disease in adults".)
- (See "Overview of medical management of high-risk, adult patients with moderate to severe Crohn disease".)

Diagnosis, pretreatment assessment, and medical management of ulcerative colitis are discussed separately:

- (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults".)
- (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis".)
- (See "Management of moderate to severe ulcerative colitis in adults".)
- (See "Management of the hospitalized adult patient with severe ulcerative colitis".)

Patients with COVID-19

Adjusting IBD medications — Adjustments to medication regimens in patients with IBD with suspected or known COVID-19 should be individualized based on the severity of infection, patient comorbidities, and the existing medication regimen. Expanding indications for SARS-CoV-2 testing (eg, screening prior to endoscopy) may result in increased identification of asymptomatic patients who are infected [6]. The goal of medication adjustment is to reduce immunosuppression during active viral infection to lower the risk of COVID-19-related complications (eg, pneumonia) [24]. Our overall approach for patients with IBD in remission includes [25-27] (see "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults"):

- Therapies that can be continued without interruption:
  - Budesonide.
  - Aminosalicylates.
  - Topical rectal therapy (eg, topical glucocorticoid).
  - Antibiotics.
- Therapies requiring adjustment:

- Systemic glucocorticoids – Reduce dose of systemic glucocorticoid (eg, prednisone dose to <20 mg daily) or transition to oral budesonide. (See "Overview of budesonide therapy for adults with inflammatory bowel disease".)

  Although systemic glucocorticoids convey an increased risk of infections, abrupt discontinuation is not possible, and patients should receive the lowest required dose for the shortest period of time necessary to minimize adverse reactions. (See "Major side effects of systemic glucocorticoids".)

- Immunomodulators – Discontinue thiopurines (ie, azathioprine, 6-mercaptopurine) and methotrexate.

- Tofacitinib – Discontinue tofacitinib, a small molecule Janus kinase inhibitor because it has been associated with an increased risk of other viral infections (ie, herpes zoster infection) and its mechanism of action is to suppress T-cell function. (See "Management of moderate to severe ulcerative colitis in adults", section on 'Tofacitinib'.)

- Biologic agents – Discontinue biologic therapy (anti-TNF agents, ustekinumab, or vedolizumab).

Resumption of therapy — The optimal time to resume immunosuppressive medications after SARS-CoV-2 infection is uncertain, while expert consensus has stated that medications can be resumed after negative testing for COVID-19 and/or a symptom-free observation period of 14 days. (See "Coronavirus disease 2019 (COVID-19): Epidemiology, virology, clinical features, diagnosis, and prevention", section on 'Diagnosis'.)

Preliminary data suggested that induction therapy for active ulcerative colitis in the setting of recent mild COVID-19 was not associated with an increased risk for progressing to severe infection. In a case report of a 54-year-old female patient with mild COVID-19 and active ulcerative colitis, treatment with infliximab at weeks 6 and 7 following the diagnosis was associated with achieving clinical remission and recovery from COVID-19 [28].

Prognosis — Case series including patients with SARS-CoV-2 infection and chronic inflammatory diseases (rheumatoid arthritis, IBD) have provided preliminary outcome data [5,28]. As an example, in a study of 86 patients with COVID-19 in the setting of immune-mediated inflammatory disease (including 37 patients with IBD), 14 patients (16 percent) required hospitalization, and the mortality rate was 7 percent [5]. In another study of 40 patients with IBD and SARS-CoV-2 infection, including 11 patients (28 percent) on immunomodulators and seven patients (18 percent) on biologic monotherapy, 21 patients (53 percent) were hospitalized, but none required intensive care unit admission [28]. However, two patients with ulcerative colitis (5 percent) died from complications of

acute respiratory distress syndrome; both of these patients were older (ie, >75 years of age), and one patient had been on methotrexate.

DISEASE REGISTRIES

Data on patients with chronic gastrointestinal or liver disease who have been infected with SARS-CoV-2 virus are accumulating, and disease-specific patient registries include:

- SECURE-IBD registry – The SECURE-IBD registry is an international database that collects data on disease severity and outcomes for patients with inflammatory bowel disease (IBD) who have been infected with SARS-CoV-2 virus [29]. The available data have suggested that hospitalization rates have been highest among patients with moderately to severely active IBD, which emphasizes the importance of treating active inflammation. (See 'Patients with COVID-19' above.)

- SECURE-Cirrhosis registry – The SECURE-Cirrhosis registry is an international database that collects data on disease severity and outcomes for patients with chronic liver disease (ie, cirrhosis, liver transplantation recipients) [30].

IMPLICATIONS FOR ENDOSCOPY

During the COVID-19 pandemic, nonurgent endoscopic procedures have been deferred with a goal of reducing transmission of SARS-CoV-2 virus infection, conserving personal protective equipment, and reserving clinical resources for managing patients with COVID-19. The decision to perform endoscopic procedures and the necessary protocols are informed by state, local, and institutional rules in addition to guidance from professional societies [31,32]. (See "Society guideline links: Coronavirus disease 2019 (COVID-19) – Guidelines for specialty care", section on 'Gastroenterology and hepatology'.)

Indications for elective procedures that should be delayed, in addition to indications for urgent or emergent procedures that should not be delayed, can be found on the American Society for Gastrointestinal Endoscopy website.

Strategies for reducing the risk of transmitting infection during gastrointestinal endoscopy that have been endorsed by professional societies, including the use of personal protective equipment, can be accessed here.

Infection control strategies for use during aerosol-generating procedures (eg, upper gastrointestinal endoscopy, endoscopic retrograde cholangiopancreatography [ERCP], endoscopic ultrasound) are

discussed separately. (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Infection control in the health care setting'.)

The approach to managing some patients with acute gastrointestinal (GI) and liver disease has been modified because of the COVID-19 pandemic [33]:

- **Patients with GI bleeding** – Early reports suggest that GI bleeding is a common indication for gastroenterology consultation during the COVID-19 pandemic, while strategies to use medical therapy and delay endoscopic evaluation have been developed [34,35]. Some centers have suggested medical therapy for patients with suspected nonvariceal upper GI bleeding including continuous intravenous proton pump inhibitor, antiemetics, and optimizing coagulation status [34]. For example, in a series of six patients with acute upper GI bleeding and COVID-19 pneumonia, management included intravenous proton pump inhibitor and clinical observation, and no patients required urgent endoscopy during their hospitalization [35]. Rationale for this conservative approach also includes data that have suggested that delaying endoscopy for 24 hours was not associated with increased mortality in patients with acute upper GI bleeding [36].

  For most patients with lower GI bleeding in the setting of COVID-19, endoscopic evaluation can be initially delayed and then performed on an outpatient basis after resolution of the acute illness [34]. Timing of endoscopy for patients with GI bleeding is discussed separately. (See "Approach to acute upper gastrointestinal bleeding in adults" and "Approach to acute lower gastrointestinal bleeding in adults".)

- **Patients with acute cholangitis or biliary obstruction** – Strategies for managing patients who have acute cholangitis and/or obstructive jaundice are informed by available resources (eg, endoscopy space, nursing, and anesthesia services), the patient's hemodynamic status and location (eg, intensive care unit) and the availability of alternatives to ERCP (eg, percutaneous transhepatic cholangiography, initial medical management) [34,37]. Management of acute cholangitis is discussed in more detail separately. (See "Acute cholangitis: Clinical manifestations, diagnosis, and management".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Coronavirus disease 2019 (COVID-19) – Guidelines for specialty care" and "Society guideline links: Coronavirus disease 2019 (COVID-19) – International and government guidelines for general care".)

SUMMARY AND RECOMMENDATIONS

- Patients with COVID-19 typically present with fever and respiratory symptoms; however, gastrointestinal symptoms (GI) (eg, anorexia, diarrhea, nausea) have been reported in patients diagnosed with COVID-19. (See 'Digestive symptoms' above.)

- We favor testing for COVID-19 in the following patients, even in the absence of respiratory symptoms (see 'When to test for COVID-19 in patients with GI symptoms' above):

  - Hospitalized patients with the new onset of GI symptoms

  - Outpatients with the new onset of GI symptoms for over 48 hours

  - Patients with established GI disease (eg, Crohn disease) with symptoms suggestive of a disease flare (eg, diarrhea, vomiting)

  While the diagnosis of COVID-19 may be suspected based on presenting symptoms, additional factors that inform the decision to perform testing include the patient's geographic location, risk of exposure, rate of community transmission, and the availability of testing.

- For patients with symptoms of active inflammatory bowel disease (IBD) (eg, diarrhea) who are also at risk for COVID-19, evaluation includes COVID-19 testing, stool studies to exclude enteric infections, noninvasive inflammatory markers (eg, fecal calprotectin), and serum drug trough levels (for patients on biologic therapy). (See 'Diagnostic considerations during pandemic' above.)

- Patients with IBD in remission should continue maintenance therapy to sustain remission. Discontinuing maintenance therapy is associated with disease relapse that may require hospitalization and/or glucocorticoid therapy, and thus, may increase the risk for COVID-19. (See 'Patients with IBD in remission' above.)

- Strategies for reducing the risk of transmitting SARS-CoV-2 virus during gastrointestinal endoscopy that have been endorsed by professional societies can be accessed here. (See 'Implications for endoscopy' above and "Society guideline links: Coronavirus disease 2019 (COVID-19) – Guidelines for specialty care".)

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