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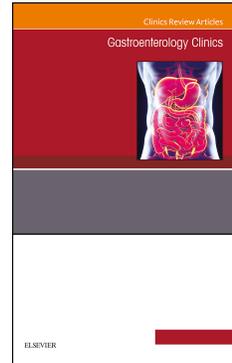
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Gastrointestinal bleeding in COVID-19-infected patients

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Abstract:

COVID-19 infection is an ongoing catastrophic global pandemic with significant morbidity and mortality that affects most of the world population. Respiratory manifestations predominate and largely determine patient prognosis, but gastrointestinal (GI) manifestations also relatively frequently contribute to patient morbidity and occasionally affect mortality. GI bleeding is uncommon relative to both the COVID-19 infection prevalence and its other GI manifestations. GI bleeding is usually noted after hospital admission and is often one aspect of this multisystem infectious disease. The incidence of GI bleeding is reported at about 1.5% to 3%, with several reported statistical outliers. The widely reported variability in incidence is attributed to variable study designs (clinical series, case-controlled studies, retrospective studies, prospective studies, meta-analyses, and systematic reviews); and different criteria for GI bleeding; and different study populations (variable ethnicities, nationalities, comorbidities, patient vaccination history, and patient ages); and variable viral strains and study time-intervals. The first phase of the pandemic (March-May 2020) was characterized by high contagiousness, appreciable mortality, no available effective vaccinations, and few therapies. Also, early in the pandemic, all acute GI bleeders, especially with upper GI bleeding, underwent prophylactic endotracheal intubation, but this recommendation was withdrawn after a few months because of the difficulty in extubating patients with respiratory compromise from COVID-19 pneumonia. Initially healthcare workers suffered some morbidity from COVID-19 infection. This risk affected the usual diagnostic and therapeutic algorithms for GI bleeding, in that physicians were reluctant to perform GI endoscopy. Indeed, the rate of performing GI endoscopy plummeted to <10% of the pre-pandemic baseline. The institution of strict personal protective equipment (PPE), including N95 face masks, and the subsequent introduction of moderately effective COVID-19 vaccines for patients and endoscopy staff, gradually increased the safety of GI endoscopy with a concomitant rise in the use of GI endoscopy. However, GI endoscopy is still somewhat reduced in frequency compared to the pre-pandemic baseline, especially for ambulatory and elective GI endoscopies. While the theoretical risk of contracting COVID-19 from GI endoscopy performed on COVID-19 infected patients remains, the actual risk does not appear to be high. Three important aspects of GI bleeding in COVID-19-infected patients are: (1) GI bleeding is often due to mucosal erosions from mucosal inflammation that causes mild bleeding; (2) severe upper GI bleeding is often from peptic ulcer disease or stress gastritis from COVID-19-related pneumonia; and (3) lower GI bleeding relatively frequently arises from ischemic colitis associated with thromboses and hypercoagulability from COVID-19 infection. The literature concerning GI bleeding in COVID-19 patients is presently reviewed.

INTRODUCTION

COVID-19 (coronavirus disease of 2019) infection caused by the highly contagious severe acute respiratory virus coronavirus 2 (SARS-CoV-2 virus) is responsible for the current global pandemic that has caused about 600 million proven acute infections and about 6 million deaths worldwide as of September 2022, including about one million deaths in America (1). It predominantly causes respiratory disease, most prominently pneumonia that can cause respiratory failure. The initial phase of the pandemic in America (March-May 2020) caused considerable mortality, especially in those with risk factors of obesity, diabetes mellitus, immunosuppression, other significant comorbidities, and old age. Subsequent phases were characterized by decreased mortality, but increased contagiousness associated with newly emerging viral strains from genetic mutations. Vaccines are now available in much of the developed world that are moderately effective in preventing infection as are specific medications, such as Paxlovid (nirmatrelvir and ritonavir) that can decrease infection severity and shorten disease duration. Public health measures, such as facemasks and patient isolation techniques, that vary regionally, likely blunted the pandemic spread. Nonetheless, COVID-19 infection remains an ongoing global crisis with notable morbidity and mortality.

Respiratory and systemic manifestations of COVID-19 infection, including dyspnea, cough, rhinorrhea, pyrexia, and malaise, predominate, but extra-pulmonary manifestations occur relatively frequently, including gastrointestinal (GI) and hepatic manifestations such as anorexia, nausea, emesis, diarrhea, abdominal pain, and elevated transaminase levels. GI manifestations can produce morbidity and occasionally contribute to mortality (2).

GI bleeding in COVID-19 subjects is relatively uncommon. A meta-analysis of symptoms among >25,000 COVID-19 subjects noted anorexia in 20%, diarrhea in 13%, and hematemesis in 9% (3). However, the incidence of GI bleeding in this study is much higher than that reported in most clinical studies at 1.5-3.0%. GI bleeding is rarely the initial manifestation of COVID-19 infection (4) and most commonly manifests after hospitalization for COVID-19 infection (5,6,7). GI bleeding usually arises from the upper GI tract, and manifests as anemia, melena, or hematemesis and less commonly arises from the lower GI tract and manifests as hematochezia, or occasionally melena. GI bleeding occurs more frequently in older patients, especially men, and especially in those with comorbidities (8).

in a large meta-analysis, about 27% of infected subjects shed COVID-19 RNA in their stool (3). The SARS-CoV-2 angiotensin converting enzyme-2 (ACE-2) receptor is highly expressed in the gut and this receptor provides a portal of entry for the virus, especially in the stomach and small intestine, that can cause local GI infection and clinical manifestations, including GI inflammation and GI bleeding (9). The host immune response, including potential cytokine storm, multiorgan viral involvement, and side-

reactions of administered medications, such as corticosteroids or anticoagulants, may contribute to gut inflammation and exacerbate the GI bleeding (10). GI bleeding from COVID-19 is usually self-limited even when caused by a “double-hit” of an initial viral cytopathic effect and secondary immune-mediated or medication-induced side-effects (11). Patients with severe COVID-19 infection may occasionally develop massive GI bleeding from physiologic stress, due sepsis, severe pneumonia, and respiratory or multiorgan failure, akin to the historically important phenomena of Cushing ulcer, related to increased intracranial pressure, and Curling ulcer, related to severe and extensive burns (12). Stress gastritis and peptic ulcer disease (PUD) are common in patients with pneumonia and respiratory failure from COVID-19 infection, which constituted a common outcome in the early pandemic (13). The propensity of the GI tract to bleed is somewhat related to the disparate effects of hypercoagulopathy in COVID-19-infected patients (perhaps reducing their bleeding tendency), administration of prophylactic anticoagulation to counteract this hypercoagulopathy that potentially promotes GI bleeding, and occurrence of thromboses potentially causing mucosal ischemia or necrosis with GI bleeding from sloughing of gastrointestinal mucosa or necrotic mucosal ulcers (14). In one case report a patient with COVID-19 infection and sickle cell disease had GI bleeding with non-erosive gastroduodenitis secondary to microthrombi (15).

METHODS

The 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 in September 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 their reason(s) for exclusion. This computerized literature review included the following search terms, key words, or phrases (with listing in parentheses identifying the number of articles found by PubMed per search term): esophagogastroduodenoscopy (EGD) and COVID [465], colonoscopy and COVID [220], flexible sigmoidoscopy and COVID [11], therapeutic gastrointestinal endoscopy and COVID [139], enteroscopy and COVID [2], capsule endoscopy and COVID [29], balloon enteroscopy (endoscopy) and COVID [5], nasal endoscopy and COVID [135], endoscopic retrograde cholangiopancreatography (ERCP) and COVID [64], disposable endoscopes and COVID [39], CT colonography and COVID [10], gastrointestinal bleeding scan and COVID [3], mesenteric angiography and gastrointestinal bleeding and COVID [5], therapeutic angiography and gastrointestinal bleeding and COVID [3], hematemesis and COVID [25], GI bleeding and COVID [182], melena and COVID [35], hematochezia and COVID [148], fecal occult blood and

COVID [84], fecal immunological testing (FIT) and COVID [610], iron deficiency anemia and COVID [40], colonoscopy screening and COVID [156], colonoscopy surveillance and COVID [104], colonic pseudo-obstruction and COVID [5], colonoscopy and decompression and COVID [2], peroral endoscopic myotomy (POEMS) and COVID [9], long COVID and GI endoscopy [8], GI endoscopy complications and COVID [33], GI endoscopy guidelines and COVID [33], and gastrointestinal endoscopy and COVID transmission [193].

Specific gastrointestinal disorders/diseases in the literature review included (with number of cited articles per search term listed in parentheses) included: Mallory-Weiss tear and COVID [2], esophageal toxicity and medications and COVID [2], nasogastric tube erosions and COVID [2], Kaposi sarcoma and COVID [24], peptic ulcer and COVID [41], gastric ulcers and COVID [21], duodenal ulcers and COVID [16], hemorrhagic esophagitis and COVID [34], Barrett's esophagus and COVID [13], gastroesophageal reflux disease (GERD) and COVID [38], gastrointestinal stromal tumor (GIST) and COVID [10], gastric antral vascular ectasia (GAVE) and COVID [1], gastric leiomyoma and COVID [1], colon and adenomas and COVID [12], colon cancer screening and colonoscopy and COVID [32], mucosal associated lymphoid tissue- (MALT-) OMA and COVID [9], Cameron lesion and COVID [1], Dieulafoy lesion and COVID [0], gastric lymphoma and COVID [0], esophageal adenocarcinoma and COVID [12], esophagus squamous cell cancer and COVID [4], gastric adenocarcinoma and COVID [22], linitis plastica and COVID [0], paraesophageal hernia & COVID [7], hemobilia and COVID [1], hemosuccus pancreaticus and COVID [0], marginal or anastomotic ulcer and COVID [35], Billroth II and COVID [6], radiation proctitis and COVID [0], radiation associated vascular ectasia (RAVE) and COVID [0], gastric varices and COVID [10], bleeding esophageal varices and COVID [7], portal hypertensive gastropathy and COVID [1], rectal ulcer and COVID [11], bleeding hemorrhoids and COVID [10], and rectal fissure and COVID [0].

DISCUSSION

Prevalence

As aforementioned, the current literature review reveals a low rate of GI bleeding in COVID-19 subjects, with most studies reporting a rate of 1.5-3%, with notable statistical outliers and considerable study variability. Moreover, much GI bleeding in COVID-19-infected patients is subclinical and decidedly less significant than the typical pulmonary manifestations of COVID-19. A global compilation of COVID-19 endoscopies noted up to nearly half of subjects had GI mucosal abnormalities such as mucosal erosions (16). A large, COVID-19 cohort, mostly from Egypt, reported a relatively high rate of GI bleeding from hematemesis in 9%, melena in 5.3%, hematochezia in 0.6%, and fecal-occult positive stools in 5% (3). Contrariwise, systematic review of 12 studies reported a prevalence of GI bleeding of only 0.06% (17). After excluding two outlier studies, another meta-analysis of 91,887 COVID-19 subjects noted a 2.0%

pooled prevalence of GI bleeding of whom 77% had upper GI bleeding (18). A European cohort of 4,128 COVID-19 subjects noted a 1.8% prevalence of GI bleeding (19). An Italian cohort of 4,871 COVID-19-infected patients noted a 0.5% prevalence of upper GI bleeding (20). A New York cohort of 11,158 COVID-19 subjects reported a prevalence of 3% of GI bleeding (21), while another New York cohort of 1,206 COVID-19-infected patients reported a 3.1% prevalence of GI bleeding (22). A Spanish cohort of 74,814 COVID-19-infected patients had a prevalence of GI bleeding of 1.1% (23), whereas a Chinese cohort of 36,358 COVID-19 subjects reported a 2% prevalence of GI bleeding (24). These disparate results reflect differences in criteria for GI bleeding, different patient demographics, different countries, different rates of COVID-19 infection, and different study designs [letters to the editor (11), case reports, case series (4, 12), case-controlled studies, retrospective studies, prospective studies, systematic reviews (17), and meta-analyses (3, 18)]. The literature on GI bleeding associated with COVID-19 infection has been sparse until recently relative to the overall number of COVID-19-related publications and much less than that reported for several other GI manifestations. In particular, relatively few studies have reported on GI endoscopic findings because of the scarcity of performing esophagogastroduodenoscopy for GI bleeding in patients with COVID-19 infection.

Evaluation of GI bleeders before endoscopy

Gastroenterologists should promptly obtain a complete but directed medical history with a focus on GI disease in any patient with acute, overt GI bleeding, but particularly when associated with severe COVID-19 infection. The GI history should focus on prior GI bleeding and its etiology; prior GI endoscopies and their findings, and endoscopic therapies because patients often bleed from the same GI lesions that they had previously bled from (25). Patients should be asked about prior GI surgery and prior GI radiologic findings. The patient should be specifically asked about medicines administered for GI diseases, including H₂ (histamine-2) receptor antagonists, proton pump inhibitors (PPIs), medications for inflammatory bowel disease (IBD), chemotherapy for GI cancers, gastrotoxic medications that increase the risk of GI bleeding such as aspirin, COX- (cyclooxygenase)- II inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), esophagotoxic medications (bisphosphonates, doxycycline), and anticoagulants (including coumadin, unfractionated heparin, low molecular heparin, clopidogrel, and rivaroxaban).

The medical history provides clues to the etiology of the GI bleed. A history of alcoholism, jaundice, or liver disease increases the likelihood of cirrhosis, portal hypertension, and bleeding from esophageal varices or portal hypertensive gastropathy (25). A history of smoking cigarettes increases the risk of duodenal ulcers. The patient should be asked about prior H. pylori infection and its therapy.

The patient with acute and overt GI bleeding should undergo a focused physical examination that includes vital signs to help assess the need for fluid resuscitation or blood transfusions; careful abdominal examination including the presence, location, intensity, and pitch of bowel sounds; abdominal tenderness; presence of rebound tenderness; and presence of splenomegaly. Stigmata of chronic liver disease should be searched for, including hepatomegaly, spider angiomas, palmar erythema, caput medusa, Dupuytren's contracture, jaundice, asterixis, and ascites because such signs suggest GI bleeding from portal hypertension or cirrhosis. Abdominal tenderness is uncommon with upper GI bleeding, except occasionally from PUD. Severe abdominal pain suggests bowel ischemia, gastrointestinal obstruction, or GI perforation. Severe direct abdominal tenderness, rebound tenderness, or involuntary guarding suggests a possible acute (surgical) abdomen which must be excluded before performing EGD for GI bleeding. Air under the diaphragm (free intraperitoneal air) on abdominal roentgenogram or on abdominal computerized tomography (CT) strongly suggests an acute abdomen. Rectal examination should be carefully performed to assess the patient for the presence, type, and quantity of rectal bleeding and check for anal masses, hemorrhoids, anal fissures, and anal stenoses. Nasogastric (NG) tube aspiration can help check for gross blood in the upper GI tract and clear the stomach of residual blood for unobstructed gastric visualization at EGD.

The presentation and appearance of the blood offers clues to the site of GI bleeding, its acuity, and its severity. Melena, recognized as black and tarry stools, mostly (90%) arises from an upper GI lesion because of degradation of blood with GI transit, but occasionally (10%) arises from small intestinal or right colonic lesions in the presence of slowed intestinal transit. Hematemesis indicates bleeding proximal to the ligament of Treitz (25). Hemorrhoidal bleeding classically presents with a clinical triad of bright red blood per rectum due to arterialized blood from the hemorrhoidal plexus, blood coating rather than admixed with stools, and post-defecatory bleeding due to traumatic stool evacuation. Hypotension, orthostatic hypotension, tachycardia at rest, mental confusion, orthostatic dizziness, cold and clammy extremities, angina, and severe palpitations may suggest hemodynamic compromise from severe GI bleeding (25). Cutaneous ecchymoses or petechia are signs of a coagulopathy.

Laboratory evaluation for the GI bleeder

Patients should have blood samples determined for routine electrolytes, chemistries, blood sugar, blood urea nitrogen (BUN), creatinine, liver function tests, lipase, and other standard biochemical parameters. Patients should have a complete blood count, including hematocrit, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count, leukocyte count, and leukocyte differential. The international normalized ratio (INR) of the prothrombin

time should be determined. Patients with upper GI bleeding typically have an elevated blood urea nitrogen (BUN) level with a BUN: creatinine ratio > 20:1 due to the combined effects of prerenal azotemia from hypovolemia and BUN elevation from GI resorption of degraded blood during intestinal transit (25). Iron level, ferritin level, and percent iron saturation are useful to demonstrate iron deficiency from chronic GI blood loss. The medical history, physical examination, and initial laboratory values are important to assess resuscitation requirements for intravenous fluids or blood transfusions; triage to regular hospital beds versus monitored beds versus an intensive care unit (ICU); and timing of endoscopy including emergency or urgent endoscopy versus delayed or deferred endoscopy. Other consultative services may be urgently required for the GI bleeder, including surgery, radiology, and the intensivist.

Patient stabilization before GI endoscopy

All patients with acute GI bleeding require hemodynamic evaluation and stabilization of vital signs before evaluation for potential GI endoscopy. Evaluation and stabilization is particularly important in patients with significant COVID-19 infection who may suffer from multiorgan failure including respiratory compromise from severe pneumonia, acute kidney injury (AKI) or chronic kidney disease with chronically depressed glomerular filtration rate (GFR), and coagulation disorders. Respiratory compromise from COVID-19 pneumonia may not necessarily present with overt hypoxia but may be subtly suggested by other abnormal vital signs, unexplained acidosis, restlessness, or unexplained severe pyrexia or sepsis. Prerenal azotemia contributed by GI bleeding may exacerbate AKI. Hematocrit levels should be followed serially with time. A serial hematocrit decline may signify significant GI blood loss because of hemodilution to compensate for acute blood loss, but a hematocrit decline is a lagging indicator of blood loss.

Patients with overt GI bleeding should have two secure, large-bore, intravenous lines placed to assure adequate fluid infusion for volume resuscitation. Patients with overt bleeding should be typed and crossed for potential transfusions of packed erythrocytes. All patients with acute upper GI bleeding should initially receive PPI therapy continuously and intravenously. This is most important for PUD or hemorrhagic esophagitis because these disorders are related to gastric acidity, but PPI therapy is also recommended for upper GI bleeding of any etiology before performing EGD because the etiology of the GI bleeding is usually uncertain before EGD and maintaining the intraluminal gastric pH>5 stabilizes a gastric clot and prevents rebleeding of GI lesions.

Patients with potential hemodynamic instability manifested by systemic hypotension, orthostatic hypotension, or significant orthostatic changes (orthostasis) with evident active GI bleeding should be evaluated for an ICU bed. Admission to an ICU bed for blood transfusions is even more important in

patients with concomitant COVID-19 pneumonia because of potential respiratory decompensation from fluid overload. In patients with active GI bleeding the preferred therapy for hypovolemia is transfusion of packed erythrocytes rather than intravenous colloid infusion or normal saline. Despite a current shortage of blood products attributed to the effects of the omicron surge during the pandemic (26), blood transfusions for acute GI bleeders are generally considered a medical emergency.

Conservative management with deferral of GI endoscopy

COVID-19 is usually transmitted from infected individuals via fine respiratory droplets. Aerosolization promotes spread with some potential for viral transmission when droplets land on surfaces. GI endoscopy, especially EGD, is a moderately high-risk procedure for COVID-19 transmission to the endoscopist and endoscopy staff due to aerosolization of droplets expired by COVID-19-infected patients. This transmission risk and the diversion of medical resources to counter the COVID-19 pandemic underlies the reluctance or deferral of performing GI endoscopy for hospitalized patients for non-urgent indications. This approach was historically reflected in publications noting the “dilemma” of performing endoscopy and the “less is more” attitude regarding performing GI endoscopy for GI bleeding in patients with COVID-19 infection (27, 28, 29). A higher threshold for performing endoscopy for GI bleeding was proposed in COVID-19 infected patients, reflected semi-quantitatively by higher Glasgow-Blatchford scores used to assess GI bleeding severity (30, 31). Guidelines promulgated by different national professional gastroenterology societies throughout the world reflect a conservative approach to GI endoscopy in COVID-19-infected patients, including deferral of GI endoscopy if possible (32,33, 34). In the early pandemic (Spring 2020) rates of GI endoscopy plummeted by ten-fold from the pre-pandemic baseline rate (35). Most GI bleeding is subclinical and therefore does not require GI endoscopy, but even overt GI bleeding was sometimes approached conservatively without GI endoscopy in COVID-19-infected patients. The pandemic generally diminished endoscopic volume for both COVID-19 and non-COVID-19 patients, but this diminished volume did not adversely affect patient outcomes in a Canadian cohort study (36). Nonetheless, COVID-19 infected patients with hemodynamically significant bleeding should be strongly considered for EGD after patient stabilization including volume resuscitation or packed erythrocyte transfusions and stabilization of the respiratory status (37).

COVID-19-infected patients with GI bleeding are more likely to, have a longer hospital stay, and less frequently undergo GI endoscopy than GI bleeders without COVID-19 infection (38). Furthermore, upper GI hemorrhage in COVID-19 patients is positively associated with ICU admission and mechanical ventilation (39). Longer time to GI endoscopy in COVID-19 subjects does not negatively impact their clinical outcomes (20, 40). GI bleeding in COVID-19 subjects is often subclinical or at least self-limited

(41). A conservative approach may be justified. A small cohort of COVID-19 subjects with GI hemorrhage did well with conservative management and the author suggested a 24-hour waiting period before evaluating GI bleeders for GI endoscopy, a position endorsed by a journal editorial (42, 43). The general principles of managing bleeders with COVID-19 infection are summarized in Box 1, with an emphasis on differences between COVID-19 infected versus non-infected patients.

In a retrospective study, 24 (1.8%) of 1342 patients with COVID-19, presented with GI bleeding of whom 23 patients had upper GI bleeding, including twenty-two (91.6%) with evident cirrhosis and 21 presented with upper GI bleeding from esophageal varices. Two patients without cirrhosis were presumed to have non-variceal bleeding. Medical therapy for esophageal variceal bleeding included vasoconstrictors, either somatostatin in 17 (73.9%) or terlipressin in 4 (17.4%). All patients with upper GI bleeding received PPIs and antibiotics. Fourteen patients (60.9%) were transfused packed erythrocytes, with a median transfusion of one unit. Initial control of upper GI bleeding was achieved in all 23 patients and none required emergency GI endoscopy. At 5-day follow-up, none rebled or died. Two patients later rebled; one from intermittently bleeding gastric antral vascular ectasia, and another rebled 19 days after hospital discharge. Three (12.5%) patients with cirrhosis succumbed to acute hypoxemic respiratory failure during the hospitalization. This study suggests that conservative management strategies including pharmacotherapy, and restrictive transfusions with close hemodynamic monitoring can successfully manage GI bleeding in COVID-19 patients and reduce their need for urgent GI endoscopy. The decision to proceed to GI endoscopy should be performed by a multidisciplinary team emphasizing limited use of GI endoscopy (44).

Concerns regarding endoscopists contracting COVID-19 infection while performing conventional (tube) GI endoscopy have promoted alternative tests for diagnosis and treatment of GI bleeding, such as disposable endoscopes (45); experimental robotic endoscopes (46); telemetric sensor capsules (47); small intestinal capsules for screening before GI enteroscopy (48); and colonic capsules for screening before colonoscopy (49) to reduce the endoscopist's risks. A novel barrier device may minimize viral transmission from infected patients to endoscopists (50). For example, positioning the endoscopist's head away from the patient's mouth during EGD decreased the endoscopist's facial exposure to visible droplets from 87% at 70 cm distance to 0% at 100 cm distance ($p < 0.001$) and thereby theoretically reduced transmission of COVID-19 infection to the endoscopist during EGD. Moreover, a physical barrier device reduced endoscopist's exposure to droplets to 0% at all distances (50). A European study suggested an interventional radiologic approach to GI bleeding among 11 COVID-19 subjects to reduce transmission of

COVID-19 to examining physicians (51). The current supply of IV contrast medium is insufficient due to the pandemic (52).

Suggested Approach to GI bleeding in COVID-19 Subjects

The advent of COVID-19 vaccination and personalized protective equipment (PPE) for endoscopic staff minimizes potential COVID-19 transmission during GI endoscopy resulting in greater safety to endoscopic staff. PPE should optimally include an N95 mask or equivalent, a disposable, waterproof (impervious) surgical gown, safety goggles, face shield, haircap, and protective footwear (53). The endoscopist and the endoscopy staff should be offered such PPE. Endoscopists should be fitted for appropriately sized N95 masks and briefly trained on how to wear them. It is important to use new N95 masks at least daily. The endoscopist should be offered the option of thicker surgical gloves (e.g., Microflex NeoPro NPG888 synthetic chloroprene disposable gloves) than the standard thin disposable gloves.

The endoscopy suite should be thoroughly cleaned between endoscopic cases with viricidal antiseptic, sterilizing solutions that are highly effective against COVID-19, concentrating on endoscopic equipment, endoscopic accessories, and the endoscopy cart to prevent COVID-19 transmission during GI endoscopy. At the endoscopy center where I worked antiseptic solutions were changed to use antiseptic solutions with proven high efficacy against COVID-19 soon after the pandemic onset throughout all clinical areas, including the sinks of bathrooms, (35). With all the aforementioned precautions, COVID-19 transmission to endoscopy staff during endoscopy is reported but highly uncommon (54). GI endoscopy should be performed judiciously and conservatively in COVID-19 subjects, with less urgency and lower priority than that recommended for non-infected patients. Elective or semi-elective endoscopy in COVID-19 infected patients may be reasonably deferred until after the patient becomes non-infected, as proven by nasal swabs testing for the viral RNA of COVID-19. It may be helpful to perform GI endoscopy on COVID-19-infected patients as the last case on the normal daily endoscopy schedule to permit extra time to disinfect the room after this last case. Endoscopy staff should minimize their time exposed to a COVID-19-infected patient. For example, they should generally avoid being present in the endoscopy suite during intubation and extubation in infected patients.

In the early pandemic (March-May 2020), GI fellows were excused from performing GI endoscopy on their patients and attending GI endoscopists were required to perform GI endoscopy by themselves. This concept was irrational and unsubstantiated by data. GI fellows tend to be relatively young, healthy, and at relatively low risk of serious complications from COVID-19 infection, whereas GI attendings are often relatively old (with about half of them >65 years old (55), relatively less healthy, with a higher

incidence of comorbidities, and at relatively high risk of severe COVID-19 complications. This recommendation negatively impacted endoscopic training of GI fellows who performed few GI endoscopies in March-May 2020 and it was withdrawn by May 2020 (35), (56). Even currently, in 2022, GI fellows report less training in GI endoscopy than fellows trained before the pandemic began because of not performing GI endoscopy during the pandemic onset and the lingering effects of the ongoing pandemic on somewhat restricting GI endoscopy.

In the beginning of the pandemic, all patients with proven COVID-19 infection were intubated prophylactically before EGD (25). However, universal endotracheal intubation for EGD in COVID-19 patients entails potential difficulty of patient extubation post-procedure, especially for patients with COVID-19 pneumonia and respiratory compromise with consequent deleterious effects on patient prognosis (57). Thus, endotracheal intubation for GI endoscopies should generally be avoided, if possible, when advocated solely for the indication of COVID-19 infection without additional reasons. However, this practice varies according to local endoscopy practice patterns, local prevalence of COVID-19 infection, and institutional policies. Ancillary services such as interventional radiology, nuclear medicine, or GI surgery may decrease the need for GI endoscopic intervention (See Figure 1).

Etiology of Upper GI tract bleeding proximal to ligament of Treitz

Peptic ulcer disease, including erosive gastritis and duodenitis, as aforementioned, is the most common etiology of upper GI bleeding in COVID-19-infected patients (16,18, 19,20,58). A small series of COVID-19 subjects noted a poor prognosis from gastric ulcers (59). However, generalized mucosal inflammation and friability is a common leitmotif of GI infection with COVID-19 that causes relatively minor GI blood loss (16). A multicenter study of 87 upper GI endoscopies reported upper GI ulcers in one quarter of patients, with gastro-duodenitis in 16%, and petechial/hemorrhagic gastropathy in 9% (16). In a New York cohort of 41 endoscopies in COVID-19-infected patients, EGD commonly revealed gastric/duodenal ulcers (60-Blacket). An Italian cohort of 38 COVID-19 subjects undergoing EGD reported 37% had esophagitis, erosive gastritis, or peptic ulcers (61-Massironi). Gastric erosions/ulcers in COVID-19 subjects may preferentially occur in the proximal stomach (62-Perez). Reflux esophagitis was a common etiology of GI bleeding but was significantly less common than PUD (16, 63). Esophageal variceal hemorrhage was also relatively common in patients with COVID-19 infection (16, 44, 64, 65), likely reflecting that liver disease is a risk factor for severe COVID-19 infection. One patient hospitalized with hematemesis had an esophageal ulcer at endoscopy with pathologic demonstration of local COVID-19 involvement (66). Case reports of GI hemorrhage include aorto-enteric fistula (67), hemobilia (68), and

hemorrhagic ulcerative duodenitis (69). One patient had Cameron lesions associated with acute COVID-19 infection. The Cameron lesion (ulcer) was due to a large paraesophageal hernia that progressed to cause acute gastric volvulus due to the patient's poor nutritional status from chronic COVID-19 infection (70). The reported causes of upper GI bleeding in COVID-19-infected patients, including rare causes, are listed in Table 1 (16; 18, 19, 20, 44; 58, 59, 62, 63, 64, 65, 66, 67, 68, 69, 70; 71, 72, 73, 74).

Diagnostic & therapeutic EGD

Relatively limited data exist regarding upper GI endoscopy for COVID-19-related GI bleeding (58). EGD is often performed with respiratory support in critically ill patients, even rarely including extracorporeal membrane oxygenation (ECMO)(75). Principles of GI endoscopy in COVID-19-infected patients are summarized in Table 2.

All the therapeutic modalities available in the general population of GI bleeders are available to patients infected with COVID-19 including injection therapy (with epinephrine or sclerosants), ablative therapy (electrocoagulation with bipolar electrocoagulation probe (BICAP) or Gold Probe), noncontact methods (argon plasma coagulation [APC]), mechanical therapy (band ligation, hemoclips, or detachable snares), or Hemospray (76, 77). However, COVID-19-infected patients have special considerations in selecting endoscopic therapy. First, performing therapeutic EGD in patients with active upper GI bleeding may place the endoscopist and the endoscopy staff at higher risk of contracting COVID-19 infection. Exposure should therefore be minimized by performing therapeutic endoscopy by a senior "master" endoscopist with considerable experience both in therapeutic endoscopy in patients at high-risk to perform the therapy expeditiously (78). Second, patients with active upper GI bleeding should be intubated endotracheally before performing EGD to protect the endoscopy staff from contracting the infection and to protect the patient's airway from aspiration of blood during EGD. Third, patients undergoing therapeutic EGD who have recently received prophylactic anticoagulation to reduce their risk of thromboembolism associated with COVID-19 infection may be best served by receiving endoscopic therapy providing the most secure and stable hemostasis (even in the face of anticoagulation in the recent past or contemplated in the future) such as endoscopic clips or band ligation (79). Endoscopic band ligation may be performed in COVID-19 infected patients for esophageal variceal hemorrhage (65). Fourth, endoscopic therapeutic modalities can be selected according to ease of performance and speed of therapy, such as favoring argon plasma coagulation (APC), to minimize exposure of the endoscopist and the endoscopy staff to potentially infectious aerosolized blood from patients with active upper GI bleeding. This may be a highly personal professional decision in that endoscopists may feel more comfortable with therapeutic modalities due to personal experience. Fifth, endoscopists may elect not to

apply therapeutic endoscopy altogether in patients with borderline indications for endoscopic therapy such as a peptic ulcer that is slowly oozing blood (Forrest IB lesion) (80). Similarly, an endoscopist may elect not to decapitate a nonbleeding adherent clot (by guillotine by snare) and expose an underlying lesion to determine whether an ulcer with stigmata of recent hemorrhage (SRH) lies underneath the clot (81) to prevent active bleeding after clot decapitation to reduce endoscopist exposure to actively bleeding infected patients. Patients with upper GI bleeding with flat spots or clean-based ulcers do not require endoscopic therapy regardless of the presence or absence of COVID-19 infection (81). Sixth, COVID-19-infected patients who fail endoscopic therapy but are good surgical candidates may reasonably be sent for GI surgery or angiographic embolization, rather than persist at an unsuccessful endoscopic therapy or perform repeat endoscopic therapy.

In a highly selective multicenter North American cohort, only about 1% of subjects underwent GI endoscopy for GI bleeding and only two patients (about 0.1%) of the entire group underwent therapeutic endoscopy (63). Ten of 18 subjects who underwent EGD for GI hemorrhage had reported esophagitis, gastritis, or ulcer, but did not receive endoscopic therapy. The authors noted low utilization of GI endoscopy despite prevalent COVID-19 GI symptoms; that inflammatory and erosive mucosal abnormalities were common in COVID-19 patients; and that most of these abnormalities were related to the underlying critical illness and not a local viral cytopathic effect (63). In another New York cohort, 10 patients deemed to have significant bleeding underwent EGD with eight having gastric or duodenal ulcers and four requiring single or combined endoscopic hemostatic therapy to control the bleeding; four patients had recurrent bleeding, but no fatalities occurred due to the GI bleeding (82). Three of four COVID-19 pneumonia patients hospitalized in ICUs required endoscopic hemostasis for bleeding ulcers in one series (37). Three patients with COVID-19 duodenal hemorrhage were successfully treated with endoscopic vacuum therapy (83).

Small intestine beyond ligament of Treitz

The vast small intestinal surface area with its high density of ACE-2 receptors renders this organ particularly susceptible to direct COVID-19 infection and injury. Infection usually manifest subclinically as only inflammation and erosions (16, 17). One patient had documented small and large intestinal mucosal sloughing with infection (84). Another had a Crohn's-like presentation with GI bleeding and fistulas (85). Another patient underwent segmental resection for hemorrhagic enteritis, without Crohn's disease, attributed directly to COVID-19 infection (86). He required surgery and survived the surgery.

Jejunal and ileal causes of GI bleeding in COVID-19 infected patients are summarized in Table 3 (16, 48, 84, 85, 86, 87, 88, 89, 90).

Capsule endoscopy & enteroscopy to evaluate small intestinal bleeding

Mucosal abnormalities were commonplace in COVID-19 subjects undergoing capsule endoscopy (48, 87). Capsule endoscopy was touted as a primary diagnostic modality because of hesitancy about performing traditional tube endoscopy in COVID-19-infected patients (88). For example, in one study (48), 146 patients with COVID-19 infection first underwent capsule endoscopy as a triage tool to investigate GI bleeding as compared to 72 historical controls undergoing standard of care evaluation for GI bleeding initially using EGD in the pre-pandemic era of January 1-January 31, 2020. Active bleeding or stigmata of recent hemorrhage were observed in 44 (59.5%) patients in the COVID-19-infected group versus 18 (25.0%) in the standard of care (SOC) group (adjusted odds ratio: 5.23; 95%CI: 2.23-12.27). Only 36 patients (48.7%) in the COVID-19-infected group required any invasive procedure during the hospitalization, compared with 70 (97.2%) in the SOC group (adjusted odds ratio: 0.01; 95%CI: 0.001-0.08). The mean (SD) number of invasive procedures was statistically significantly lower in the capsule endoscopy group: 0.59 (0.77) per patient in the COVID-19 group versus 1.18 (0.48) per patient in the SOC group (adjusted difference, -0.54; 95% CI: -0.77 to -0.31). The authors concluded that the number of invasive GI endoscopies could be significantly decreased in COVID-19 patients when capsule endoscopy was performed as the initial test without increasing the rate of rebleeding or other complications.

Only one case report of push enteroscopy has been reported in COVID-19 infected patients: a 34-year-old man suffered sequelae of subacute GI obstruction and failure to thrive 2 months after a prolonged admission for COVID-19 infection (85). He subsequently underwent push enteroscopy which was performed safely and was diagnostic: it revealed residual jejunal ulcers and multiple proximal jejuno-jejunal fistulae. The push enteroscopy directly led to laparotomy which revealed strictures with dense intra-abdominal adhesions, a large jejuno-jejunal fistula, and evident prior jejunal perforation from severe COVID-19 infection. The patient recovered after small bowel resection with anastomoses and was discharged home, but represented with dyspnea, acute chest pain and cardiac arrest six weeks postoperatively and subsequently died. The death was believed unrelated to the push enteroscopy 6 weeks earlier. A literature review revealed no data on single or double balloon enteroscopy performed in COVID-19 infected patients. Small intestinal bleeding from Crohn's disease is reviewed in the accompanying chapter by Summa and Hanauer in this monograph.

Etiology of colonic bleeding

Sparse colonoscopic data report ischemic colitis is a common cause of lower GI bleeding (91). Ischemic or hemorrhagic colitis was noted in 13% to 33% of patients in several colonoscopy series (16, 61,63, 91). Ischemic colitis has also been reported after tocilizumab therapy (92), and after COVID-19

vaccination (93). Hemorrhagic colitis can occur with COVID-19 infection, with concomitant cytomegalovirus reported in one case (94,95). Other colonoscopic studies revealed rectal ulcers (60, 82-Martin), often due to indwelling rectal tubes (82). For GI bleeding in COVID-19 patients with inflammatory bowel disease, either ulcerative colitis or Crohn's disease, please see the accompanying chapter by Summa and Hanauer in this monograph. Five COVID-19 patients with GI bleeding underwent colonoscopy in one study with non-specific findings, including presumptive bleeding from colonic diverticulosis or internal hemorrhoids (16). Clinically manifest lower GI bleeding including hematochezia is uncommon in relation to frequent mucosal abnormalities consistent with the same pattern for upper GI bleeding. Some bleeding may be incidental to COVID-19 infection (16,18,19,17,63). Colonoscopy is generally deferred in COVID-19-infected patients, with colon capsule exam proposed as an initial diagnostic alternative to colonoscopy (49). Interventional radiology should be considered for colonic bleeding if resources are available (29,51,96). Table 4 lists causes of colonic bleeding in COVID-19-infected patients (16, 63, 82, 91, 92 93, 94, 95).

Outcomes of GI bleeding

The spectrum of upper GI bleeding in COVID-19 patients commonly includes presentation with subclinical bleeding related to mucosal friability; anemia and hemoccult positive stools possibly requiring transfusions; but also includes clinically apparent bleeding in critically ill patients with COVID-19 pneumonia. COVID-19 infection may be incidental to the presentation with GI hemorrhage, especially in areas where COVID-19 infection is omnipresent (4). Rarely, GI bleeding in a COVID-19 patient may be massive and fatal (12,97,98). The literature has somewhat conflicting results concerning predisposing factors and the relation of GI bleeding to outcome, including mortality. This variability may reflect differences in study design, demographics, and statistical analysis. A consistent finding was decreased utilization of GI endoscopy for GI bleeding and greater length of stay for patients with GI bleeding during the pandemic than for patients prior to the pandemic (30,99).

In an Italian cohort, 78% had GI bleeding associated with thromboprophylaxis with anticoagulants (20). A European study also noted this strong association (19). Other studies have not reported anticoagulation as a significant risk factor (21,82,100).

Mortality secondary to GI bleeding was often not stratified and outcome seemed most related to pulmonary or multisystem failure, including sepsis and thrombosis. GI hemorrhage in COVID-19 subjects in some analyses was not clearly associated with increased overall mortality, though COVID-19 infected patients had greater mortality than non-COVID-19 subjects, at least for all patients presenting with upper

GI bleeding (23,40). Other studies found GI bleeding was associated with increased COVID-19 mortality (3, 101).

Emerging Trends

COVID-19 infection is a moving and evolving target due to emergent new viral mutations that are likely more infections and less lethal, changes in the biology of the infection due to improved host defenses from vaccinations and improved antiviral treatments including improved critical care, better management of respiratory compromise, and the introduction of moderately effective antiviral therapy. These changes are reflected in decreasing mortality and likely decreasing morbidity from the virus, that may reduce the burden of GI disease including GI bleeding. Long COVID is being increasingly appreciated, but it does not appear so far to frequently cause significant GI bleeding (see accompanying chapter by Tindade et al. on Long COVID). Although there is a theoretical risk of transmission of COVID-19 infection to uninfected patients, endoscopy staff, and the gastrointestinal endoscopist from aerosolization of viral particles, particularly in patients with active upper GI bleeding, the risks of spread to these groups appears to be less than initially feared, partly due to use of PPE, isolation techniques, and viricidal cleaning solutions, as well as universally recommended vaccinations. This change has allowed a gradual increase in the use of GI endoscopy from <10% of baseline rate during the pandemic onset to substantial but still incomplete recovery in the use of GI endoscopy towards the pre-pandemic baseline. Although the data on GI endoscopy was particularly sparse early in the pandemic, these data have been accumulating recently with the recovery of GI endoscopy towards pre-pandemic levels. This review is best considered a snapshot of the current state of GI bleeding with COVID, with likely future advancements and improvements in clinical therapy, management, and prognosis over time.

CONCLUSIONS

GI symptoms and GI pathology are common in COVID-19 infection, but overt GI bleeding is uncommon. Mucosal abnormalities are frequently noted at GI endoscopy and capsule endoscopy. However, GI hemorrhage associated with COVID-19 is often subclinical. The presentation of GI bleeding in COVID-19 ranges from the bleeding patient incidentally found to have COVID-19 infection to the critically ill COVID-19 subject with pneumonia and multisystem disorders. Use of anticoagulant and antiplatelet drugs and the known association of physiologic “stress” bleeding in critically ill patients with respiratory illness may be predisposing factors in this population. Modest endoscopic data suggests that PUD, including erosive gastro-duodenitis, are very common etiologies of GI bleeding. Ischemic colitis has a known association with COVID-19, but uncommonly manifests as overt bleeding. The approach to COVID-19 subjects with GI bleeding resembles that of the general population with the cogent exception

of often deferring endoscopy and reserving endoscopy for patients with more severe GI bleeding likely requiring therapeutic endoscopy. International and national guidelines reflect this philosophy and practice. Better understanding of COVID-19 pathogenesis and the advent of preventive measures such as vaccination and improved medications, such as Paxlovid, may ultimately render a conservative approach to GI endoscopy no longer tenable.

The editor of this monograph on GI manifestations and therapy of COVID hopes to contribute to this general advancement on COVID-19 therapy and prognosis by hereby offering the first volume or monograph devoted exclusively to the GI, liver, and pancreatic manifestations of COVID infection. Although COVID-19 is primarily a respiratory disease with prominent respiratory symptoms and frequent respiratory compromise, GI manifestations play an important secondary role in the morbidity and even occasionally the mortality of this infection.

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Figure legend and tables

Figure 1. Approach to GI Bleed in COVID Patient

Box 1. General principles of GI bleeding in COVID-19-infected patients

1. Literature on GI bleeding in COVID-19-infected patients is sparse relative to respiratory manifestations or many other GI disorders. This may relate to relative infrequency of performing GI endoscopy due to perceived risks to patients and endoscopy staff from the infection.
2. Higher threshold and less urgency for performing GI endoscopy on COVID-19 infected patients. May relate to perceived risks to patients and to endoscopy staff during the pandemic.
3. Often GI bleeding in COVID-19 infected patients is clinically mild and does not require GI endoscopy.
4. GI endoscopy may be deferred in acutely ill patients with mild-to-moderate GI bleeding because such patients often have multiple acute medical problems, especially respiratory failure.
5. Concern about transmission of COVID-19 to endoscopic staff during GI endoscopy. However, the risk to GI endoscopic staff of contracting COVID-19 infection during GI endoscopy is apparently not high if strict universal precautions are applied to all GI endoscopies performed during the pandemic.
6. Concern about prophylactic endotracheal intubation for EGD. In the initial stages of the pandemic (March-April 2020), endotracheal intubation was nearly universally performed before EGD, but subsequently endotracheal intubation is rarely and selectively performed for EGD.
7. Many-to-most critically ill COVID-19 infected patients receive anticoagulation, which must usually be withheld peri-procedurally.
8. Modest need for endoscopic hemostasis during GI endoscopy in COVID-19 infected patients because the bleeding is often not severe. Endoscopic therapy may not be feasible in patients receiving anticoagulation (see point 7).
9. Need for percutaneous endoscopic gastrostomy in intubated and ventilated patients with COVID-19 infection but fortunately rarely causes bleeding complications.
10. Therapies often used in patients with COVID-19 infection, including corticosteroids, anticoagulation, and tocilizumab, negatively impacts the GI tract and enhance GI bleeding.

GI – gastrointestinal, EGD-esophagogastroduodenoscopy

Table 2. Gastrointestinal endoscopy for GI bleeding in patients with COVID-19 infection

General principles/topic	Clinical applications	Reasons
PCR testing for COVID-19 infection	Many institutions with high institutional prevalence of COVID-19 infection standardly screen all patients scheduled for GI endoscopy by PCR testing for COVID-19 infection. Alternatively, institutions screen all patients with planned GI endoscopy for 1) history of exposure to someone with known COVID-19 within <14 days, and for 2) symptoms suspicious of COVID-19 (e.g., cough or dyspnea, diarrhea). Patients who have at least one such exposure or symptom should undergo PCR testing for SARS-CoV-2.	Reduce COVID-19 exposure of endoscopy staff
EGD is theoretically a high-risk procedure for transmitting COVID-19 infection from a patient with COVID-19 to endoscopy staff due to the presence of aerosolized infective droplets. However, the actual risk of transmission from a actual risk appears to be manageable. Risk to endoscopy staff may be higher in an infected patient with active overt hematemesis.	Endoscopy staff should strongly consider using PPE, including wearing an N95 face mask during endoscopy performed on COVID-19 infected patients.	Reduce personnel exposure to COVID-19 infection from infected patients
Much less performance of EGD for elective indications in patients with active COVID-19 infection as compared to non-infected patients	Generally, defer EGD for elective indications until patient recovers from acute COVID-19 infection.	Some risks to endoscopy staff from exposure to patient with COVID-19 infection during GI endoscopy. Patient with complicated acute COVID-19 infection may not tolerate EGD as well as non-infected patients. Some patients with COVID-19 infection (e.g., patients with severe pneumonia) may require prophylactic endotracheal intubation for EGD
Similar frequency of performing EGD for emergency/urgent indications in patients with acute COVID-19 infection versus non-infected patients	Perform EGD for overt life-threatening GI bleeding, when therapeutic EGD is likely needed, and when EGD is needed before contemplated GI surgery.	Cannot wait for patient to recover from acute COVID-19 infection when EGD is required emergently or urgently. Maximize patient hemodynamic stability and respiratory status before performing EGD.
Deferral of elective GI endoscopy in a COVID-19 infected patient	Wait a few weeks after the acute infection provided until the patient tests negative by PCR on a new COVID-19 test.	Reduce risk to endoscopy staff and reduce risks of endoscopy in a patient with active COVID-19 infection
Prophylactic intubation for EGD in COVID-19-infected patients	In the initial pandemic surge (March-May 2020) patients were generally intubated before EGD. From June 2020 and on only selected patients underwent prophylactic intubation for specific reasons	Reason for current selective policy for endotracheal intubation before EGD is difficulty in extubating patients with respiratory compromise (especially from COVID-19 pneumonia)
Precautions during EGD in COVID-19-infected patients	Endoscopy staff should exercise universal precautions when performing EGD on all patients during the pandemic, but especially in	EGD proper performed with precautions appears to result in a low risk of COVID-19 transmission to endoscopy staff

	performing EGD on COVID-19-infected patients	
Routine screening and surveillance colonoscopy often deferred in patients with active COVID-19 infection until after the patient clears the virus as proven by nasal swab		No reason to subject patient to increased risks of elective colonoscopy when the patient has active COVID-19 infection. No reason to subject the endoscopy staff, to the risks of contracting the virus from infected patients
Patients with GI bleeding associated with COVID-19 infection may have higher risks of morbidity and mortality than patients with GI bleeding without COVID-19 infection.	Patients with GI bleeding associated with severe COVID-19 pneumonia, respiratory compromise, and other serious complications of COVID-19 should generally be followed by an intensivist in an ICU	Patients with severe pneumonia, respiratory compromise, and other serious complications of COVID-19 are at higher risk of mortality
Protecting endoscopy personnel during EGD performed on a COVID-19-infected patient	Endoscopy personnel in the endoscopy suite should be minimized during intubation & extubation of patients with COVID-19 infection.	Reduce exposure of endoscopy staff to COVID-19 infection
Management of anticoagulation in COVID-19 patients with GI bleeding appear to have higher rates of thrombotic complications. Anticoagulation can complicate the management of GI bleeding. This may be particularly important in planning endoscopic therapy for overt, active GI bleed which may require withholding anticoagulation just before and after therapeutic endoscopy.	Contemplated endoscopic therapy for overt, active GI bleed may require withholding anticoagulation just before and just after therapeutic endoscopy.	COVID-19 patients likely have higher rates of thrombotic complications. Anticoagulation can complicate the management of GI bleeding. This may be particularly important in planning endoscopic therapy for overt, active GI bleed which may require withholding anticoagulation just before and after therapeutic endoscopy.
Telemedicine	May be considered as an alternative to ambulatory physical patients visits for follow-up after GI endoscopy.	Reduce hospital staff exposure to COVID-19-infected patients

EGD – esophagogastroduodenoscopy,

Table 1. Reported etiologies of upper GI bleeding proximal to the ligament of Treitz in patients with COVID-19 infection

Lesion	Putative mechanism(s)	Selected references
Angiodysplasia	One case reported in a large series of 87 EGDs performed mostly for overt GI bleeding	16
Aorto-enteric fistula	Case report	67
Dieulafoy lesion	One case reported in a large series of 87 EGDs mostly performed for overt GI bleeding	16
Cameron lesion associated with acute COVID-19 infection.	Case report. Cameron lesion/ulcer was due to a large paraesophageal hernia that progressed to cause acute gastric volvulus due to patient's poor nutritional status from COVID-19 infection	70
Esophageal candidiasis (without bleeding)	Two cases among 87 patients undergoing EGD	16
Esophageal ulcer	One case due to primary COVID-19 infection. Five cases reported in a large endoscopic series of 87 EGDs performed mostly for overt GI bleeding	16,66
Esophageal variceal hemorrhage	Increased reporting of esophageal variceal hemorrhage in COVID-19 infection may result from increased susceptibility of patients with cirrhosis, chronic liver disease, or advanced alcoholic liver disease to contracting COVID-019 infection	16, 44, 64, 65
Esophagitis moderately frequent	Hemorrhagic esophagitis from gastroesophageal reflux disease is moderately common but less frequently reported in COVID-19 patients than peptic ulcer disease	16,63
Gastric leiomyoma/inflammatory fibroid polyp	One case report of a patient with COVID-19 associated severe pneumonia requiring extracorporeal membrane oxygenation (ECMO) who had upper GI bleeding from a gastric inflammatory polyp successfully treated with endoscopic hemostasis	71
Gastrointestinal stromal tumor	Case report	72
Gastropathy-petechial/hemorrhagic	Common reported finding (occurring in 9.2%) in a large study of COVID-19 patients undergoing EGD	16
Hemobilia	Two case reports of hemobilia	68
Marginal (anastomotic) ulcer	Case report	73
Portal hypertensive duodenopathy	One case reported in a large endoscopic series of 87 endoscopies mostly performed for overt GI bleeding	16
Portal hypertensive gastropathy	Case report	74

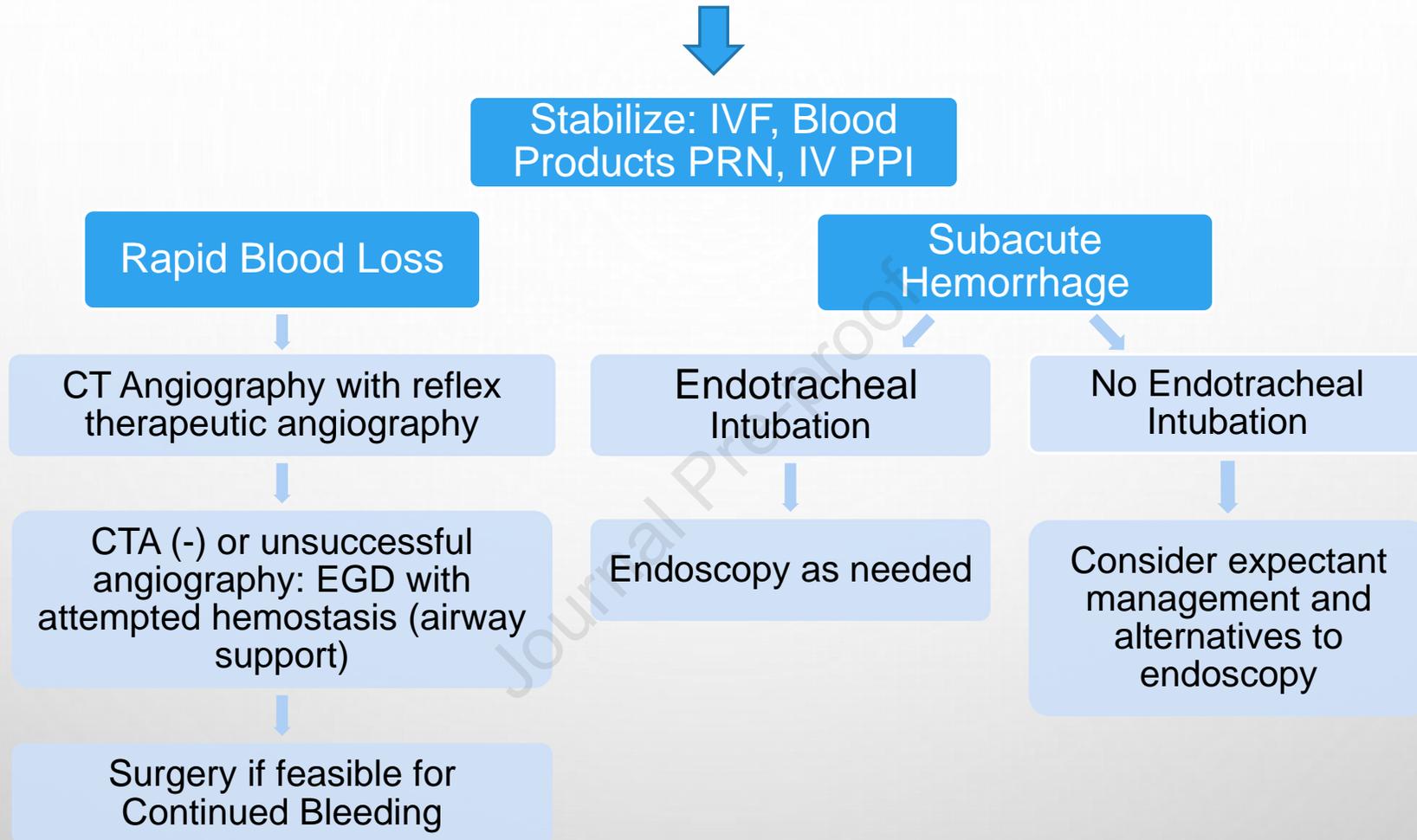
Table 3. Reported etiologies of jejunal and ileal bleeding in patients with COVID-19 infection

Lesion	Putative mechanism(s)	Selected references
Jejunal ulcers and multiple proximal jejuno-jejunal fistulae.	Scattered reported cases (one with only jejunal ulcers)	16,85,87
Hemorrhagic enteritis	Two independent case reports. Lesions attributed to COVID-19 infection	86, 89
Small and large intestinal mucosal sloughing	One case report	84
GIST in jejunum	Case report	90
Ileal angiodysplasia		89

Table 4. Reported etiologies of lower GI bleeding associated with COVID-19 infection

Lesion	Putative mechanism(s)	References
Ischemic colitis	Reported in 13% to 33% of patients with COVID-19 infection undergoing colonoscopy Association believed due to COVID-19 infections promoting thrombosis	16,63,91
Ischemic colitis	Associated with tocilizumab therapy	92
Ischemic colitis	After COVID-19 vaccination	93
Rectal ulcers	Often related to placement of rectal tubes	82
Hemorrhagic colitis	Need to recheck	94
Hemorrhagic colitis can occur with COVID-19 infection	One case associated with concomitant cytomegalovirus infection	95
Colonic angiodysplasia	Two cases reported in a review of 27 colonoscopies mostly performed for overt GI bleeding	16
Bleeding hemorrhoids	One case reported in a review of 27 colonoscopies mostly performed for overt GI bleeding	16
Colonic diverticulosis with bleeding	Four cases reported in a review of 27 colonoscopies mostly performed for overt GI bleeding	16

COVID PATIENT WITH GI HEMORRHAGE



Expectant Management: Monitor, transfuse PRN, reversal anticoagulation and antiplatelet drugs if feasible.

Alternative methods: Nuclear bleeding scan, CT angiography, Capsule endoscopy