A Review of Gastrointestinal Aspects of COVID-19 Disease

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Abstract

The novel coronavirus disease 2019 (COVID-19) is currently causing a major pandemic. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the Betacoronavirus genus that also includes the SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). While patients typically present with fever and a respiratory illness, some patients also report gastrointestinal symptoms such as anorexia, diarrhoea, vomiting and abdominal pain. Studies have identified the SARS-CoV-2 RNA in stool specimens of infected patients, and its viral receptor angiotensin converting enzyme 2 (ACE2) was found to be highly expressed in gastrointestinal tract. This has important implications to the disease management, transmission, and infection control. In this article, we review the important gastrointestinal aspects of the disease.

Keywords: COVID-19, ACE2 receptor, hepatitis, IBD, endoscopy.

Introduction

The outbreak of novel coronavirus (2019-nCoV) pneumonia initially developed in one of the largest cities, Wuhan, Hubei province of China, in early December 2019 and has been declared the sixth public health emergency of international concern by the World Health Organization. Up to the submission date, there are more than 60,00,000 confirmed cases worldwide, affecting all age groups from infants to elderly people, according to the World Health Organization (WHO). SARS-CoV-2 is an enveloped, positively charged, single-stranded RNA virus belonging to the beta coronavirus genus. SARS-CoV-2 enters cells via the angiotensin converting enzyme 2 (ACE2) receptor and is highly homologous to SARS-CoV. Zhang *et al*[1], reported that ACE2 was highly expressed in oesophageal epithelial cells and the absorptive enterocytes from ileum and colon, suggesting possible faecal transmission. Patients typically present with fever and respiratory symptoms, nevertheless, some patients also have gastrointestinal manifestations with diarrhoea, vomiting and abdominal pain. Studies have identified the SARS-CoV-2 RNA in anal/rectal swabs, and stool specimens of COVID-19 patients, even after the clearance of the virus in the upper respiratory tract. Together these suggest that SARS-CoV-2 can actively infect and replicate in the gastrointestinal tract. This has important implications to the disease management, transmission, and infection control. In this article, we review the important gastrointestinal aspects of COVID-19 disease.

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Gastrointestinal Symptoms of COVID-19 Patients

Gastrointestinal symptoms including anorexia, diarrhoea, vomiting, abdominal pain during course of the disease and liver injury are reported in up to 40% of patients with COVID-19. As the severity of the disease increases, digestive symptoms and liver injury become more pronounced. About 10% of patients presented with gastrointestinal symptoms alone without respiratory features; these patients have delayed diagnosisof COVID-19. Patients with gastrointestinal sympto ms have increased risk of severe or critical disease, and development of acute respiratory distress syndrome. In a large case series (n=1141) of patients admitted to hospital with COVID-19, 183 (16%) pesented with gastrointestinal symptoms only. Wang and colleagues also found that around 10% of patients initially presented with diarrhoea and nausea 1–2 days before the development of fever and dyspnoea. Current literature shows that anorexia is the most frequent digestive symptom in adults (39.9%-50.2%), while diarrhoea is the most common symptom both in adults and children (2%-49.5%), and vomiting is more common in children. About 3.6%-15.9% of adult patients present with vomiting and 6.5%-66.7% in children. Nausea accounts for 1%-29.4%, and gastrointestinal bleeding in 4%-13.7%; abdominal pain (2.2%-6.0%) is more frequent in severely ill patients [2].

It is evident that patients can present with gastrointestinal symptoms early in the disease course. For example, the first COVID-19 patient in the US had nausea and vomiting two days before going to hospital, and developed diarrhoea on the second day of admission, whereas the two young adults in the early familial COVID-19 cluster had diarrhoea upon presentation to the hospital. Diarrhoea can be one initial symptom and may even occur earlier than pyrexia or respiratory symptoms in some cases [3].

Stool Shedding

Emerging data suggest the prolonged presence of SARS-CoV-2 RNA in stool samples or rectal swabs even after the patient's respiratory specimens become negative. Much attention has been paid to the possibility of viral shedding from the gastrointestinal tract and faecal–oral transmission. Pooled estimate of the presence of SARS-CoV-2 viral RNA positivity in faecal samples of Covid-19 patients has shown prevalence of 54% (95% CI 44–64). Viral positivity can persist for as long as 47 days after symptom onset [4]. Data from Wu and colleagues suggest the possibility of extended duration of viral shedding in faeces, for nearly 5 weeks after the patient's respiratory samples tested negative for SARS-CoV-2. This faecal source can lead to fomite transmission, especially when infective aerosols are generated from the toilet plume.

Mechanism of Gastrointestinal Tract Involvement[5]

It is widely accepted that coronavirus human transmissibility and pathogenesis mainly depend on the interactions, including virus attachment, receptor recognition, protease cleaving and membrane fusion, of its transmembrane spike glycoprotein (S-protein) receptor-binding domain, specific cell receptors (ACE2), and host cellular transmembrane serine protease (TMPRSS), with binding affinity of 2019-nCoV about 73% of SARS-CoV. Recent bioinformatics analysis revealed that ACE2 was not only highly expressed in the lung AT2 cells, but also in esophagus upper and stratified epithelial cells and absorptive enterocytes from ileum and colon. With the increasing gastrointestinal wall permeability to foreign pathogens once virus infected, enteric symptoms like diarrhea will occur by the invaded enterocytes malabsorption, which in theory indicated the digestive system might be vulnerable to COVID-19 infection. However, the exact mechanism of COVID-19–induced gastrointestinal symptom largely remains elusive. Xiao et al, reported staining of viral nucleocapsid protein in cytoplasm of gastric, duodenal and rectal epithelium. These data have provided valuable insights into the receptor-mediated entry into the host cells, and provided basis for its possible transmission route through the faecal contents.

Liver Injury in COVID-19 Patients

Apart from gastrointestinal symptoms, patients with COVID-19 can have liver injury with raised enzymes found in blood tests. Current data indicates that 14.8-53.1% of COVID-19 patients had abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during the course of disease, with mostly mild elevation in serum bilirubin. In a study that described a cohort of COVID-19 patients, gamma-glutamyl transferase (GGT) was elevated in 54% of the patients. Most of the liver injuries are mild and transient, although severe liver damage can occur. The proportion of liver injury was also higher in patients with severe COVID-19 disease. In the cohort that described 99 patients in Wuhan, 43 patients had raised ALT or AST; one patient with critical COVID-19 had severe hepatitis with serum ALT increased up to 7590 U/L [6].

While the mechanism of liver injury is not fully understood, the injury can be due to:

1. Direct viral infection and cellular injury
2. Immune-related injury
3. Drug hepatotoxicity

There is also suggestion that the virus may bind to cholangiocytes through the ACE2 receptor to dysregulate the liver function. Notably, histological examination of the liver biopsy from a deceased COVID-19 patient showed microvesicular steatosis and mild lobular activity. These histological changes could be caused by SARS-CoV-2 infection or drug-induced liver injury. Nevertheless, no viral inclusion was observed in the liver.

Moreover various drugs used for treatment of COVID-19 like Remdesivir, Tocilizumab, Favipiravir, and rarely Hydroxychloroquine can cause elevations in ALT levels, but clinically apparent liver injury with jaundice seem to be rare.

COVID-19 and Chronic Liver Disease

While pre-existing liver disease is not specifically listed in the published cohort studies, elevated alanine aminotransferase (ALT) levels, reduced platelet counts and reduced albumin levels at the time of admission have been associated with higher mortality, although not all of these alterations are independent risk factors. Possibly, patients with advanced chronic liver disease are at increased risk of infection due to cirrhosis-associated immune dysfunction. The same could be true for patients after liver transplantation and possibly those with autoimmune liver diseases who receive immunosuppressive therapies and dose reductions should be considered under special circumstances (e.g. Medication-induced lymphopenia, or bacterial/fungal superinfection in case of severe COVID-19). Patients with non-alcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH) may suffer from metabolic comorbidities such as diabetes, hypertension and obesity putting them at increased risk of a severe course of COVID-19 [7].

COVID-19 and Inflammatory Bowel Disease (IBD)

Despite the potential for increased exposure to SARS-CoV-2, the limited available data and expert opinion suggest that patients with IBD do not appear to have a baseline increased risk of infection with SARS-CoV-2 or development of COVID-19. It is unclear whether inflammation of the bowel per se is a risk for infection with SARS-CoV-2, but it is sensible that patients with IBD should maintain remission in order to reduce the risk of relapse and need for more intense medical therapy or hospitalization. The general recommendation is to stay on IBD therapies with a goal of sustaining remission, ideally defined as a composite of both symptomatic (clinical) remission and objectively confirmed inflammation control (endoscopic improvement and normalized laboratory values). Patients should be advised to maintain their current regimens and to avoid relapse.

In regard to the IBD therapies for patients who develop active COVID-19 illness, aminosalicylates, topical rectal therapy, dietary management, and antibiotics are considered safe and may be continued. Oral budesonide is likely safe as well and can continue if it is needed for ongoing control of the IBD. Systemic corticosteroids should be avoided and discontinued quickly, if possible, with appropriate caution if there is a concern for adrenal insufficiency from chronic corticosteroid use. Thiopurines, methotrexate, and tofacitinib should be discontinued during the acute illness. Anti-TNF therapies and ustekinumab should also be held during the viral illness. It is uncertain if holding vedolizumab was necessary in this situation, but in a patient whose IBD is stable, holding it during the time of viral illness is appropriate. The severity of the COVID-19 and the severity of the IBD should result in careful risk-benefit assessments regarding treatments for COVID-19 and escalating treatments for IBD [8].

COVID-19 and Endoscopy

All endoscopic procedures should be considered aerosol-generating procedures (AGPs). Coughing and retching can occur during upper endoscopy, generating aerosols. Likewise, patients undergoing colonoscopy may pass flatus. Positive insufflation during endoscopic procedures could pose a risk of generating aerosol and increase the risk of SARS-CoV-2 transmission. Patient-contaminated fluids often splatter when inserting or removing an accessory from the endoscope's working channel, adjusting the air/water button, retrieving tissue from a biopsy sample bottle, and performing precleaning. Patient's saliva can contaminate the pillow or the bed, and stool mixed with water often drips to the bed during colonoscopy [9]. Considering these risks, it is recommended to consider only emergency and urgent endoscopy procedures till the current threat owing to COVID-19 is over. Routine endoscopic procedures can be postponed, unless a change in a patient's clinical status mandates an emergency or urgent endoscopy in the intervening period [10].

Conclusion

In conclusion, gastrointestinal symptoms and liver injury are not uncommon in patients with COVID-19.

Compared with patients with non-severe disease, those with severe COVID-19 have a higher risk of developing gastrointestinal symptoms and liver injury. Children with COVID-19 have a similar risk of gastrointestinal symptoms to that of adult patients. A tenth of patients with COVID-19 might present only with gastrointestinal symptoms without respiratory symptoms; such patients could have delayed diagnosis. Patients with gastrointestinal symptoms have a tendency to develop severe or critical disease and have a poor disease course. Moreover, patients with pre- existing gastrointestinal disease like chronic liver disease and IBD who develop COVID-19 disease require special consideration in view of complex interplay between them and might require drug and dose modification for both COVID-19 and gastrointestinal disease. While more studies are needed to completely understand the interaction between COVID-19 and gastrointestinal system, the current understanding would necessitate a need to consider several clinical policies, such as evaluation of role of incorporation of rectal swab testing before discharging patients, keeping high degree of suspicion for COVID-19 among patients who present only with gastrointestinal symptoms and monitoring them for development of respiratory symptoms, as well as preparedness for personal protective equipment in the endoscopy setting.

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