Gastrointestinal manifestations in COVID-19

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Coronavirus disease 2019 (COVID-19), a respiratory viral infection, has affected more than 78 million individuals worldwide as of the end of December 2020. Previous studies reported that severe acute respiratory syndrome coronavirus 1 and Middle East respiratory syndrome–related coronavirus infections may affect the gastrointestinal (GI) system. In this review we outline the important GI manifestations of COVID-19 and discuss the possible underlying pathophysiological mechanisms and their diagnosis and management. GI manifestations are reported in 11.4–61.1% of individuals with COVID-19, with variable onset and severity. The majority of COVID-19–associated GI symptoms are mild and self-limiting and include anorexia, diarrhoea, nausea, vomiting and abdominal pain/discomfort. A minority of patients present with an acute abdomen with aetiologies such as acute pancreatitis, acute appendicitis, intestinal obstruction, bowel ischaemia, haemoperitoneum or abdominal compartment syndrome. Severe acute respiratory syndrome coronavirus 2 RNA has been found in biopsies from all parts of the alimentary canal. Involvement of the GI tract may be due to direct viral injury and/or an inflammatory immune response and may lead to malabsorption, an imbalance in intestinal secretions and gut mucosal integrity and activation of the enteric nervous system. Supportive and symptomatic care is the mainstay of therapy. However, a minority may require surgical or endoscopic treatment for acute abdomen and GI bleeding.

Keywords: COVID-19, diarrhoea, gastrointestinal manifestations, inflammatory bowel disease, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is currently a pandemic and as of 26 December 2020 there have been >79 million cases worldwide and >1.7 million deaths. Several vaccines have been developed to control the pandemic. The earliest record of coronavirus infections among animals was in the late 1920s, where acute respiratory infections occurred in domesticated chickens in North America. Human coronaviruses were discovered in the 1960s and presently seven strains cause disease. Human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), human coronavirus 229E (HCoV-229E) and human coronavirus NL63 (HCoV-NL63) cause mild disease, while the severe acute respiratory syndrome coronavirus (SARS-CoV-1), Middle East respiratory syndrome–related coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may potentially cause severe disease. Outbreaks of SARS-CoV-1 and MERS-CoV infections occurred in 2002 and 2012, respectively. SARS-CoV-2 has 70% and 40% genetic sequence similarity with SARS-CoV-1 and MERS-CoV. Although fever and respiratory symptoms predominate in coronavirus infections, gastrointestinal (GI) manifestations were seen in SARS-CoV-1, MERS-CoV and SARS-CoV-2 patients (Table 1). Herein we outline the important GI manifestations of COVID-19 and discuss the possible mechanisms and aspects relating to their diagnosis and management.

Literature search

We searched the PubMed, Google Scholar and Clinical Trials databases from 1 January 2020 to 30 December 2020 for articles that describe the GI effects of COVID-19 using the search terms ‘COVID-19 and gastrointestinal tract’, ‘COVID-19 and gastrointestinal symptoms’, ‘COVID-19 and upper gastrointestinal tract’, ‘COVID-19 and lower gastrointestinal tract’, ‘COVID-19 and gastrointestinal inflammation’, ‘SARS-CoV-2 and gastrointestinal tract’, ‘COVID-19 and stool RNA’, ‘gut microbiome and COVID-19’, ‘management of COVID-19’, ‘gastrointestinal tract and coronaviruses’, ‘COVID-19 and GI manifestations’, ‘treatment of COVID-19’ and ‘gastrointestinal side effects and COVID-19’. The article title and abstract were read for the initial selection and
Table 1. GI involvement in SARS-CoV-1, MERS and COVID-19

| Disease | SARS-CoV-1 | MERS | COVID-19 |
|---------|------------|------|----------|
| Start of outbreak | 2002 | 2012 | 2019 |
| Virus | SARS-CoV-1 | MERS-CoV | SARS-CoV-2 |
| Origin | bat → civets; China, Guangdong Province | bat → camels; Saudi Arabia | bat → unknown; China, Wuhan Province |
| GI symptoms | Diarrhoea, 16–73%; Nausea and vomiting, 20–35% | Diarrhoea, 25%; Nausea, 14%; Vomiting, 8% | Abdominal pain/discomfort, 4.4% |
| Time of onset of diarrhoea | Onset or during illness | Onset or during illness | Onset or during illness |
| RNA shedding in stools | Maximum duration 126 d | Seen in 14.6% of patients | Mean duration 17.2 d |
| Stool RT-PCR positive rate from the time of diagnosis | 47% week 1; 97% week 2; 54% week 3 | 16% week 1; 14% week 2; NA week 3 | 25% week 1; 37.5% week 2; NA week 3 |
| Viral load (log10 copies/mL or CT value) | 6.52 week 1; 7.95 week 2 | 4.5 week 1; 4 week 2 | 31.65 CT week 1; 26.5 CT week 2 |
| Entry receptor | ACE2 receptor | DPP4 receptor | Intestines: mucosal damage in oesophagus with multiple round herpetic erosions and ulcers and numerous infiltrating plasma cells and lymphocytes as well as interstitial oedema in the lamina propria of the stomach, duodenum and rectum |
| Pathology | Intestines: no obvious pathological changes/non-specific changes; depletion of mucosal lymphoid tissue | Intestines: no obvious pathological changes reported | Intestines: mucosal damage in oesophagus with multiple round herpetic erosions and ulcers and numerous infiltrating plasma cells and lymphocytes as well as interstitial oedema in the lamina propria of the stomach, duodenum and rectum |

CT value: cycle threshold value; DPP4: dipeptidyl peptidase-4; NA: not applicable.

then the full-text article was read. Reference lists of the full-text articles were scanned to identify any additional studies. All types of research articles, including original research articles, reviews, case series, short communications and case reports were considered. A total of 244 full-text articles were assessed for eligibility and 87 were included in this review (Figure 1).

Coronaviruses and the gastrointestinal system

There are two genera of human coronaviruses: alpha (HCoV-229E and HCoV-NL63) and beta (HCoV-HKU1, HCoV-OC43, SARS-CoV-1, MERS-CoV and SARS-CoV-2). SARS-CoV-2 and SARS-CoV-1 have high degrees of genomic similarity and use angiotensin-converting enzyme 2 (ACE2) as an entry receptor. There is comparatively more literature on the GI effects of SARS-CoV-1 and MERS-CoV than the other coronaviruses. This may be due to differential levels of GI involvement by these coronaviruses.

HCoV-NL63 and HCoV-HKU1

Early studies found coronavirus-like particles in intestinal lesions and the stools of infants with necrotizing enterocolitis. Esper et al. identified HCoV-HKU1 in stool samples from children and adults with GI disease. No stool samples were positive for HCoV-NL63, HCoV-229E or HCoV-OC43. In a study by Vabret et al. in France, of six HCoV-HKU1-infected individuals, three were admitted to hospital for acute enteric disease and HCoV-HKU1 was detected in stool samples in two of them. Studies done by Kanwar et al. and Kumthip et al. found HCoV-HKU1 caused GI
symptoms (diarrhoea, vomiting, nausea and abdominal pain) in up to 57% and 38% of infected individuals, respectively. Bouvier et al.29 noted that among otherwise healthy adolescents and adults, HCoV-HKU1-related GI symptoms tend to occur on the fourth day of illness.

**SARS-CoV-1**

During the SARS-CoV-1 outbreak, 30–70% of patients had GI involvement.17 In a small study, Srikantiah et al.30 found vomiting and diarrhoea in 63% and 75%, respectively, of SARS-CoV-1-infected patients. Hui et al.13 found nausea/vomiting (20–35%) and diarrhoea (20–25%) to be the common GI manifestations. On day 14 of illness, the positivity rates of SARS-CoV-1 in urine, nasopharyngeal aspirate and faeces were 42%, 68% and 97%, respectively. Other studies found diarrhoea in up to 25% of patients.31–33 Chan et al.34 found 5.8% of their patients had fever and diarrhoea (mainly watery without blood or mucus) as the presenting symptom.

**MERS-CoV**

MERS-CoV patients had high levels of GI involvement.35 Zumla et al.36 reported nausea (21%), vomiting (21–33%) and diarrhoea (26–33%) in MERS-CoV patients. Abdullah et al.37 noted GI manifestations in 35% of patients they studied in eastern Saudi Arabia.

**Gastrointestinal manifestations in COVID-19**

GI manifestations are reported in 11.4–61.1% of individuals with COVID-19. The majority of COVID-19-associated GI symptoms are mild and self-limiting and include anorexia, diarrhoea, nausea, vomiting and abdominal pain/discomfort (Table 2).15,16,21,22,38–60 In some studies, anorexia and diarrhoea were the most common GI symptoms,61 while in others nausea and vomiting were more prominent.44 Although Han et al.15 found COVID-19-associated GI symptoms to be more common in females (65.7% vs 51.1%), no other studies have found such a pattern.

**Diarrhoea**

Diarrhoea has been reported in 2–50% of cases62 and was found to be more common in severe disease (moderate 69.2%, severe 100%).16 Han et al.15 found 20% of their patients experienced diarrhoea as a first symptom, while in the rest it occurred up to 10 d after the onset of respiratory symptoms. A majority of patients are reported to have had non-severe, non-dehydrating,
Table 2. Clinical characteristics of patients with COVID-19 and GI manifestations

| First author, year (country) | Article type | Total no of patients | Average age (years) | Patients with GI symptoms, n (%) | GI symptoms, n (%) | Other findings |
|-----------------------------|--------------|----------------------|---------------------|----------------------------------|-------------------|---------------|
|                             |              |                      |                     | Anorexia | Diarrhoea | Nausea or vomiting | Abdominal pain/discomfort | GI/rectal bleeding | Other findings |
| Chen N, 2020 (China)        | RA           | 99                   | 55.5                | 3 (3)    | NA       | 2 (2)             | 1 (1)             | NA              | NA             |
| Chen Y, 2020 (China)        | RA           | 42                   | 52                  | 8 (19)   | NA       | 7 (16.67)         | Nausea: 4 (9.52) Vomiting: 3 (7.14) | 5 (11.9)         | RNA positive in faeces, 28 (66.67%) |
| Guan, 2020 (China)          | RA           | 1099                 | 47                  | 97 (8.8) | NA       | 42 (3.8)          | Nausea or vomiting: 55 (5) | NA              | NA             |
| Han, 2020 (China)           | RA           | 206                  | 62.5                | 117 (56.8) | 102 (49.5) | 67 (32.5) | Vomiting: 24 (11.7) | 9 (4.4) | 19.4% experienced diarrhoea as the first symptom in their illness Concurrent fever was found in 62.4% of patients with a digestive symptom Patients with GI symptoms presented for care later (16 vs 11.6 d; \( p < 0.001 \)) and were more likely to be faecal virus positive (73% vs 14%; \( p < 0.05 \)) |
| First author, year (country) | Article type | Total no of patients | Average age (years) | Patients with GI symptoms, n (%) | GI symptoms, n (%) | Other findings |
|-----------------------------|--------------|----------------------|--------------------|----------------------------------|--------------------|---------------|
| Huang, 2020<sup>41</sup> (China) | RA | 38 | 49 | NA | NA | NA | NA |
| Jin, 2020<sup>42</sup> (China) | RA | 65 | 46.14 | 74 (11.4) | NA | 1 (3) | NA | NA |
| Lin, 2020<sup>43</sup> (China) | RA | 95 | NA | 58 | 17 (17.9) | 23 (24.2) | 2 (2.1) | NA |
| Luo S, 2020<sup>44</sup> (China) | RA | 114 | 53.8 | 183 (16) | 180 (98) | 68 (37) | NA | 45 (25) | NA | Upper GI bleeding 76% Gastric or duodenal ulcers 12% Lower GI bleeding 24% Rectal ulcers 7% |
| Martin, 2020<sup>45</sup> (USA) | RA | 41 | 70.4 | 41 | NA | NA | NA | NA | 41 (33.4) | Occurrence of GI symptoms onset to admission 4 d 10.8% had pre-existing liver disease RNA positive in faeces: 52.4% of patients and it was high among patients with GI symptoms GI symptoms on admission 11.6% Developed during hospitalisation 49.5% |
| First author, year (country) | Article type | Total no of patients | Average age (years) | GI symptoms, n (%) | Other findings |
|-----------------------------|--------------|----------------------|--------------------|-------------------|----------------|
| Mauro, 2020\(^{46}\) (Italy) | RA           | 4871                 | 75                 | 23                | Occurrence of GI symptoms onset to admission 4 d |
|                             |              |                      |                    |                   | Gastric or duodenal ulcer 44% |
|                             |              |                      |                    |                   | Erosive or haemorrhagic gastritis 22% |
|                             |              |                      |                    |                   | Variceal bleeding 6% |
|                             |              |                      |                    |                   | Mallory–Weiss 11% |
|                             |              |                      |                    |                   | Dieulafoy's lesion 11% |
|                             |              |                      |                    |                   | Rebleeding 17% |
| Mo, 2020\(^{47}\) (China)  | RA           | 155                  | 54                 | NA                | NA |
|                             |              |                      |                    | 26 (31.7)         | NA |
|                             |              |                      |                    | 7 (4.5)           | Nausea: 3 (3.7) |
|                             |              |                      |                    |                   | Vomiting: 3 (3.7) |
| Pan, 2020\(^{16}\) (China) | RA           | 204                  | 52.9               | 103 (50.5)        | NA |
|                             |              |                      |                    | 81 (78.6)         | Vomiting: 4 (3.9) |
|                             |              |                      |                    | 35 (34)           | NA |
|                             |              |                      |                    |                   | Nausea: 4 (5) |
|                             |              |                      |                    |                   | Vomiting: 5 (3.6) |
| Seeliger, 2020\(^{21}\) (France) | RA | 5                    | NA                 | NA                | Peritoneal fluid RT-PCR negative in all |
| Shi, 2020\(^{48}\) (China) | RA           | 81                   | 49.5               | NA                | NA |
|                             |              |                      |                    | 1 (1)             | Nausea: 14 (10.1) |
|                             |              |                      |                    |                   | Vomiting: 5 (3.6) |
| Wang, 2020\(^{49}\) (China) | RA           | 138                  | 56                 | NA                | NA |
|                             |              |                      |                    | 55 (39.9)         | NA |
|                             |              |                      |                    | 14 (10.1)         | NA |
|                             |              |                      |                    |                   | Nausea: 14 (10.1) |
|                             |              |                      |                    |                   | Vomiting: 5 (3.6) |
| Xu, 2020\(^{50}\) (China)  | RA           | 62                   | 41                 | NA                | NA |
|                             |              |                      |                    | 3 (8)             | NA |
|                             |              |                      |                    |                   | Nausea: 3 (8) |
|                             |              |                      |                    |                   | Vomiting: 3 (30) |
| Xu, 2020\(^{51}\) (China)  | RA           | 10                   | 12                 | NA                | NA |
|                             |              |                      |                    | 3 (30)            | NA |
|                             |              |                      |                    |                   | Nausea: 3 (17) |
| Young, 2020\(^{52}\) (Singapore) | RA | 18                   | 47                 | NA                | Viral RNA in rectal swabs: 80% remained detectable after nasopharyngeal swabs turned negative |
### Table 2. Continued

| First author, year (country) | Article type | Total no of patients | Average age (years) | Patients with GI symptoms, n (%) | GI symptoms, n (%) |
|-----------------------------|--------------|----------------------|---------------------|----------------------------------|-------------------|
|                             |              |                      |                     | Anorexia | Diarrhoea | Nausea or vomiting | Abdominal pain/discomfort | GI/rectal bleeding | Other findings                      |
| Zhang, 202053 (China)       | RA           | 505                  | 51.2                | 164 (32.5) | 93 (56.7) | 62 (37.8) | Nausea: 27 (16.5) | 17 (10.4) | NA | NA |                      |
| Zhang, 202054 (China)       | RA           | 140                  | 57                  | 55 (39.6)  | 17 (12.2) | 18 (12.9) | Nausea: 24 (17.3) | 8 (5.8)  | NA | Occurrence of GI symptoms onset to admission 8 d |
| Zhou, 202055 (China)        | RA           | 191                  | 56                  | NA        | NA        | 9 (5)      | 7 (4)        | NA        | NA | NA |                      |
| Gadiparthi, 202056 (USA)    | BC           | 3                    | 64                  | 3         | NA        | 1 (33.33) | NA          | NA        | 3 (100) | NA |                      |
| Xiao, 202022 (China)        | BC           | 73                   | 43                  | NA        | NA        | 26 (35.6) | NA          | NA        | NA | NA |                      |
| Case reports               |              |                      |                     |           |           |            |              |           |     |     |                      |
| Aloysius, 202057 (USA)      | CR           | 1                    | 36                  | 1         | NA        | Yes        | Yes         | NA        | NA | GI symptoms onset to admission 8 d |
|                            |              |                      |                     |           |           |            |              |           |     |     | Abdominal signs: epigastric tenderness GI diagnosis: acute pancreatitis complicated with ARDS |
| First author, year (country) | Article type | Total no of patients | Average age (years) | Patients with GI symptoms, n (%) | GI symptoms, n (%) | Other findings |
|-----------------------------|--------------|----------------------|---------------------|---------------------------------|-------------------|---------------|
| Coccolini, 2020<sup>58</sup> (Italy) | CR | 1 | 78 | 1 | NA | NA | NA | GI diagnosis: intestinal obstruction secondary to small bowel volvulus with no perforation or gut ischaemia RNA positive in peritoneal fluids |
| Holshue, 2020<sup>59</sup> (USA) | CR | 1 | 35 | 1 | NA | Yes | Yes | Yes | NA | Occurrence of GI symptoms onset to admission 2 d |
| Hosoda, 2020<sup>60</sup> (Japan) | CR | 1 | 81 | 1 | NA | Yes | NA | Yes | NA | Occurrence of GI symptoms onset to admission 6 d No respiratory symptoms on admission Stool RNA positive until day 15 GI diagnosis: acute enterocolitis without ileus or pneumonia |

BC: brief communication; CR: case report; NA: not available; RA: research article.
low-volume diarrhoea, lasting on average 5.4 d and showing improvement by day 13 of illness.

**Nausea and vomiting**
Luo et al.\(^4\) found high levels of nausea and vomiting following COVID-19, while the incidence was lower in most other studies. A higher incidence of nausea was associated with more severe disease. Patients presenting with nausea, vomiting and diarrhoea are more likely to have fever than those having one of the symptoms alone.\(^5\) Neonates with COVID-19 had vomiting and milk refusal associated with the respiratory symptoms.\(^6\)

**Abdominal pain**
Abdominal pain is found at a lower rate than other GI symptoms but was common among patients receiving intensive care unit (ICU) care.\(^1\) A minority of patients presenting with abdominal pain had an important abdominal cause such as acute pancreatitis, acute appendicitis, intestinal obstruction, small bowel ischaemia, sigmoid ischaemia, haemoperitoneum, haemopneumoperitoneum or abdominal compartment syndrome. Seelinger et al.\(^2\) described seven COVID-19 patients who underwent an emergency surgical procedure due to an acute abdomen.

**Anorexia**
In a meta-analysis of 60 studies, 26.8% had anorexia as the most common symptom\(^3\) and this accounted for difficulties with enteral feeding and maintenance of adequate nutritional status.\(^4\) Furthermore, individuals who later developed refractory pneumonia had a higher incidence of anorexia on admission.\(^5\)

**Other GI manifestations**
Prominent GI symptoms such as bloody diarrhoea are more common in those with severe disease.\(^6\) Constipation and haemorrhagic colitis are other less common GI manifestations.\(^7\) Endoscopic evaluation carried out by Lin et al.\(^8\) in a patient presenting with GI bleeding associated with COVID-19 showed multiple round herpetic erosions and ulcers. Similarly, Seeliger et al.\(^9\) reported ulcerative and ischaemic changes in rectosigmoidoscopy in patients with severe symptoms.

The time of onset of GI symptoms is variable. In some they are present at the start of the illness (before the other clinical manifestations), while in most they develop later. Of the 61.1% of COVID-19 patients with GI symptoms reported by Lin et al.\(^8\), only 11.6% had symptoms on admission to hospital, while the rest developed them later. Those with predominant GI symptoms had significantly later hospital admissions than those with respiratory symptoms (9 vs 7.3 d\(^1\) and 16 vs 11.6 d\(^1\)). There was an associated delay in diagnosis and treatment.\(^1\) The group of patients with predominantly GI symptoms had a significant delay in presenting to hospital and a delay in the diagnosis as well.\(^1\) Their clinical course was stormy and there was a higher incidence of progression to severe disease (needing mechanical ventilation and ICU care) compared with their non-GI counterparts.\(^5\)

**Mechanisms for GI involvement in COVID-19**
SARS-CoV-2 enters host cells through ACE2 receptors.\(^6\) High cell entry efficacy is achieved in three ways: high binding affinity of the receptor-binding domain (RBD) of the spike protein, evasion of the host immune system by reduced exposure of the RBD to the outside and Furin protease activation of the virus before entry into host cells, thus reducing its dependence on target cell proteases such as transmembrane protease, serine 2 (TMPRSS2).\(^7\)

Upon viral binding, the ACE2 receptor and virus are endocytosed, leading to a reduction in cell surface ACE2 levels.

**ACE2 receptor expression**
The ACE2 receptor is expressed in both hollow and solid intestinal organs. ACE2 messenger RNA (mRNA) is highly expressed in the GI tract and is stabilized by the neutral amino acid transporter B0AT1 (SLC6A19), found in the intestinal epithelium.\(^8\) In gut epithelial cells, ACE2 is needed for maintaining amino acid homeostasis, antimicrobial peptide expression and the ecology of the gut microbiome. Thus a reduction of ACE2 may interrupt these processes and increase inflammation.

A study using single-cell transcriptomics found elevated ACE2 expression in the upper oesophagus.\(^9\) However, in a different case–control study, decreased expression of ACE2 and nucleocapsid proteins were found in the oesophagus by immunohistochemistry.\(^10\) Such discrepant results may be due to patient or assay-related variations and ACE2 mRNA expression patterns may differ from its protein expression due to post-translational modification. Oesophageal bleeding with erosions is noted in some severe COVID-19 patients and may be due to high expression of ACE2 in stratified epithelial cells.\(^11\) SARS-CoV-2 is usually not found in the stomach and this may be because of the highly acidic environment. ACE2 expression has been noted in the lamina propria and enterocytes of the stomach. Thus, although the virus is able to infect cells in the stomach, the low pH may be
SARS-CoV-2 RNA is found in saliva and may play an important role in human-to-human viral transmission. Viral loads in saliva decline with persistence of the disease. Saliva may be used for viral detection during the acute phase and has some advantages over nasopharyngeal swabs such as ease of sampling, less risk to healthcare workers and lower cost.

Oesophagus, stomach and small and large intestines
SARS-CoV-2 RNA has been found in biopsies from the oesophagus, stomach, duodenum and rectum. Involvement of the GI tract during COVID-19 may be due to direct viral injury and/or an inflammatory immune response and may lead to malabsorption, an imbalance in intestinal secretions and activation of the enteric nervous system. Entry of SARS-CoV-2 into host cells may trigger an inflammatory response. This leads to recruitment of T-helper cells, a cytokine storm and organ damage. Individuals with diabetes are more susceptible to cytokine storm effects of COVID-19. Virus-induced diarrhoea may be due to an alteration of intestinal permeability leading to enterocyte malabsorption. Anal swabs have been reported to be persistently RT-PCR positive for SARS-CoV-2, even after throat swabs become negative. Positivity rates are higher among asymptomatic children, and this would have implications for its transmission potential.

Histological changes in the GI tract and viral particles on ultrastructure
Histology shows occasional lymphocyte infiltration in the oesophagus and partial epithelial degradation, necrosis and mucosal shedding in the stomach. There is dilation and congestion of small blood vessels and oedema of the lamina propria and submucosa of the stomach and small intestine. Immune cell (lymphocytes, monocytes and plasma cells) infiltration is observed in the stomach and intestines. In human small intestinal organoids, enterocytes are readily infected by SARS-CoV-2, as demonstrated by confocal and electron microscopy. The studies demonstrate that intestinal epithelium supports SARS-CoV-2 replication.

Stool viral RNA in COVID-19
SARS-CoV-2 viral shedding may occur through faeces. Chen et al. did not find an association between stool viral RNA positivity and GI symptoms. Of 42 COVID-19 patients, 66.7% had SARS-CoV-2 RNA in their faeces but only 19% had GI symptoms. However, patients presenting with digestive symptoms are more likely to be faecal viral RNA positive than those with respiratory symptoms (73.3% vs 14.3%). Patients with digestive symptoms also take longer to clear the virus from their stools. Zhang et al. found a higher positivity rate of the virus in faeces compared with respiratory samples (83% vs 67%). The virus was present in the stools for a longer period compared with upper respiratory specimens (22 vs 14 d). Chen et al. found faecal shedding to occur for 6–10 d after pharyngeal swabs became negative and a similar pattern was seen among children. The presence of faecal viral RNA does not correlate with disease severity. The longer positivity of viral RNA in the stools of patients with digestive symptoms compared with those with only respiratory symptoms may be due to the high viral load in such patients. It may also be due to direct viral infectivity of the GI tract. Medications such as corticosteroids affect viral clearance. Ling et al. found a significant delay in the viral clearance from faeces compared with oropharyngeal swabs (20 vs 11 d) in patients who received corticosteroids.

Viral proliferation in the digestive tract may increase the risk of faecal–oral transmission. However, the presence of viral RNA in stools does not correlate with transmissibility, as nucleic acid detection does not differentiate infective from non-infective (dead or antibody-neutralized) viruses. The detection of faecal viral RNA by RT-PCR testing in COVID-19 patients at different time points may be helpful in management (especially so in patients with GI symptoms). It may help with evaluating the effectiveness of treatment and for determining when quarantine may be ended.

Gut microbiome and COVID-19
The gut microbiome may play an important role in COVID-19. As the gut microbiota is known to affect pulmonary health, it may influence the pathogenesis of SARS-CoV-2 infections. Furthermore, respiratory infections are known to cause a change in the composition of the gut microbiota. Increased mortality and morbidity from COVID-19 is associated with the elderly, those with comorbidities such as diabetes and obesity and immunocompromised individuals. These groups of individuals are known to have an impaired gut microbiome structure and function. SARS-CoV-2 infections may further disturb the commensal microbe composition in the gut and lead to gut dysbiosis. The dysbiosis may cause increased cytokine levels, systemic inflammation and exaggerated immune responses. Factors released during systemic inflammation, such as C-reactive protein, are related to the severity of COVID-19. Gou et al. reported that around 20 blood proteins are associated with COVID-19.

A study done in Hong Kong characterised the gut microbiome alterations in COVID-19. An abundance of Coprobacillus, Clostridium ramosum and Clostridium hathewayi correlated with COVID-19 severity, while the abundance of Faecalibacterium prausnitzii (an anti-inflammatory bacterium) showed an inverse correlation. Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis and Bacteroides ovatus were associated with low faecal SARS-CoV-2 viral loads. Detailed characterisation of the gut microbiome may be useful in predicting disease severity in COVID-19 and large prospective studies are needed to explore this aspect further. The use of probiotics or prebiotics may help re-establish a more normal gut microbiota. Adequate dietary intake of high-quality proteins, vitamin A and branched chain fatty acids may increase the production of antibodies. Consumption of dietary components with known anti-inflammatory and antioxidant properties (omega-3, vitamin C, vitamin E and ...
phytochemicals such as carotenoids and polyphenols) may help blunt an exaggerated inflammatory response and thus prevent dysregulated immune-mediated damage. Low vitamin D levels increase susceptibility to severe disease and death. Adequate fibre intake reduces the relative risk of mortality from infectious and respiratory diseases by 20–40% and is associated with a lower risk of chronic obstructive pulmonary disease.58

Segal et al.89 found the gut microbiota influences GI ACE-2 receptor expression and thus may play a role in influencing COVID-19 infectivity and disease severity. A study done in India found diet plays a crucial role in modulating the gut microbiota. The authors suggested a plant-based, fibre-rich diet may be advantageous during this pandemic, as it helps replenish the host gut microbiota, leading to various health benefits including enhanced immunity.90 Van der Lelie et al.91 have discussed the ‘gut–lung axis,’ where the gut microbiota composition influences lung susceptibility to viral infections and viral infections of the lung alter the gut microbiota composition toward a pro-inflammatory and dysbiotic state. Such dysregulation may influence disease progression and the risk of developing complications. The gut microbiota could influence immune responses and thus affect COVID-19 disease progression. Both overactive and underactive immune responses may lead to clinical complications in COVID-19. Safe and inexpensive prebiotics and probiotics should be considered as adjunctive treatment to limit COVID-19 progression in infected patients or as a preventive strategy in non-infected persons at risk.92

Management of COVID-19-related GI manifestations

Diagnostic aspects

Most GI manifestations in patients with COVID-19 are mild and self-limiting.93 In such patients, no further investigations specific to the GI system are needed. Routine endoscopy is not useful in the diagnosis of mild disease and should be performed cautiously due to the risk of exposure of healthcare workers. Mild cases have a normal endoscopy, but in one study, endoscopic biopsy showed plasma cells and lymphocytes in the lamina propria of the stomach, duodenum and rectum despite having a macroscopically normal GI epithelium.22 Endoscopy is useful in selected patients with GI bleeding for both diagnostic and therapeutic purposes. Lin et al.43 found multiple round herpetic erosions and ulcers in the oesophagus. Martin et al.45 found gastric or duodenal ulcers in 80% of endoscopies for upper GI bleeding and rectal ulcers in 60% of endoscopies when there was lower GI bleeding. Mauro et al.46 described 11 patients who had active peptic ulcers, erosive gastritis and bleeding from gastro-oesophageal varices. A summary of the reported investigation findings and treatments used are provided in Table 3.15,16,21,22,38–60 Although stool RT-PCR, peritoneal biopsies and peritoneal fluid RNA tests have been performed, their usefulness in management is limited. Selected patients with abdominal manifestations such as acute abdomen and peritonitis should have an abdominal computed tomography scan and angiogram. The reported positive findings include small bowel volvulus, acute enterocolitis, splenic flexure contrast extravasation, acute appendicitis, haemoperitoneum and haemopneumoperitoneum. As there are no accepted protocols for investigation of GI manifestations in COVID-19, the decision should be made based on individual circumstances considering the therapeutic benefit of the intervention and the potential risk of exposure to healthcare workers.

Protective measures during endoscopy

Procedures such as upper and lower GI endoscopy should follow the recommended guidelines.94 As positive viral RNA is seen in the oesophagus, stomach, duodenum and rectum, endoscopic procedures warrant extra precautions to ensure the safety of staff and prevent cross-contamination and nosocomial outbreaks among patients. During the COVID-19 pandemic, specific infection control guidelines have been implemented in different countries for endoscopic procedures.94 Endoscopies should be performed only after clinical discussion and should be considered when it is essential for reaching a therapeutic decision that cannot be made using other non-invasive tests.

General measures and universal precautions

Human-to-human transmission of SARS-CoV-2 occurs mainly through the respiratory tract via infected droplets/aerosols. Contact with contaminated surfaces is another possible mode of transmission. Thus wearing proper face masks, hand hygiene and social distancing are fundamental for infection prevention. Healthcare workers should wear appropriate personal protective equipment. Since the virus is found in stools for varying lengths of time, extra precautions may be needed to avoid faecal–oral transmission. Contact with infected saliva or stools should be avoided. Appropriate infection prevention and control measures should be in place for preventing nosocomial spread. There are case reports of the detection of virus in peritoneal fluid during laparotomy. Therefore adherence to special precautionary infection control measures for preventing aerosolization of the virus during laparoscopic procedures or when using electrocautery in open procedures should be considered.58

Supportive measures

As most virus-induced GI manifestations are mild and self-limiting, supportive care and symptomatic treatment are usually sufficient.95–98 Supportive treatment with oxygen, optimal hydration, analgesics and anti-emetics may be necessary.99 Although studies are limited, endoscopy in selected patients has shown ulceration and bleeding. Avoidance of non-steroidal anti-inflammatory drugs (NSAIDs) and gastric acid prophylaxis should be considered in patients with GI manifestations. Those with paralytic ileus or excessive vomiting may require nasogastric tube decompression and nothing by mouth. Patients with diarrhoea need appropriate rehydration therapy and anti-diarrheal medications. Those with GI manifestations have increased rates of electrolyte disturbance62 and thus regular monitoring and correction of electrolytes is needed and medications that may induce electrolyte imbalance should be administered with caution. Those with severe GI manifestations or acute abdomen should be managed by a specialised multidisciplinary team including a physician, critical care specialist, nutritionist, gastroenterologist and surgeon.
| First author, year (country) | Article type | Total patients, N | Imaging | Endoscopy | Pathology | General management and nutrition | Drugs specific for GI manifestations | Complications and surgical management | Outcome of GI manifestations and follow-up data |
|-----------------------------|--------------|------------------|---------|-----------|-----------|-----------------------------------|-------------------------------------|-----------------------------------------|------------------------------------------|
| Chen, 2020<sup>38</sup> (China) | RA           | 99               | NA      | NA        | NA        | NA                                | No                                  | No                                      | NA                                       |
| Chen, 2020<sup>39</sup> (China) | RA           | 42               | NA      | NA        | NA        | NA                                | NA                                  | No                                      | NA                                       |
| Guan, 2020<sup>40</sup> (China) | RA           | 1099             | NA      | NA        | NA        | NA                                | NA                                  | No                                      | NA                                       |
| Han, 2020<sup>15</sup> (China) | RA           | 206              | NA      | NA        | Direct invasion of virus through the intestinal mucosa | NA                                | NA                                  | No                                      | Recovered/discharged: 100% |
| Huang, 2020<sup>41</sup> (China) | RA           | 41               | NA      | NA        | NA        | NA                                | NA                                  | No                                      | NA                                       |
| Jin, 2020<sup>42</sup> (China) | RA           | 651              | NA      | NA        | NA        | NA                                | NA                                  | No                                      | ARDS 6.76%                                |

Shock 1.35%
Liver injury 17.57%
Mechanical ventilation 6.76%
ICU care 6.76%
Death 1.35%
| First author, year (country) | Article type | Total patients, N | Imaging | Endoscopy | Pathology | General management and nutrition | Drugs specific for GI manifestations | Complications and surgical management | Outcome of GI manifestations and follow-up data |
|-----------------------------|--------------|-------------------|---------|-----------|-----------|---------------------------------|---------------------------------|---------------------------------|----------------------------------------|
| Lin, 202043 (China)         | RA           | 96                | NA      | In patients with GI bleeding, source of bleeding localised to the oesophagus by endoscopy at a distance of 26 cm from incisors | Multiple round herpetic erosions and ulcers in the oesophagus with a diameter of 4–6 mm | NA | NA | No | In hospital 61.1% Discharged 38.9% |
| Luo, 202044 (China)         | RA           | 1141              | NA      | NA        | NA        | NA | NA | NA | Recovered 96.2% Death 3.8% |
| Martin, 202045 (USA)        | RA           | 41                | UGIB, NG| UGIB, esophagastroduodenoscopy (32%); treated with epinephrine injection, endoclips or cautery in 40% | UGIB, gastric/duodenal ulcers in 80% of endoscopies | Blood transfusion and monitoring | UGIB, high-dose PPIs | GI bleeding (upper 31, lower 10) requiring blood transfusion | ICU care 46% |
|                            |              |                   |         | LGIB, CT angiogram in 1 patient =>active extravasation at splenic flexure but angiography was negative | LGIB, flexible sigmoidoscopy or colonoscopy (50%) | LGIB, rectal ulcers in 60% of endoscopies | LGIB, NA | Mechanical ventilation 46% | Death 27% |
| First author, year (country) | Article type | Total patients, N | Imaging | Endoscopy | Pathology | General management and nutrition | Drugs specific for GI manifestations | Complications and surgical management | Outcome of GI manifestations and follow-up data |
|-----------------------------|--------------|-------------------|---------|-----------|-----------|---------------------------------|-------------------------------------|----------------------------------------|---------------------------------------------|
| Mauro, 202046 (Italy)       | RA           | 4871              | UGIE in 11 patients; treated with adrenaline injection and clips in 5, cyanoacrylate gel in 1 | UGIB, active peptic ulcers (44%), erosive or haemorrhagic gastritis (22%), variceal bleeding from gastro-oesophageal varices (4.5%) | Blood transfusion and monitoring | High-dose PPIs | Upper GI bleeding in 23 patients | Discharged 78% |
| Mo, 202047 (China)          | RA           | 155               | NA      | NA        | NA        | NA                              | NA                                  | NA                                    | NA                                           |
| Pan, 202016 (China)         | RA           | 204               | NA      | NA        | NA        | NA                              | No                                  | No                                     | Recovered 81.55% |
| Seeliger, 202021 (France)   | RA           | 7                 | CT abdomen, small bowel ischaemia, appendicitis, sigmoid ischaemia, haemoperitoneum, haemopneumoperitoneum and stab wound in liver | Sigmoidoscopy, ulcerative and ischaemic changes | Small bowel ischaemia, appendicitis, sigmoid ischaemia, haemoperitoneum, haemopneumoperitoneum and stab wound in liver | NA                              | NA                                  | Complications, small bowel ischaemia, sigmoid ischaemia, haemoperitoneum, haemopneumoperitoneum, abdominal compartment syndrome | Recovered/discharged 40% |
| First author, year (country) | Article type | Total patients, N | Imaging | Endoscopy | Pathology | General management and nutrition | Drugs specific for GI manifestations | Complications and surgical management | Outcome of GI manifestations and follow-up data |
|-----------------------------|-------------|------------------|---------|-----------|-----------|-------------------------------|-----------------------------------|------------------------------------|--------------------------------------|
| Shi, 2020 (China)           | RA          | 81               | NA      | NA        | NA        | NA                            | NA                                | NA                                 | NA                                   |
| Wang, 2020 (China)          | RA          | 138              | NA      | NA        | NA        | NA                            | NA                                | NA                                 | NA                                   |
| Xu, 2020 (China)            | RA          | 62               | NA      | NA        | NA        | NA                            | NA                                | NA                                 | NA                                   |
| Xu, 2020 (China)            | RA          | 10               | NA      | NA        | NA        | NA                            | NA                                | NA                                 | NA                                   |
| Young, 2020 (Singapore)     | RA          | 18               | NA      | NA        | NA        | NA                            | NA                                | NA                                 | Recovered/discharged 100% Mechanical ventilation 0 ICU care 0 |
| Zhang, 2020 (China)         | RA          | 505              | NA      | NA        | NA        | NA                            | NA                                | NA                                 | NA                                   |
| First author, year (country) | Article type | Total patients, N | Imaging | Endoscopy | Pathology | General management and nutrition | Drugs specific for GI manifestations | Complications and surgical management | Outcome of GI manifestations and follow-up data |
|-----------------------------|--------------|------------------|---------|-----------|-----------|---------------------------------|---------------------------------|---------------------------------|----------------------------------------------|
| Zhang, 2020 (China)         | RA           | 140              | NA      | NA        | NA        | NA                              | NA                              | NA                              | NA                                           |
| Zhou, 2020 (China)          | RA           | 191              | NA      | NA        | NA        | NA                              | NA                              | NA                              | NA                                           |
| Gadiparthi, 2020 (USA)      | BC           | 3                | Patient 1, not done | Not done | Patient 1, possibly from an anastomotic ischaemic ulcer from previous Roux-end-Y gastric bypass | Conservative management with blood transfusion and monitoring | All 3 patients were given high-dose PPIs | Complications, GI bleeding requiring blood transfusion | Recovered/discharged 33.3% |
|                             |              |                  |         |           |           |                                 |                                 |                                 |                                 |
|                             |              |                  | Patient 2, CT angiogram did not localize the bleeding vessel | Patient 2, gastroduodenal bleeding | Patient 3 underwent a faecal management system for large volume watery diarrhoea | No surgical management | Patient 3, rectal ulcer or direct trauma from faecal management system | Death 66.7% |                                 |
|                             |              |                  |         |           |           |                                 |                                 |                                 |                                 |
### Table 3. Continued

| First author, year (country) | Article type | Total patients, N | Imaging | Endoscopy | Pathology | General management and nutrition | Drugs specific for GI manifestations | Complications and surgical management | Outcome of GI manifestations and follow-up data |
|-----------------------------|--------------|--------------------|---------|-----------|-----------|---------------------------------|--------------------------------|---------------------------------|--------------------------------------------------|
| Xiao, 2020<sup>22</sup> (China) | BC           | 73                 | NA      | Mucous epithelium of oesophagus, stomach, duodenum and rectum showed no significant damage | Infiltration of occasional lymphocytes in oesophageal squamous epithelium. In lamina propria of stomach, duodenum and rectum, numerous infiltrating plasma cells and lymphocytes seen with interstitial oedema. Positive staining of GI epithelium for ACE2 and viral RNA | NA                              | NA                              | NA                              | NA                                               |
| Case reports Aloysius, 2020<sup>57</sup> (USA) | CR           | 1                  | CT abdomen, normal gall bladder, normal biliary tract and unremarkable pancreas | NA | ACE2 receptor mediated damage to pancreatic islet cells causing acute pancreatitis | Nothing by mouth, fluid resuscitation (crystalloid) | Analgesia, not specified | No | Recovered/discharged |
|                              |              |                    |         |           |           |                                  |                                  |                                 |                                                  |
| First author, year (country) | Article type | Total patients, N | Imaging | Endoscopy | Pathology | General management and nutrition | Drugs specific for GI manifestations | Complications and surgical management | Outcome of GI manifestations and follow-up data |
|----------------------------|--------------|-------------------|---------|-----------|-----------|---------------------------------|-------------------------------|----------------------------------|-----------------------------------------------|
| Coccolini, 2020 (Italy)    | CR 1         | CT abdomen, intestinal occlusion due to a small bowel volvulus with no signs of gut ischaemia | NA      | NA        | Volvulus due to omental band attached to RIF (past history of open appendectomy 20 years ago). Bowel vital and viable; no perforation, no bowel ischaemia, no colonic diverticula | NA | NA | Complications, intestinal occlusion Surgical management, yes, adhesiolysis without intestinal resection | Recovered                         |
| Holshue, 2020 (USA)       | CR 1         | NA                | NA      | NA        | Normal saline | Ondansetron | No | Recovered                         |
| Hosoda, 2020 (Japan)      | CR 1         | CT abdomen, acute enterocolitis without ileus | NA      | NA        | NA | NA | No | Recovered                         |

ARDS: acute respiratory distress syndrome; BC: brief communication; CR: case report; LGIB: lower gastrointestinal endoscopy; NA: not available; RA: research article; UGIE: upper gastrointestinal endoscopy.
Medications
To date, no specific antiviral medications have been shown to reduce mortality in COVID-19 patients. The antiviral drugs used for treatment of COVID-19 include remdesivir and lopinavir–ritonavir. Remdesivir was shown to reduce hospital stays in patients with severe disease. A myriad of other treatment modalities aimed at symptom control and management of complications have been used. Immunomodulatory agents including glucocorticoids, convalescent plasma and anti-cytokine therapy have been used to reduce the negative effects of the overwhelming systemic inflammatory response. However, except for dexamethasone, the other agents have not shown definite therapeutic benefits, although they may be beneficial in selected subgroups. Moreover, evidence on the efficacy of these agents in treating GI manifestations is limited and further studies are required. There is an ongoing debate about the use of ACE inhibitors and renin–angiotensin–aldosterone system blockers in the treatment of COVID-19. Although beneficial mechanisms such as blocking viral entry into the host cell have been proposed, the clinical significance of these agents is yet to be conclusively proven.

The loss of gut mucosal integrity and dysfunction of intestinal flora are important complications in severe viral illnesses, including COVID-19. The use of probiotics has been suggested to improve GI symptoms of SARS-CoV-2 infection. Irrational use of broad-spectrum antibiotics should be avoided, as they cause the loss of commensal intestinal flora and alteration of gut mucosal integrity. COVID-19 treatment guidelines in China have included the use of probiotics and micro-ecological regulators for maintaining gut mucosal integrity and to minimise secondary bacterial infections.

Nutrition
SARS-CoV-2 patients may have a reduced oral intake due to the severity of their disease or as a side effect of the medicines that are used. Enteral nutrition is important for maintaining gut mucosal integrity, especially in patients with severe disease. In patients with severe disease, specialist nutritional assessment should be done and a high-calorie, immunomodulatory diet should be administered. In patients who are mechanically ventilated, nasogastric or nasojugal tube insertion and enteral feeding is an option. In patients who cannot tolerate enteral feeding, parenteral nutrition should be administered. However, enteral feeding should be commenced early following improvement of the clinical condition.

Surgical measures
Rarely, patients with COVID-19 may present with an acute abdomen either due to a complication of the disease or due to a coexisting pathology. Conditions such as acute pancreatitis and abdominal compartment syndrome have been reported in association with COVID-19. Thus such conditions should be suspected in a deteriorating SARS-CoV-2 patient with an acute abdomen. As thrombotic complications are well-described in SARS-CoV-2 patients, mesenteric thrombosis should be suspected early in a clinically deteriorating patient with acute abdomen and appropriate anticoagulation should be initiated promptly after confirming the diagnosis through imaging. In patients with GI bleeding that does not settle with medical management, therapeutic endoscopy with clipping or cautery has been found to be successful.

Surgical treatment has been reported for conditions such as intestinal obstruction, bowel ischaemia, acute appendicitis and haemoperitoneum/haemopneumoperitoneum in association with SARS-CoV-2 (Table 3). Such cases are extremely rare and require a high degree of clinical suspicion and relevant imaging to reach the diagnosis. Standard surgical procedures have been performed with appropriate personal protective equipment and infection control measures to prevent transmission of infection. Furthermore, in such critically ill patients, postoperative care in an ICU is necessary.

GI side effects of medications used for COVID-19
A number of medications used in patients with COVID-19 have documented GI side effects (Table 4).

Antivirals
Antivirals and antibiotics may cause diarrhoea and alter the gut microbiome. Remdesivir has a number of GI side effects, including nausea, vomiting, gastroparesis and constipation. The antimalarial agents chloroquine/hydroxychloroquine and lopinavir/ritonavir cause nausea, vomiting, loss of appetite and abdominal cramps.

Immunomodulatory agents
Immunomodulatory agents such as corticosteroids can increase the risk of peptic ulceration and GI bleeding. The Janus kinase inhibitor baricitinib can cause diarrhoea. Immunomodulators such as tocilizumab may cause GI bleeding, nausea, vomiting and ulceration. The GI side effects of intravenous immunoglobulins are minimal.

Proton pump inhibitors (PPIs) and COVID-19
The use of PPIs are a risk factor for rotavirus, influenza virus, norovirus and MERS viral infections. Individuals using PPIs once or twice daily had significantly higher odds of a positive COVID-19 test compared with those not taking it. A larger study done by Lee et al. in 14 163 current and 6242 past PPI users with COVID-19 found SARS-CoV-2 test positivity was not associated with current or past use of PPIs. However, current use of PPIs conferred a 79% higher risk of severe clinical outcomes following SARS-CoV-2 infection. In contrast, Ta¸stemur and Ataseven hypothesised that PPI may be used for treatment and prophylaxis of COVID-19, owing to their anti-inflammatory, antioxidant, immunomodulatory and antifibrotic properties.
Table 4. GI side effects of medications used for COVID-19

| Type          | Drug                               | Dosage                                                                 | Administration          | GI side effects                                                                 | References |
|---------------|------------------------------------|------------------------------------------------------------------------|-------------------------|--------------------------------------------------------------------------------|------------|
| Antivirals    | Remdesivir (in phase 3 clinical trials) | Not needing invasive mechanical ventilation/ECMO: 5 d Needs mechanical ventilation or ECMO: 10 d Loading dose 200 mg over 30–120 min on day 1 followed by 100 mg once daily for remaining 4–9 d | Intravenous             | 1–10%: nausea, liver enzyme derangement, hyperbilirubinaemia frequency not known: vomiting, gastroparesis, rectal bleeding | 108–111    |
|               |                                    |                                                                        |                         |                                                                                 |            |
|               | Lopinavir/ritonavir (Kaletra)      | 400/100 mg twice daily or 800/200 mg once daily for 14 d               | Oral (administer with or without food) | 1–10%: abnormal appetite, diarrhoea, nausea, vomiting, dry mouth, GI discomfort, GI disorders, hepatic disorders, pancreatitis 0.1–1%: cholangitis, constipation, hyperbilirubinaemia | 112,113    |
|               |                                    |                                                                        |                         |                                                                                 |            |
|               | Ribavirin (in phase 2 clinical trials) | 400 mg twice daily for 14 d (in clinical trials), dosing not defined   | Oral (administer with food) | 1–10%: decreased appetite, constipation, diarrhoea, nausea, vomiting, dry mouth, GI discomfort, GI disorders, throat pain 0.1–1%: hepatic disorders <0.1%: cholangitis, hepatic failure, pancreatitis; frequency not known: tongue discolouration, ulcerative colitis | 114        |
|               | Oseltamivir                         | 75 mg twice daily for 5 d                                             | Oral                    | 1–10%: hyperuricaemia (5%), diarrhoea (5%), liver enzyme derangement (2%)        | 115,116    |
|               | Arbidol                             | For prevention, 200 mg once a day Therapeutic dose 600 mg/d (200 mg three times/d) for 5 d | Oral                    | 1–10%: nausea, vomiting, GI discomfort <0.1%: GI haemorrhage (children), hepatic disorders | 117        |
|               |                                    |                                                                        |                         |                                                                                 |            |
| Type               | Drug                  | Dosage                                                                 | Administration                  | GI side effects                                                                 | References |
|-------------------|-----------------------|------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------|------------|
| Immunomodulatory  | Interferon-α/β        | Interferon-1β 0.25 mg alternated for 3 d (in clinical trials), dosing not established | Subcutaneous injection         | 1–10%: low appetite, diarrhoea, nausea, vomiting                               | 108        |
|                   |                       |                                                                        |                                | 0.1–1%: hepatic disorders, autoimmune hepatitis                                |            |
|                   |                       |                                                                        |                                | <0.1%: haemolytic uraemic syndrome, pancreatitis                                |            |
|                   |                       |                                                                        |                                | Frequency not known: abdominal pain, constipation                                |            |
|                   | Tocilizumab           | 4–8 mg/kg (maximum 800 mg) over 1 h or 400 mg once                     | Intravenous infusion           | 1–10%: abdominal pain, GI disorders, oral disorders                            | 108        |
|                   |                       | Consider additional dose 8–12 h later if continued clinical decompensation (maximum of 2 doses) |                                | Frequency not known: hepatic disorders                                          |            |
|                   | Sarilumab (Kevzara)   | 400 mg                                                                 | Intravenous                    | 1–10%: liver enzyme derangement                                                 | 119        |
| IL-6 inhibitor    | Baricitinib (completed clinical trial) | 4 mg once daily baricitinib+antiviral therapy administration for 2 weeks | Oral                           | 1–10%: nausea                                                                    | 120,121    |
|                   |                       |                                                                        |                                | Frequency not known: abnormal liver enzymes                                     |            |
|                   | Antiparasitic         | Nitazoxanide 500 mg twice daily (duration not specified)               | Oral (administer with or without food) | 1–10%: abdominal pain (8%), diarrhoea (2%), nausea (3%), vomiting (1%)          | 108        |
|                   |                       |                                                                        |                                | <1%: increased ALT, anorexia, increased appetite, flatulence, salivary gland enlargement |            |
|                   |                       | Chloroquine 500 g twice daily for 10 d                                | Oral (administer with food)    | <0.1%: hepatitis                                                                  | 109        |
|                   |                       |                                                                        |                                | Frequency not known: abdominal pain, GI disorders, nausea, diarrhoea, vomiting, metallic taste |            |
### Table 4. Continued

| Type        | Drug                  | Dosage                                                                 | Administration       | GI side effects                                                                                      | References |
|-------------|-----------------------|------------------------------------------------------------------------|----------------------|---------------------------------------------------------------------------------------------------|------------|
|             | Hydroxychloroquine    | Loading dose of 400 mg twice daily for 1 d, followed by 200 mg twice daily for 4 d | Oral (administer with food) | 1–10%: low appetite, diarrhoea, nausea, vomiting, abdominal pain Frequency not known: acute hepatic failure | 108        |
| Steroids    | Dexamethasone         | 6 mg daily for 7–10 d                                                  | Intravenous          | 1–10%: GI discomfort, peptic ulcer, nausea 0.1–1%: increased appetite, pancreatitis                | 122–124    |
|             | Methylprednisolone    | 0.5–1 mg/kg/day in two divided doses                                    | Intravenous          | 1–10%: GI discomfort, peptic ulcer, nausea 0.1–1%: increased appetite, pancreatitis Frequency not known: diarrhoea, vomiting | 125–127    |
|             | Budesonide            | Levamisole 50–100 mg every 8 h                                         | Oral and inhaled     | 1–10%: GI discomfort, peptic ulcer, nausea 0.1–1%: increased appetite, pancreatitis                | 128        |
|             |                       | Budesonide + formoterol inhaled 1–2 puffs every 12 h                    |                      |                                                                                                   |            |
|             | Immunoglobulins       | IVIG with moxifloxacin 20–25 g/d (0.1–0.5 g/kg/day) for 5–15 d with moxifloxacin | Intravenous          | 1–10%: low appetite, constipation (in adults), diarrhoea, GI discomfort (in adults), nausea, vomiting 0.1–1%: antibiotic-associated colitis (in adults), low appetite (in children), GI discomfort (in children), hepatic disorder, gastritis <0.1%: antibiotic-associated colitis (in children), pancreatitis, abdominal pain | 129,130    |

ALT: alanine transaminase; ECMO: extracorporeal membrane oxygenation.
COVID-19 in patients with diagnosed GI disorders

The presence of comorbidities (including pre-existing digestive disorders) is associated with poor clinical outcome in COVID-19.

Inflammatory bowel disease (IBD)

Chronic inflammatory conditions such as IBD have a theoretical risk of making an individual more susceptible to COVID-19 or to a more severe course of illness. Thus far there has not been definitive evidence for either scenario. Of the patients who contracted COVID-19, the most prominent clinical manifestations were fever and cough, similar to the general population. Diarrhoea was noted in about 20% of patients, making the clinical distinction between disease flare and COVID-19 essential for further management. In those who do not have COVID-19, continuation of biologic therapy for IBD is recommended. However, in those with COVID-19, the severity of the IBD needs to be considered and treatment balanced with the severity of COVID-19.

Bezzio et al. found that active IBD leads to a negative outcome requiring longer hospitalization and assisted ventilation. Treatment did not change this, emphasizing the importance of prevention of acute flares by adherence to therapy. IBD patients > 70 y of age or with other associated comorbidities were at highest risk of complications. IBD patients who are pregnant may have a high risk of COVID-19. A woman in the first trimester with an acute severe ulcerative colitis and COVID-19 suffered an abortion, but the exact reason for this was not clear. Optimal management of IBD in pregnancy during the COVID-19 pandemic is yet to be defined. No or limited use of steroids and the use of cyclosporine and infliximab as salvage therapy on a case-by-case basis has been suggested. Symptomatic anal fistula in Crohn's disease requires proper and timely treatment. Although exploration under anaesthesia is the gold standard for diagnosis, during the COVID-19 pandemic outpatient exploration may be a more suitable option. This would minimize the number of medical personnel required and avoid higher-risk anaesthetic procedures.

GI malignancies

The pandemic has affected multiple steps in the diagnosis and management of GI malignancies. Interruption of endoscopic services due to the increased risk of disease transmission and added cost of infection prevention measures (especially in developing countries) has caused considerable delays in the diagnosis of GI malignancies. Elective cancer therapies and surgeries have been delayed to allow increased capacity for dealing with COVID-19 patients. Such delays may adversely impact optimal care for cancer patients and worsen long-term outcomes. A delay in surgical resection in colorectal cancer worsens the survival rate and studies have found disease progression in patients with pancreatic malignancies. Patients with GI cancers needing frequent hospital visits may be at higher risk of hospital-acquired COVID-19 transmission. Yu et al. studied 1524 cancer patients and found them to have a twofold increased risk of COVID-19 infection when compared with the general population.

Other GI disorders

The outcomes of patients with pancreatitis, celiac disease or irritable bowel syndrome who get COVID-19 have been poorly studied.

Limitations

Limitations of this review include the small number of studies reporting on certain GI manifestations, making it difficult to provide more definitive conclusions on such aspects. It is possible that subtle GI findings were not documented (and thus underestimated) during the early part of the pandemic. Well-conducted studies from different regions of the world will help expand the evidence base and provide better answers to the many questions at hand. Ours is a broad overview of the main reported GI manifestations in COVID-19 and their management. A more comprehensive and detailed profile of specific aspects should emerge as more data are published from different countries.

Future recommendations

During the present pandemic, testing for SARS-CoV-2 should be considered in patients with GI symptoms, irrespective of them not having the other typical symptoms of COVID-19. The long-term effects of the different GI manifestations should become better defined as more studies using GI imaging and histological findings become available. Detailed and systematically conducted histopathology and autopsy studies should shed light on aspects of pathogenesis and pathology that are still undefined.

Conclusions

GI manifestations are an important feature in some COVID-19 patients. The findings reported so far provide us with new and important insights for understanding the GI effects of SARS-CoV-2 and their underlying pathogenesis. Further studies should help with better delineation of the many uncertain aspects of COVID-19 and the GI tract. In this review we outlined the important GI manifestations of COVID-19 and discussed the possible mechanisms and aspects relating to their diagnosis and management.

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