



Review Article

COVID-19 and Alimentary Tract: Current Evidence and Recent Recommendations

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ABSTRACT

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The pandemic of coronavirus disease 2019 (COVID-19), first reported in China, in December 2019 and since then the digestive tract involvement of COVID-19 has been progressively described. In this review, I summed recent studies, which have addressed the pathophysiology of COVID-19-induced gastrointestinal symptoms, their prevalence, and bowel pathological and radiological findings of infected patients. The effects of gut microbiota on SARS-CoV-2 and the challenges of nutritional therapy of the infected patients are depicted. Moreover, I provide a concise summary of the recommendations on the management of inflammatory bowel disease, colorectal cancer, and performing endoscopy in the COVID era. Finally, the COVID pancreatic relation was explored. Conclusions: digestive symptoms in COVID-19 patients can be the only manifestation and they may be correlated with worse clinical outcomes. The likelihood of fecal-oral transmission of COVID-19 has significant consequences and requires further research. A clear link may exist between the gut microbiome and COVID-19 progression and it may have a therapeutic and prognostic value. No evidence for an increased frequency of covid-19 cases in IBD and stopping immunosuppressive medications is not advised. Triage and risk assessment of patients with suspected or confirmed COVID-19 before endoscopy is essential; deferral of elective endoscopies should be considered.

Introduction

The outbreak of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, in December 2019, and now the pandemic spreads worldwide. (1) As of October 8, 2020, nearly 36 million confirmed positive cases of COVID-19, with more than one million deaths, were reported to WHO, and the number continues to rise. (2) Acute respiratory syndrome, manifested by fever, cough, and dyspnea is the most classical presentation of COVID-19. However, as the outbreak grows, gastrointestinal manifestations are increasingly

reported in COVID-19 patients. (3) Enteric symptoms of SAR-CoV2 not only carry a significant diagnostic challenge to physicians when dealing with patients who initially presented with mild COVID-19-related GIT symptoms but also signifies the probability of fecal transmission of this virus. Moreover; COVID-19 has impacts on the management of patients with co-and pre-existing digestive diseases. (1,4) In this review, the studies investigating the pathophysiology of COVID-19-related GIT manifestations, pathological, and radiological imaging results in COVID-19 patients presenting with digestive symptoms have been summarized. This review also

discusses both the prevalence and prognostic impact of digestive system involvement in COVID-19 patients. We briefly address the issue of SARS-CoV-2 fecal shedding and its possible culprit role in viral transmission. Moreover, the impacts of gut microbiota on SARS-CoV-2 infection and its diagnostic and therapeutic values are depicted. Besides, we showed the challenges of nutritional therapy of infected patients. Also, we outlined the most recent recommendations by GIT societies on the management of IBD, colorectal cancer, and performing endoscopy in the post-COVID pandemic era. Lastly, we explored the COVID - Pancreatic link.

Pathophysiology of GIT involvement in COVID patients

Possible mechanisms for GIT symptoms in SARS-nCoV-2 infection include direct injury to the gut, a simple manifestation of viremia, and systemic inflammation. (5) Evidence from prior SARS studies showed that the corona family has a tropism to the GIT tract (6). Furthermore, the examination of both biopsy and autopsy samples by electron microscopy revealed active viral replications in both small and large intestinal epithelia. The virus's ability to attach to the ACE2 facilitates its entry to these cells. (7,8) Xu et al. indicated that GIT tract organs had greater ACE2 expression compared to the lung tissue. (9) Moreover, Xiao et al's (10) work on COVID tissues revealed that viral nucleocapsid expression level in the areas of the GI tract showed a positive correlation to ACE2 expression. Also, furin, an essential enzyme for proteolytic activation and attachment of the virus, is extensively distributed in the small bowel. (11,12) ACE2 receptors of the enterocytes may provide an entrance spot for SARS-CoV-2 for the systemically circulated virus, allowing it to re-enter the body ("re-entry" or "second hit hypothesis"). (12) Furthermore, partial or complete blockage of ACE2 by SARS-CoV-2 results in a malfunction of the amino acid and sodium transport of the gut, leading to malnutrition. Also, gut inflammation increases intestinal permeability, allowing enhanced uptake of bacterial antigens and other toxins, further complicating the septic state of COVID patients. (12) Likewise, SARS-CoV-2 via binding to ACE2 in the GIT tract decreases its available receptors, disturbs the absorption of tryptophan via the BOAT1/ACE2 transport pathway, and eventually destroys the steady-state of the gut flora, which can cause digestive symptoms such as diarrhea (pellagra-like state). Disorders of the respiratory tract flora also affect the digestive tract through immune regulation. This link is called the "gut-lung axis". Effector CD4+ T cells (increase following viral respiratory infection) entering the intestinal mucosa are key cells for mucosal immunity and chronic enteritis. (13) On the other hand, the small bowel likely plays a greater effect in the dynamics of Covid-19, as it is likely a key site for cytokine storm progression and an origin of amplification of the systemic inflammatory response syndrome sequel. (14)

Gut pathology and radiological imaging

Histological involvement of the alimentary tract is sparse in a limited number of cases examined either endoscopically or postmortem. (15) Possible reasons for bowel pathological findings in COVID-19 infected patients such as direct viral invasion, small vessel thrombosis, and nonocclusive mesenteric ischemia. (16) The

autopsy finding of early examined cases with COVID- 19 showed small intestinal segmental dilatation, and stenosis with different degrees of degeneration, necrosis, and shedding of the gastrointestinal mucosa. (17) Infection doesn't cause marked macroscopic inflammation on endoscopy. Whereas profuse infiltrating plasma cells and lymphocytes with interstitial edema of lamina propria were observed during histologic examination of endoscopically obtained tissues from the stomach, duodenum, and rectum of infected patients, mucosal epithelial cells of the GIT tract may be normal (10). Acute hemorrhagic colitis could even occur in a COVID-19 patient with digestive discomfort as the primary symptom. (18)

A retrospective study that enrolled COVID patients, who were evaluated with abdominal imaging, showed that pneumatosis intestinalis or portal venous gas, were demonstrated on the fifth of CT scans done to critical patients, pathology revealed ischemic enteritis associated with patchy necrosis and fibrin thrombi in arterioles. (16) A recent report on abdominopelvic radiological CT results in COVID-positive individuals demonstrated bowel wall thickening and fluid-filled colon in 31% of cases, indicative of diarrhea (16), another study yielded a positive finding in 57% of 141 abdominopelvic CT of patients, with 31% of those findings involves GIT tract include acute appendicitis, retained colonic stool, small bowel obstruction, and mural thickening. (19) More than 50% of critically ill COVID-19 patients have either clinical or radiographic evidence of an ileus/pseudo-obstruction. (20) Other studies shed the light on COVID-associated ischemic colitis. (21–23) This could be attributed to COVID-19-associated coagulopathy, which is a well-defined phenomenon in those patients. (24) Moreover, shock or hemodynamic compromise which is commonly associated with severe COVID-19 pneumonia can lead to non-occlusive mesenteric ischemia. (25)

COVID's related GIT Symptoms

The incidence of gastrointestinal manifestations has ranged from 12% to 61% in patients infected with COVID-19. (26) In a meta-analysis of 4,243 COVID-19 patients, the prevalence of gastrointestinal symptoms was 17.6%, with anorexia as the commonest symptom (26.8%), diarrhea (12.0%), nausea or vomiting (10.0%), and abdominal pain (9.0%). Another meta-analysis that enrolled 6064 patients showed diarrhea in 9%, nausea and/or vomiting in 7%, anorexia in 21%, and abdominal pain in 3%. (27) GI symptoms usually develop less likely in COVID-19 compared to SARS and MERS, with an average of 5–7% versus 20–25% of cases. (28) The real prevalence of any gastrointestinal symptoms may be underestimated since other gastrointestinal symptoms other than diarrhea were not documented in several earlier studies and those with mild GIT symptoms encountered delayed diagnosis compared to patients with respiratory symptoms alone. (4,29) In patients with gastrointestinal symptoms, the prevalence of severe disease was more common compared to those without. (13,30,31) One explanation is that gut symptoms indicate a higher viral burden and replication within the gastrointestinal tract, which leads to more severe disease. Another possibility is the later hospital presentation of those patients compared to those with respiratory symptoms (9.0

vs. 7.3 days). (4,32) whereas almost two-thirds of patients with no digestive manifestations recovered and were discharged, only a third of the patients with digestive symptoms recovered. (32) They also had substantially higher rates of fever, dyspnea, and headache. (33) Patients presenting with initial digestive symptoms are at increased risk of acute respiratory distress syndrome. (27) However, they have no higher mortality risk. (34) When compared with patients without gastrointestinal symptoms, those with gastrointestinal symptoms, have elevated levels of neutrophils, and higher C-reactive protein, thus the inflammation is more serious, their complications are more common, and that they are more likely to develop severe disease. (13) Elevated alanine aminotransferase, lower monocyte count, lower hemoglobin levels, and prolonged prothrombin time were also noted in COVID patients with GIT symptoms. (32,35) On the other hand, no statistically significant difference in the severity of COVID-19 among patients with and without GI symptoms was observed in other studies. (32,36,37)

The first described case of COVID-19 in the United States had a 2-day initial history of nausea and vomiting. (38) in most of the studies, Anorexia is the most common GI symptom (26.8%). It may be to some degree elucidated by olfactory and gustatory dysfunction, which were found as high as 85.6% and 88.0 % respectively in COVID-19 patients. (39) Moreover, it could be attributed to systemic inflammation, (40) liver function injury, depression, or adverse reactions to therapeutics. (41) As regards, the pain, patients with severe COVID-19 infection were almost seven times more likely than patients with non-severe COVID-19 disease to experience abdominal pain. (42) Henry BM et al. also noted that abdominal pain is accompanied by a four time's higher risk of developing critical illness in infected subjects with nausea and vomiting. (43) Cases of afebrile acute abdominal pain were also reported as the first presentation of COVID-19. (44) Moreover, Esophageal bleeding with erosions and ulcers was also revealed in COVID-19 severe patients. (45)

COVID's diarrhea

In a pooled analysis that involves 10,676 patients, the prevalence of diarrhea symptoms across these studies was 7.7%. Diarrhea was reported as one of COVID-19's initial presenting symptoms in two pooled analyses which involve 9717 and 8070 (46) The SARS-CoV-2 infection of the ACE2-expressing enterocytes leads to mucosal inflammation (47), which was verified by an increased level of fecal calprotectin, which also significantly correlated with serum interleukin-6 concentration. (48) A meta-analysis involved 1517 patients found that patients were more likely to have diarrhea in the severe COVID-19 group when compared with its non-severe disease but this was not statistically significant. (49) It may even occur earlier than pyrexia or respiratory symptoms in some cases in an estimated 22.2% of patients. COVID-19 can sometimes be misdiagnosed as viral gastroenteritis leads to possible delayed diagnosis. Medications such as hydroxychloroquine and lopinavir/ritonavir can be a secondary cause of diarrhea in patients with COVID-19. (42) The use of oseltamivir and arbidol can be related to serious intractable diarrhea.; The incidence of diarrhea is 55.2 % in COVID patients taking these medications. Remdesivir can

cause diarrhea as well. (13) Remarkably, the prevalence of diarrhea in outpatients is lower than in hospitalized patients. (33) Importantly, presenting with constipation shouldn't rule out COVID-19. (50)

Findings from a single Wuhan center have shown that diarrhea begins within 1-8 days after the onset of the COVID-19 (with the median time 3.3 days), the total course of the disease was 1–14 days, the average duration was (4.1 ± 2.5) days and bowel movement could reach up to 9 motions per day, with the average (3.3 ± 1.6) times per day and in most instances, the stool was watery in about 34.3%. (49) Diarrhea can present as the only symptom.(33,51) Compared to patients with diarrhea and respiratory symptoms, patients with diarrhea alone had a milder disease, shorter hospital stays, and better outcomes, (52) also patients with chest symptoms in addition to diarrhea are more likely to need mechanical ventilation and have acute respiratory distress syndrome (33) and they may require more close monitoring. The SARS-CoV-2 disease can be included in the differential diagnosis of acute diarrhea and/or vomiting, at least for the time of this pandemic. (53) Moreover, Diarrhea in COVID-19 positive subjects can contribute to spreading the virus. Essential treatment of severe diarrhea such as fluid and electrolyte replacement need to be accompanied by applying anti-diarrheic measures such as stopping the administration of antibiotics (if such are administered) or by shifting to a different type. Besides, the administration of substances modulating the gut microbiome (e.g. probiotics, rifaximin) can help to recover from dysbiosis. (40)

COVID -19 fecal shedding and transmission

SARS-CoV-2 is found in fecal samples in about half of COVID-19 cases (54). This proportion is higher in patients with diarrhea compared to those without diarrhea, and recent data also propose that it may occur independently of the development of diarrhea (55). However, Lin and colleagues failed to find a correlation between the presence of SARS-CoV-2 in the stool and gastrointestinal symptoms (45). In a Chinese study which involved 14 laboratory-confirmed COVID-19 patients, the molecular diagnosis of COVID-19 using fecal specimens was similarly accurate with that of the oropharyngeal swab (56) Malfertheiner et al. reported continued fecal shedding of SARS-CoV-2 in COVID-19 patients up to five weeks after the disappearance of the pulmonary symptoms and after throat swabs turn negative, supporting the suggestion that the residual persistence of the virus within the digestive system components may be a cause for the recurrence of the disease. (40). X Wang et al. found that the median duration of SARS-CoV-2 RNA persistence was noticed to be significantly longer in fecal samples than in oropharyngeal swabs by almost 9 days. (57)

A meta-analysis that included 436 patients with established diagnoses by Wong et al. (58) showed that the stool detection rate among them was 43.7%, he also noted that female patients, those who are symptomatic or those with more severe disease had a higher detection rate. Interestingly, asymptomatic patients with RT-PCR positive for SARS-CoV-2 RNA in their stool samples have been identified. (59) Thus, the lack of gastrointestinal manifestations is not a good predictor of negative GI specimen tests. (58) Real-time RT-PCR virus testing in feces may be valuable in disease monitoring

and surveillance. (60) The patients with stool specimens that are positive for the virus had earlier incidence and longer duration of diarrhea, which indicated the higher viral burden in the digestive tract was related to a longer total disease course. (52)

A study conducted by Wolfel et al. revealed that although COVID-19 RNA was found in the fecal samples of the patients, infectious SARS-CoV-2 particles were not detected despite high concentrations of virus RNA (61). On the contrary, others were able to isolate live virus from stool samples, also viral nucleocapsid protein was visualized in the cytoplasm of gastric, duodenal, and rectum glandular epithelial cell (10,62) Several studies have indicated that SARS-CoV-2 replicates in enterocytes, via using human small intestine organoids. (63,64) Moreover, robust transcriptional signature of SARS-CoV-2 infectivity in feces of those infected with COVID-19 even without GI symptoms (65). All these raise the possibility of fecal-oral transmission (66) There is very limited data about the survival of SARS-CoV-2 under acidic conditions. (67) Zang et al. published a remarkable study on SARS-CoV-2 infection which showed that although the viruses are capable of entering the intestinal cells, they are not able to survive in the alimentary tract due to gastric fluid with low pH and the intestinal environment with bile and digestive enzymes. (68) This suggests that it is quite early to mention the fecal-oral transmission route of SARS-CoV-2 with limited data we have to date and we require more experimental studies about it. Additional screening methodologies to the current donor screening measures should be implemented to prevent SARS-CoV-2 transmission by fecal microbiota transplantation. (69)

Gut microbiome and COVID-19

First reports of COVID-19 patients' gut microbiota demonstrated a significant decrease in diversity and abundance compared to healthy control (70). Evidence shows that intestinal microbiota can remotely enhance host immune reaction to respiratory viral infections. Shortly after infection, SARS-CoV-2 replicates in the intestinal tract, reduces the ACE2 expression and activity contributing to a gut dysbiosis and gastrointestinal tract manifestations development, and predisposes patients to secondary, sometimes serious, bacterial infections often of a more severe clinical outcome. (71) Moreover, numerous experimental and clinical observations have proposed the key role played by gut microbiota in the pathogenesis of sepsis and ARDS. (72) The increased number of bowels associated microbiota such as Lachnospiraceae and Enterobacteriaceae predicted fewer ventilator-free days, and an increase in Lachnospiraceae was a strong marker of reduced survival in ARDS patients. These findings indicate that the microbiota can be used as a predictor for ARDS development and the outcome of COVID-19. (73) Moreover, microbiota dysbiosis is linked to a poor course in COVID-19 patients with age-related comorbidities. (74)

Zou et al. reported that abundance in baselines of Coprobacillus, Clostridium hathewayi, and ramosum is associated with severity of COVID-19, and there was a negative relationship of the abundance of A. onderdonkii, L. bacterium, and Faecalibacterium prausnitzii and severity of the disease, (70) others were positively associated with CRP. (75) Downregulation of ACE2 expression in the bowel by

Bacteroides dorei, thetaiotaomicron, massiliensis, and ovatus, was negatively related to SARS-CoV-2 load in patient stool samples (70) Collinsella aerofaciens and Morganella morganii, were enriched in stool samples of patients with COVID-19 who had high SARS-CoV-2 infectivity. On the contrary P. merdae, B. stercoris, A. onderdonkii were enriched in the fecal samples with a signature of low- to none SARS-CoV-2 infectivity. (65) The effect of probiotics on COVID-19 should be further studied, as some may be beneficial via interacting with the intestinal microbiota and modulating the immune system. (76) To maintain bowel balance and to avoid secondary bacterial infection, China's National Health Commission suggests using the probiotics for management of patients with severe COVID-19 infection (77) Many ongoing trials are conducted to investigate the potential beneficial effect of fecal microbiota transplantation on gastrointestinal symptoms, gut dysbiosis, and immune status in COVID-19 patients. (78–80) Till now, blind use of conventional probiotics for COVID-19 is not recommended. (81)

Nutrition and COVID-19

Appropriate dietary ingestion may be vital to protect against an excessive inflammatory response to SARS-Cov-2 infections, hindering the progression of the infection to critical disease or even during COVID-19, improving its outcome. (82) Certain nutrients were identified as being potentially essential for prevention and treatment of COVID-19, including the vitamins of A, D, E, zinc, and selenium. (83) providing appropriate enteral nutrition for critically ill COVID patients has proven to be challenging due to intestinal dysmotility, bowel ischemia, and malabsorption. Those patients may have significant nutritional deficits and more aggressive early nutritional support with TPN may be warranted. (84) COVID-19 patients need more energy than normal; it is advised to supply 84-126 kJ/kg/day. (85) In the early acute stage of severe disease, a standard rich-protein (> 20% protein) polymeric isosmotic enteral formula must be used. Also, there should be a 50 % rise in the supplied amount of branched-chain amino acids, to prevent muscle loss, enhance the strength of respiratory muscles. (86)

The European Society for clinical nutrition and metabolism (ESPEN) recently published guidelines for the dietary management of individuals with SARS-CoV-2 infection. These recommendations center on providing early enteral nutrition (EN) (within 24-36 hours following ICU admission or 12 hours after initiation of the mechanical ventilation), starting peripheral nutrition (PN) if EN is not tolerated, and using EN post-extubation if oral nutrition is not tolerated. Early enteral nutrition starting with a hypocaloric prescription is recommended. Continuous feeding is endorsed to decrease the incidence of diarrhea and decrease the exposure of health care workers to infection. Prokinetics are endorsed to boost motility if there is GI intolerance. (87) As the patient and the GI dysfunction improves, fiber should be added for the non-nutritional benefits to the gut microbiota. (88) The threshold for shifting to parenteral nutrition in patients with COVID-19 disease may need to be lowered to minimize the risk of ischemic bowel and reduce further excessive exposure of health-care staff. Nutrition societies recommend early enteral nutrition for these patients in prone positioning. (89) Reverse Trendelenburg with the head of the bed

elevated to at least 10 to 25 degrees is recommended in those patients to decrease the risk of aspiration. (90)

IBD and COVID-19

In general, IBD patients are at greater risk for infections, particularly while they are being treated with steroids, immunosuppressants, or biologics. Besides, receiving infusion therapies or having endoscopic interventions at medical facilities may both increase the hazard of exposure to SARS-CoV-2. (91–93) No evidence has been shown yet that the IBD itself increased the hazard of SARS-CoV-2 infections and the prevalence of COVID-19 in IBD patients was equivalent to those in the general public. (94,95) Interestingly, COVID-19 manifestations tend to be milder in IBD patients, with a relatively lower frequency of serious and complicated cases compared to the general population. (96–99) Moreover, a recent study from Wuhan and Bergamo, Italy studied 318 and 522 patients respectively with IBD during the outbreak of the disease, and no COVID-19 cases were recorded. (97,100) The soluble ACE2 level is up-regulated in the serum of IBD patients, and this form of ACE2 has been shown in vitro studies to be a competitive SARS-CoV-2 interceptor by hindering binding of full-length ACE2 to the viral particle. (101)

Bezzio et al revealed that active IBD was associated with a negative COVID-19 prognosis (pneumonia, respiratory assist, hospital admission, and death). Moreover, the active disease may also lead to corticosteroid use which can increase susceptibility and severity of COVID-19 and/or hospitalization which may inadvertently lead to COVID-19 exposure. (102) About 50% of IBD patients who developed pneumonia, and 50% of patients who died, were not under any immunosuppressive therapy. These results demonstrate that complications and deaths of COVID-19 in IBD patients represent COVID-19's natural history and are not attributable to the use of immunosuppressive medication. (98). A negative outcome in IBD infected patients was related to age older than 65, having over 2 comorbidities, and sulfasalazine/5-aminosalicylate use. (103) it seems to be difficult to differentiate diarrhea related to COVID-19 from a disease flare in IBD patients (104). Testing all IBD patients presenting diarrhea for SARS-CoV-2 infection during the outbreak is recommended, to discriminate an IBD flare from diarrhea due to SARS-CoV-2 infection and avoid inappropriate using of corticosteroids or other therapies that may favor the progression of COVID-19 (102)

Burgueño et al. showed that CD-11b enriched cell ACE2 expression was reduced by anti-TNFs, vedolizumab, ustekinumab, and steroids. Therefore, it seems that most drugs for IBD do not affect ACE2 intestinal expression adversely. TNF inhibitors may decrease organ damage effectively via decreased shedding of the ACE2 ectodomain, which is vital for the penetration of SARS-CoV-2 into the cell. Severe SARS-CoV infection was strongly correlated with TNF production, inhibition of TNF has been proposed as a treatment for the cytokine release syndrome and ARDS that can arise in some COVID patients. 9% of patients treated with anti-TNF-agents required hospitalization, and only a minority (3%) experienced unfavorable outcomes. Conversely, 66% of patients

receiving oral or parenteral steroids required hospital admission, with 26% having poor outcomes. (103) Immunomodulators could be related to a higher risk for viral infections, they can cause lymphopenia. Patients of SARS-CoV-2 induced lymphopenia have an unfavorable prognosis and a greater viral associated mortality risk. (105) Respiratory tract infections and severe infections seem not to be higher in long-term follow-up studies of 5-ASA medications, sulfasalazine, ustekinumab, or vedolizumab. However, Tofacitinib can decrease immunity to viral infections in long-term follow-up trials. (106)

Most societies suggest continued IBD-specific therapy because the likelihood of active disease was considered to be greater than the uncertain risk of immunosuppression that would predispose to a higher risk of SARS-CoV-2 infection. It is universally advised to reduce corticosteroid exposure once feasible by rapid tapering. BSG also suggesting topical corticosteroids or exclusive enteral nutrition as alternatives for patients experiencing a flare. As regards Mesalamine, most guidelines encourage continuing treatment, but its dose should be optimized in cases of disease relapse with the addition of topical 5-ASA. As regard patient with IBD (in remission) who is infected with SARS-CoV-2 (with or without manifestations of COVID-19), AGA advises that patients voluntarily switch to fewer prednisone doses (<20 mg/d) or shifting to budesonide when applicable. Thiopurine, methotrexate, and tofacitinib can be withheld briefly. Anti-TNF treatment, ustekinumab, or vedolizumab doses should be deferred for 2 weeks whilst monitoring the progression of COVID-19 in asymptomatic patients. Both BSG and ECCO recommend initiation of anti-TNF therapies in monotherapy, while elective switching from intravenous to subcutaneous is not recommended. For symptomatic patients, they can be restarted after complete symptom resolution or, if available, when follow-up viral testing is negative or serologic tests demonstrate the convalescent stage of illness. For COVID-19 patients with moderate to severe active IBD, holding therapies may not be safe or practicable. In this setting, the risks and benefits of escalating IBD therapy must be cautiously balanced against COVID-19 severity. The initiation of immunomodulators is discouraged, but their suspension or reduced dose is not recommended. Stopping in patients >65 years and/or comorbidities in stable remission should be considered. we can continue tofacitinib but ideally at the lesser dose (5 mg) twice daily. (107). When possible, complex IBD surgeries might be postponed but emergency procedures should continue to be managed as part of routine care. (108) AGA recommends that the evaluation of IBD with dysplasia must not be postponed.

COVID-19 and colorectal cancer

In this COVID-19 outbreak, the greatest concern for cancer patients is the failure to access essential health services. (109) Globally, there is no major COVID-19 risk in colorectal cancer patients compared with the general public. However, cancer patients receiving anticancer regimens have been generally believed to be at a greater risk of COVID-19 infection than those cancer patients who are not. Moreover, the mortality risk of infected cancer patients was considerably higher than non-cancer patients. (110) Corley et al reported on 70,124 patients with a positive fecal immunochemical

test and found no substantial difference in disease outcomes of colorectal cancer when the colonoscopy was performed within 8 to 30 days following the positive test versus delaying it up to 6 months. Another study by Lee, et al has similar findings (111) Therefore, even if a test suggests a suspected polyp or tumor, delay of the colonoscopy for some period might not be hazardous to the patients undergoing colorectal cancer screening. (112) During the COVID pandemic, endoscopy priority must be given to those with alarming symptoms or those at greater risk for GI-cancer based on previous test results (positive (FIT) or radiographic suspicion). Conversely, follow up of patients at average or low risk of cancer, including post-polypectomy or post-surgery colorectal cancer patients can continue to be postponed. (113) As regards, Adjuvant therapy for early colon cancer, using capecitabine in combination with oxaliplatin instead of infusional 5-FU is advised during the COVID era. Moreover, we may consider, on the basis of oxaliplatin-identified side effects, applying treatment for 3 instead of 6 months. Also, delaying adjuvant treatment by 12 weeks is advisable. When appropriate, short-course radiation is used for neoadjuvant therapy of rectal malignancy is recommended with a delay to surgery for 4-8 weeks after the radiation therapy. Consider a high threshold for using prophylactic GCSF when post-op (Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil) FLOT is used. A watch-and-wait approach may be appropriate sometimes to avoid surgery and its resulting hospitalization during the pandemic. Likewise, Patients that are scheduled for metastasis resection also can be kept on oral chemotherapy or even on treatment holiday until the surgery is safe. (114–116)

COVID-19 and endoscopy

The COVID-19 pandemic represents a major challenge for health care systems worldwide. The hazard of exposure to endoscopy staff can not only be limited to the upper endoscopy procedures only considering the recent detection of SARS-CoV in biopsy and stool specimens. (117) Recent data suggest an increased risk for personnel of GI endoscopy units for SARS-CoV-2 infections. Several societies have provided recommendations for the current situation. All GIT societies recommended using personal protective equipment during the procedure. Gloves, mask, goggles, gown, hairnet; double gloves, and use of N95 or FFP2/3 masks were advised in suspected or confirmed cases. Most societies recommended temporarily postponing elective procedures (All except endoscopic emergencies for example GIT bleeding, acute cholangitis, biliary pancreatitis, foreign body extraction, and certain cases of obstructive jaundice); they also recommended stratifying patients for risk of COVID-19 before the examination (118,119) (ASGE) suggests to perform endoscopic procedures in a negative-pressure room. (120) AGA also considers delaying colonoscopy for lower GI bleeding. In contrast, a patient presenting with an upper GIT bleeding should have an esophagogastroduodenoscopy performed within one day. (121) An Italian multi-center survey included 41 endoscopy units aimed to investigate the impact of the COVID-19 pandemic on endoscopy units and to assess the probability of viral transmission from these units. No cases of medical staff infection attributed to endoscopic procedures in COVID-19 patients were reported in their survey.

(122) pre-screening of patients before the procedure is highly recommended by the American Society of Gastrointestinal Endoscopy. (123). ESGE and ESGENA both propose a risk stratification to be done 1 day before GI endoscope (per phone preferably) and again on endoscopy day for probable COVID-19 infections., they also consider tracing and contacting patients at 7 and 14 days to inquire about any new COVID-19 diagnosis or evolution of symptoms post-endoscopy. (124) No data exists on the virucidal potency of chemical agents against SARS-CoV-2; therefore, our recommendations are based on studies done for other coronaviruses. (123)

COVID-19 and pancreas

The pancreatic injury mechanism in COVID-19 is triggered by ACE2 expression in both exocrine and endocrine pancreatic cells (125). Pancreatic enzymes may be also elevated during the COVID course as infected patients have a series of complications including gastroenteritis, acidosis, renal failure, and diabetes that are accompanied by elevated serum levels of pancreatic enzymes. (4,126) Wang et al. noticed that at admission, 17% of patients with COVID-19 related pneumonia had a pancreatic injury, which was defined as any abnormality in amylase or lipase. The incidence of abdominal discomfort, lack of appetite, diarrhea, and more severe disease at the time of admission were increased in patients with a pancreatic injury compared with those without a pancreatic injury; (127) Moreover, Damage of the pancreatic islets leads to acute diabetes, In the same study 6 COVID-19 patients with associated pancreatic injury were found to have abnormally higher blood glucose levels. (128) In a retrospective study, 189 patients who presented with pancreatitis on admission, of which 17 percent were diagnosed with COVID-19, and it was reported that COVID-positive pancreatitis patients have a higher need for mechanical ventilation, they also have almost 4 times the length of hospitalization. (129) Moreover, they have a higher risk of multi-organ failure and mortality. (130) In a retrospective study total, 14235 individuals were tested positive for SARS-CoV-2 of which 0.7% had a history of acute or chronic pancreatitis. This suggests that patients with a previous history of pancreatitis might be more vulnerable to COVID-19. (131)

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