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REVIEW ARTICLE

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.[1] Several vaccines have been developed to control the pandemic.[2] The earliest record of coronavirus infections among animals was in the late 1920s, where acute respiratory infections occurred in domesticated chickens in North America.[3] Human coronaviruses were discovered in the 1960s[4] 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.[5–7] Outbreaks of SARS-CoV-1 and MERS-CoV infections occurred in 2002 and 2012, respectively.[8] SARS-CoV-2 has 70% and 40% genetic sequence similarity with SARS-CoV-1 and MERS-CoV.[9] 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).[8,10–22] 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 COVD-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[10]; China, Guangdong Province	bat → camels[11]; Saudi Arabia	bat → unknown[12] ; China, Wuhan Province
GI symptoms	Diarrhoea, 16–73%[8] Nausea and vomiting, 20–35%[13] Abdominal pain	Diarrhoea, 25%[8] Nausea, 14%[14] Vomiting, 8%[14] Abdominal pain	Diarrhoea, 32.5%[15] Nausea, 11.7%[15] Vomiting, 3.9%[16] Abdominal pain/discomfort, 4.4%[15]
Time of onset of diarrhoea	Onset or during illness[17]	Onset or during illness [8]	Onset or during illness[15]
RNA shedding in stools	Maximum duration 126 d[18]	Seen in 14.6% of patients[14]	Mean duration 17.2 d[18] Maximum duration 126 d[18]
Stool RT-PCR positive rate from the time of diagnosis	47% week 1[19] 97% week 2[19] 54% week 3[19]	16% week 1[19] 14% week 2[19] NA week 3[19]	25% week 1[19] 37.5 week 2[19] NA week 3[19]
Viral load (log10 copies/mL or CT value)	6.52 week 1[19] 7.95 week 2[19] 5.33 week 3[19]	4.5 week 1[19] 4 week 2[19] 0 week 3[19]	31.65 CT week 1[19] 26.5 CT week 2[19] NA week 3[19]
Entry receptor	ACE2 receptor	DPP4 receptor	ACE2 receptor
Pathology	Intestines: no obvious pathological changes/non-specific changes; depletion of mucosal lymphoid tissue[20]	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[21,22]

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.[9] 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.[23,24] Esper et al.[25] 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.[26] 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.[27] and Kumthip et al.[28] found HCoV-HKU1 caused GI

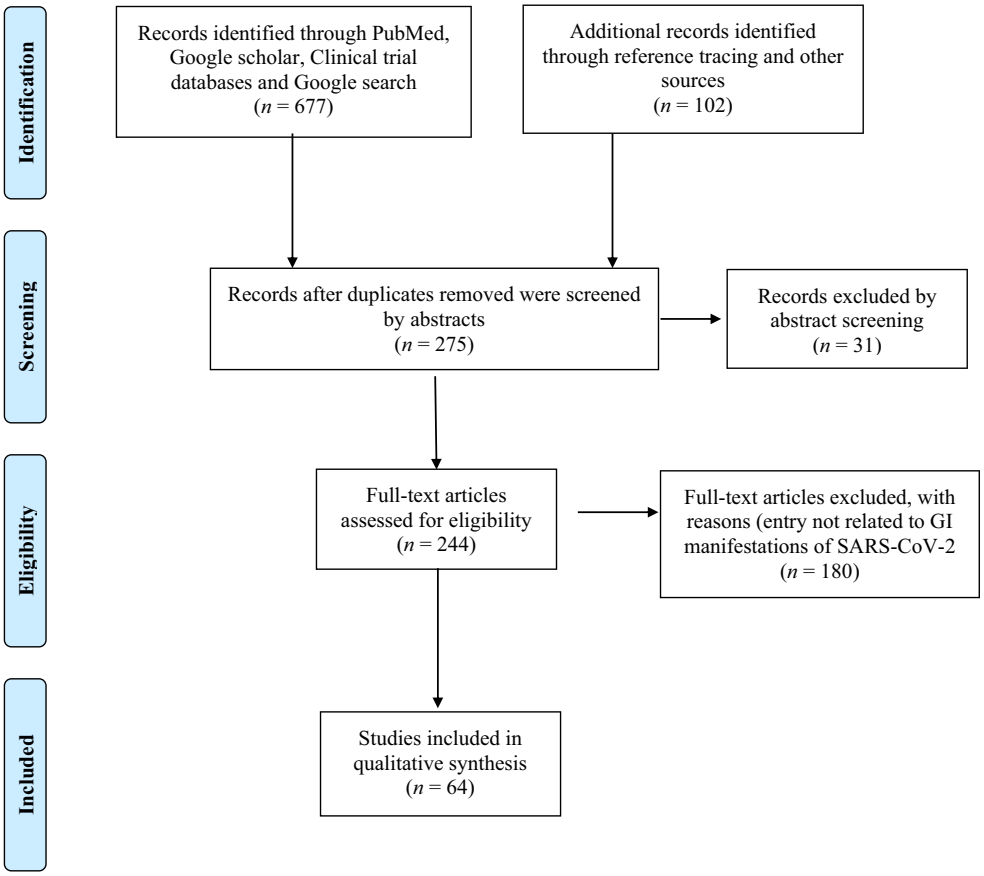

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

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 cases[62] 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	
Chen N, 2020[38] (China)	RA	99	55.5	3 (3)	NA	2 (2)	1 (1)	NA	NA	NA
Chen Y, 2020[39] (China)	RA	42	52	8 (19)	NA	7 (16.67)	Nausea: 4 (9.52) Vomiting: 3 (7.14)	5 (11.9)	NA	RNA positive in faeces, 28 (66.67%) Duration of stool viral shedding after negative conversion in pharyngeal swabs was 7 d (range 6–10) Patients who tested SARS-CoV-2 RNA positive exhibited no higher occurrence rate of GI symptoms or severe disease
Guan, 2020[40] (China)	RA	1099	47	97 (8.8)	NA	42 (3.8)	Nausea or vomiting: 55 (5)	NA	NA	NA
Han, 2020[15] (China)	RA	206	62.5	117 (56.8)	102 (49.5)	67 (32.5)	Vomiting: 24 (11.7)	9 (4.4)	NA	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%; $p<0.05$)

Table 2. Continued

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	
Huang, 2020[41] (China)	RA	38	49	NA	NA	1 (3)	NA	NA	NA	NA
Jin, 2020[42] (China)	RA	651	46.14	74 (11.4)	NA	53 (8.1)	Nausea: 10 (1.5) Vomiting: 11 (1.6)	NA	NA	Occurrence of GI symptoms onset to admission 4 d 10.8% had pre-existing liver disease
Lin, 2020[43] (China)	RA	95	NA	58	17 (17.9)	23 (24.2)	Nausea: 17 (17.9) Vomiting: 4 (4.2)	2 (2.1)	NA	RNA positive in faeces: 52.4% of patients and it was high among patients with GI symptoms GI symptoms on admission11.6% Developed during hospitalisation 49.5%
Luo S, 2020[44] (China)	RA	1141	53.8	183 (16)	180 (98)	68 (37)	Nausea: 134 (73) Vomiting: 119 (65)	45 (25)	NA	NA
Martin, 2020[45] (USA)	RA	41	70.4	41	NA	NA	NA	NA	41 (33.4)	Upper GI bleeding 76% Gastric or duodenal ulcers 12% Lower GI bleeding 24% Rectal ulcers 7%

Table 2. Continued

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	
Mauro, 2020[46] (Italy)	RA	4871	75	23	NA	NA	NA	NA	23 (0.5)	Occurrence of GI symptoms onset to admission4 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	26 (31.7)	7 (4.5)	Nausea: 3 (3.7) Vomiting: 3 (3.7)	3 (1.9)	NA	NA
Pan, 2020[16] (China)	RA	204	52.9	103 (50.5)	81 (78.6)	35 (34)	Vomiting: 4 (3.9)	2 (1.9)	NA	NA
Seeliger, 2020[21] (France)	RA	5	NA	NA	NA	NA	NA	NA	NA	Peritoneal fluid RT-PCR negative in all
Shi, 2020[48] (China)	RA	81	49.5	NA	1 (1)	3 (4)	Vomiting: 4 (5)	NA	NA	NA
Wang, 2020[49] (China)	RA	138	56	NA	55 (39.9)	14 (10.1)	Nausea: 14 (10.1) Vomiting: 5 (3.6)	3 (2.2)	NA	NA
Xu, 2020[50] (China)	RA	62	41	NA	NA	3 (8)	NA	NA	NA	NA
Xu, 2020[51] (China)	RA	10	12	NA	NA	3 (30)	NA	NA	NA	Viral RNA in rectal swabs: 80% remained detectable after nasopharyngeal swabs turned negative
Young, 2020[52] (Singapore)	RA	18	47	NA	NA	3 (17)	NA	NA	NA	NA

Table 2. Continued

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	
Zhang, 2020[53] (China)	RA	505	51.2	164 (32.5)	93 (56.7)	62 (37.8)	Nausea: 27 (16.5) Vomiting: 13 (7.9)	17 (10.4)	NA	NA
Zhang, 2020[54] (China)	RA	140	57	55 (39.6)	17 (12.2)	18 (12.9)	Nausea: 24 (17.3) Vomiting: 7 (5.0)	8 (5.8)	NA	Occurrence of GI symptoms onset to admission 8 d
Zhou, 2020[55] (China)	RA	191	56	NA	NA	9 (5)	7 (4)	NA	NA	NA
Gadiparthi, 2020[56] (USA)	BC	3	64	3	NA	1 (33.33)	NA	NA	3 (100)	NA
Xiao, 2020[22] (China)	BC	73	43	NA	NA	26 (35.6)	NA	NA	NA	NA
Case reports										
Aloysius, 2020[57] (USA)	CR	1	36	1	NA	Yes	Yes	NA	NA	GI symptoms onset to admission8 d Abdominal signs: epigastric tenderness GI diagnosis: acute pancreatitis complicated with ARDS

Table 2. Continued

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	
Coccolini, 2020[58] (Italy)	CR	1	78	1	NA	NA	NA	Yes	NA	GI diagnosis: intestinal obstruction secondary to small bowel volvulus with no perforation or gut ischaemia RNA positive in peritoneal fluids
Holshue, 2020[59] (USA)	CR	1	35	1	NA	Yes	Yes	Yes	NA	Occurrence of GI symptoms onset to admission 2 d
Hosoda, 2020[60] (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.[54] 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.[15] Neonates with COVID-19 had vomiting and milk refusal associated with the respiratory symptoms.[63]

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.[49] 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.[21] 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[61] and this accounted for difficulties with enteral feeding and maintenance of adequate nutritional status.[64] Furthermore, individuals who later developed refractory pneumonia had a higher incidence of anorexia on admission.[47]

Other GI manifestations

Prominent GI symptoms such as bloody diarrhoea are more common in those with severe disease.[40,65] Constipation and haemorrhagic colitis are other less common GI manifestations.[65,66] Endoscopic evaluation carried out by Lin et al.[43] in a patient presenting with GI bleeding associated with COVID-19 showed multiple round herpetic erosions and ulcers. Similarly, Seeliger et al.[21] 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.,[43] 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[16] and 16 vs 11.6 d[15]). There was an associated delay in diagnosis and treatment.[16] The group of patients with predominantly GI symptoms had a significant delay in presenting to hospital and a delay in the diagnosis as well.[16] 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.[15,16,42,49,53] They also had a longer hospital stay, as their discharge was delayed until viral clearance was achieved. The causes for this observation may be multifactorial. While treatment delay may have played a part, studies have also found higher viral replication and viral loads in patients with GI manifestations.[67] Han et al.[15] recommended doing routine reverse transcription polymerase chain reaction (RT-PCR) testing in patients presenting with GI symptoms, as they had higher rates of faecal RT-PCR positivity than others. On the other hand, some studies have not found an association between positive PCR results and the incidence of GI symptoms or disease severity.[43,67] Variations in GI manifestations and time of onset may be due to several factors, including ethnic/geographical differences, associated comorbidities or the use of different clinical and diagnostic criteria.[68] It is important to be aware of the range of GI manifestations in COVID-19 so as to consider this possibility at an early stage. Clinicians should have a high degree of suspicion in patients with fever and GI symptoms, as this may be the only indicator of COVID-19 and may forecast progression to severe disease and the development of complications. Apart from pre-existing liver disease, there were no other predisposing factors documented for the development of GI manifestations, making the prediction of developing such symptoms challenging.[42]

Mechanisms for GI involvement in COVID-19

SARS-CoV-2 enters host cells through ACE2 receptors.[69] 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).[70] 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.[22] 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.[71] However, in a different case–control study, decreased expression of ACE2 and nucleocapsid proteins were found in the oesophagus by immunohistochemistry.[22] 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.[43] 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[22] and enterocytes[72] of the stomach. Thus, although the virus is able to infect cells in the stomach, the low pH may be

preventing this. There is high ACE2 expression in proximal and distal enterocytes of the small intestine,[68] with the highest expression seen at the brush border of intestinal enterocytes.[72] Interestingly, ACE2 and TMPRSS2 are more highly expressed on absorptive enterocytes of the ileum and colon than in the lung.[73]

Saliva

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.[74] 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.[43] 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.[73] 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.[75] Virus-induced diarrhoea may be due to an alteration of intestinal permeability leading to enterocyte malabsorption.[62] Anal swabs have been reported to be persistently RT-PCR positive for SARS-CoV-2, even after throat swabs become negative.[50,76] 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.[22,77–79] 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.[72]

Stool viral RNA in COVID-19

SARS-CoV-2 viral shedding may occur through faeces. Chen et al.[67] 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.[15] Zhang et al.[80] 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).[61] Chen et al.[67] found faecal shedding to occur for 6–10 d after pharyngeal swabs became negative and a similar pattern was seen among children.[51] The presence of faecal viral RNA does not correlate with disease severity.[67] 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.[81] 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 raises the potential of faecal–oral transmission.[82] 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.[83] 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.[84] 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.[85] Factors released during systemic inflammation, such as C-reactive protein, are related to the severity of COVID-19. Gou et al.[86] 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.[87] 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.[88]

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 disturbance[42] 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.

Table 3. Assessment and treatment of patients with COVID-19 and GI manifestations

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[38] (China)	RA	99	NA	NA	NA	NA	No	No	NA
Chen, 2020[39] (China)	RA	42	NA	NA	NA	NA	NA	No	NA
Guan, 2020[40] (China)	RA	1099	NA	NA	NA	NA	NA	No	NA
Han, 2020[15] (China)	RA	206	NA	NA	Direct invasion of virus through the intestinal mucosa	NA	NA	No	Recovered/ discharged: 100%
Huang, 2020[41] (China)	RA	41	NA	NA	NA	NA	NA	No	NA
Jin, 2020[42] (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%

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
Lin, 2020[43] (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, 2020[44] (China)	RA	1141	NA	NA	NA	NA	NA	NA	Recovered 96.2% Death 3.8%
Martin,2020[45] (USA)	RA	41	UGIB, NG	UGIB, esophagogastroduodenoscopy (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%

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
Mauro,2020[46] (Italy)	RA	4871	Radiological embolization in 1 patient with an early rebleed	UGIE in 11 patients; treated with adrenaline injection and clips in 5, cyanoacrylate gel in 1 Endoscopic re-treatment in 1 patient with an early rebleed	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 Vasoactive agent for suspicious variceal bleeding in 1 patient	Upper GI bleeding in 23 patients	Discharged 78% Death 22%
Mo, 2020[47] (China)	RA	155	NA	NA	NA	NA	NA	NA	NA
Pan, 2020[16] (China)	RA	204	NA	NA	NA	NA	NA	No	Recovered 81.55% Death 18.45% ICU care 5.94%
Seeliger, 2020[21] (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%

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
								Surgical management, yes, open small bowel resection, laparoscopic appendectomy, open drainage of haemoperitoneum/ haemopneumoperitoneum, reduction of incarcerated small bowel	ICU care 60%
Shi, 2020[48] (China)	RA	81	NA	NA	NA	NA	NA	NA	NA
Wang, 2020[49] (China)	RA	138	NA	NA	NA	NA	NA	NA	NA
Xu, 2020[50] (China)	RA	62	NA	NA	NA	NA	NA	NA	NA
Xu, 2020[51] (China)	RA	10	NA	NA	NA	NA	NA	NA	Recovered/discharged 100% Mechanical ventilation 0 ICU care 0
Young, 2020[52] (Singapore)	RA	18	NA	NA	NA	NA	NA	NA	Mechanical ventilation 25% ICU care 50% Recovered/discharged 100% Death 0
Zhang, 2020[53] (China)	RA	505	NA	NA	NA	NA	NA	NA	NA

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
Zhang, 2020[54] (China)	RA	140	NA	NA	NA	NA	NA	NA	NA
Zhou, 2020[55] (China)	RA	191	NA	NA	NA	NA	NA	NA	NA
Gadiparthi, 2020[56] (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, gastro-duodenal bleeding		Patient 3 underwent a faecal management system for large volume watery diarrhoea	No surgical management	Death 66.7%
			Patient 3, not done		Patient 3, rectal ulcer or direct trauma from faecal management system				

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[22] (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 [57] (USA)	CR	1	CT abdomen, normal gall bladder, normal biliary tract and unremark-able pancreas	NA	ACE2 receptor mediated damage to pancreatic islet cells causing acute pancreatitis	Nothing by mouth, fluid resuscitation (crystalloid) Parenteral nutrition	Analgesia, not specified	No	Recovered/discharged

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
Coccolini, 2020[58] (Italy)	CR	1	CT abdomen, intestinal occlusion due to a small bowel volvulus with no signs of gut ischaemia	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[59] (USA)	CR	1	NA	NA	NA	Normal saline	Ondansetron	No	Recovered
Hosoda, 2020[60] (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.[99] However, except for dexamethasone, the other agents have not shown definite therapeutic benefits, although they may be beneficial in selected subgroups.[100] 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.[101]

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.[101] 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.[102]

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 nasojejunal 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.[57,103] 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.[104] 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.[105,106] Furthermore, in such critically ill patients, postoperative care in an ICU is necessary.[107]

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).[108–130]

Antivirals

Antivirals and antibiotics may cause diarrhoea and alter the gut microbiome.[131] Remdesivir has a number of GI side effects, including nausea, vomiting, gastroparesis and constipation.[132,133] The antimalarial agents chloroquine/hydroxychloroquine and lopinavir/ritonavir cause nausea, vomiting, loss of appetite and abdominal cramps.[108,113]

Immunomodulatory agents

Immunomodulatory agents such as corticosteroids can increase the risk of peptic ulceration and GI bleeding.[134] The Janus kinase inhibitor baricitinib can cause diarrhoea.[108] Immunomodulators such as tocilizumab may cause GI bleeding, nausea, vomiting and ulceration. The GI side effects of intravenous immunoglobulins are minimal (Table 4).

Proton pump inhibitors (PPIs) and COVID-19

The use of PPIs are a risk factor for rotavirus, influenza virus, norovirus and MERS viral infections.[135] Individuals using PPIs once or twice daily had significantly higher odds of a positive COVID-19 test compared with those not taking it.[136] A larger study done by Lee et al.[137] 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, Taştemur and Ataseven[138] 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
	Favipiravir	1800 mg twice daily on day 1 followed by 800 mg twice daily on day 2 to maximum of 14 d	Oral	1–10%: hyperuricaemia (5%), diarrhoea (5%), liver enzyme derangement (2%)	115,116
	Oseltamivir	75 mg twice daily for 5 d	Oral	1–>10%: nausea, vomiting, GI discomfort <0.1%: GI haemorrhage (children), hepatic disorders	117
	Arbidol	For prevention, 200 mg once a day Therapeutic dose 600 mg/d (200 mg three times/d) for 5 d	Oral	Diarrhoea, nausea, vomiting, deranged liver enzymes	118

Table 4. Continued

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 0.1–1%: hepatic disorders, autoimmune hepatitis <0.1%: haemolytic uraemic syndrome, pancreatitis Frequency not known: abdominal pain, constipation	108
	Tocilizumab	4–8 mg/kg (maximum 800 mg) over 1 h or 400 mg once Consider additional dose 8–12 h later if continued clinical decompensation (maximum of 2 doses)	Intravenous infusion	1–>10%: abdominal pain, GI disorders, oral disorders Frequency not known: hepatic disorders	108
	Sarilumab (Kevzara) IL-6 inhibitor	400 mg	Intravenous	1–10%: liver enzyme derangement	119
	Baricitinib (completed clinical trial)	4 mg once daily baricitinib+antiviral therapy administration for 2 weeks	Oral	1–>10%: nausea Frequency not known: abnormal liver enzymes	120,121
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%) <1%: increased ALT, anorexia, increased appetite, flatulence, salivary gland enlargement	108
	Chloroquine	500 g twice daily for 10 d	Oral (administer with food)	<0.1%: hepatitis Frequency not known: abdominal pain, GI disorders, nausea, diarrhoea, vomiting, metallic taste	109

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 Budesonide+formoterol inhaled 1–2 puffs every 12 h	Oral and inhaled	1–>10%: GI discomfort, peptic ulcer, nausea 0.1–1%: increased appetite, pancreatitis	128
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 definite 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.[139] 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.[140]

Bezzio et al.[141] 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.[142] 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 cyclosporine and infliximab as salvage therapy on a case-by-case basis has been suggested.[143] 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.[144]

GI malignancies

The pandemic has affected multiple steps in the diagnosis and management of GI malignancies.[145,146] 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.[147] Elective cancer therapies and surgeries have been delayed to allow increased capacity for dealing with COVID-19 patients.[148,149] 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.[150] Patients with GI cancers needing frequent hospital visits may be at higher risk of hospital-acquired COVID-19 transmission. Yu et al.[151] 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.[64]

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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References

1 Word Health Organization. Coronavirus disease (COVID-2019) situation reports. Geneva: World Health Organization; 2020.

2 Seneviratne S, Jayarajah U, Abeysuriya V, et al. COVID-19 vaccine landscape. J Ceylon Coll Physicians. 2020;51(2):120–31.

3 Estola T. Coronaviruses, a new group of animal RNA viruses. Avian Dis. 1970;14(2):330–6.

4 Kahn JS, McIntosh K. History and recent advances in coronavirus discovery. Pediatr Infect Dis J. 2005;24(11 Suppl):S223–7, discussion S6.

5 Corman VM, Muth D, Niemeyer D, et al. Hosts and sources of endemic human coronaviruses. Adv Virus Res. 2018;100:163–88.

6 Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1–23.

7 Forgie S Marrie TJ, eds. Healthcare-associated atypical pneumonia. Semin Respir Crit Care Med; 2009;30(1):67–85.

8 Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? Lancet Gastroenterol Hepatol. 2020;5(4):335–7.

9 Chu H, Fuk-Woo Chan J, Wang Y, et al. SARS-CoV-2 induces a more robust innate immune response and replicates less efficiently than SARS-CoV in the human intestines: an ex vivo study with implications on pathogenesis of COVID-19. Cell Mol Gastroenterol Hepatol. 2021;11(3):771–81.

10 Wenzel RP, Edmond MB. Managing SARS amidst uncertainty. N Engl J Med. 2003;348(20):1947–8.

11 Fact sheet on Middle East respiratory syndrome coronavirus (June 2015). Wkly Epidemiol Rec. 2015;90(24):305–8.

12 Word Health Organization. Origin of SARS-CoV-2, 26 March 2020. WHO/2019-nCoV/FAQ/Virus_origin/2020.1. Geneva: World Health Organization; 2020. Available from: https://apps.who.int/iris/handle/10665/332197 [accessed 2 March 2021].

13 Hui DS, Wong PC, Wang C. SARS: clinical features and diagnosis. Respirology. 2003;8(Suppl 1):S20–4.

14 Kim MN, Kim EC. Considering revision the criteria for patients under investigations for MERS-CoV infections: diarrhea or not. J Korean Med Sci. 2018;33(53):e344.

15 Han C, Duan C, Zhang S, et al. Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. Am J Gastroenterol. 2020;115(6):916–23.

16 Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol. 2020;115(5):766–73.

17 Leung WK, To KF, Chan PK, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. Gastroenterology. 2003;125(4):1011–7.

18 Cevik M, Tate M, Lloyd O, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe. 2021;2(1):e13–22.

19 Yan Y, Chang L, Wang L. Laboratory testing of SARS-CoV, MERS-CoV, and SARS-CoV-2 (2019-nCoV): current status, challenges, and countermeasures. Rev Med Virol. 2020;30(3):e2106.

20 Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Am J Pathol. 2007;170(4):1136–47.

21 Seeliger B, Philouze G, Benotmane I, et al. Is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present intraperitoneally in patients with coronavirus disease 2019 (COVID-19) infection undergoing emergency operations? Surgery. 2020;168(2):220–1.

22 Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020;158(6):1831–3.e3.

23 Rousset S, Moscovici O, Lebon P, et al. Intestinal lesions containing coronavirus-like particles in neonatal necrotizing enterocolitis: an ultrastructural analysis. Pediatrics. 1984;73(2):218–24.

24 Resta S, Luby JP, Rosenfeld CR, et al. Isolation and propagation of a human enteric coronavirus. Science. 1985;229(4717):978–81.

25 Esper F, Ou Z, Huang YT. Human coronaviruses are uncommon in patients with gastrointestinal illness. J Clin Virol. 2010;48(2):131–3.

26 Vabret A, Dina J, Gouarin S, et al. Detection of the new human coronavirus HKU1: a report of 6 cases. Clin Infect Dis. 2006;42(5):634–9.

27 Kanwar A, Selvaraju S, Esper F. Human coronavirus-HKU1 infection among adults in Cleveland, Ohio. Open Forum Infect Dis. 2017;4(2):ofx052.

28 Kumthip K, Khamrin P, Ushijima H, et al. Enteric and non-enteric adenoviruses associated with acute gastroenteritis in pediatric patients in Thailand, 2011 to 2017. PLoS One. 2019;14(8):e0220263.

29 Bouvier M, Chen WJ, Arnold JC, et al. Species-specific clinical characteristics of human coronavirus infection among otherwise healthy adolescents and adults. Influenza Other Respir Viruses. 2018;12(2):299–303.

30 Srikantiah P, Charles MD, Reagan S, et al. SARS clinical features, United States, 2003. Emerg Infect Dis. 2005;11(1):135–8.

31 Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA. 2003;289(21):2801–9.

32 Hsu L-Y, Lee C-C, Green JA, et al. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. Emerg Infect Dis. 2003;9(6):713–7.

33 Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. N Engl J Med. 2003;348(20):1995–2005.

34 Chan PK, Tang JW, Hui DS. SARS: clinical presentation, transmission, pathogenesis and treatment options. Clin Sci. 2006;110(2):193–204.

35 Zhou J, Li C, Zhao G, et al. Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. Sci Adv. 2017;3(11):eaao4966.

36 Zumla AI, Memish ZA. Middle East respiratory syndrome coronavirus: epidemic potential or a storm in a teacup? Eur Respir J. 2014;43(5):1243–8.

37 Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med. 2013;369(5):407–16.

38 Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13.

39 Chen Y, Chen L, Deng Q, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020;92(7):833–40.

40 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.

41 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.

42 Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020;69(6): 1002–9.

43 Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69(6):997–1001.

44 Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol. 2020;18(7):1636–7.

45 Martin TA, Wan DW, Hajifathalian K, et al. Gastrointestinal bleeding in patients with coronavirus disease 2019: a matched case–control study. Am J Gastroenterol. 2020;115(10):1609–16.

46 Mauro A, De Grazia F, Lenti MV, et al. Upper gastrointestinal bleeding in COVID-19 inpatients: incidence and management in a multicenter experience from northern Italy. Clin Res Hepatol Gastroenterol. 2020; doi: 10.1016/j.clinre.2020.07.025.

47 Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. 2020; doi: 10.1093/cid/ciaa270.

48 Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20(4):425–34.

49 Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9.

50 Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368:m606.

51 Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med. 2020;26(4):502–5.

52 Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA. 2020;323(15):1488–94.

53 Zhang H, Liao YS, Gong J, et al. Clinical characteristics of coronavirus disease (COVID-19) patients with gastrointestinal symptoms: a report of 164 cases. Dig Liver Dis. 2020;52(10):1076–9.

54 Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730–41.

55 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.

56 Gadiparthi C, Perisetti A, Sayana H, et al. Gastrointestinal bleeding in patients with severe SARS-CoV-2. Am J Gastroenterol. 2020;115(8):1283–5.

57 Aloysius MM, Thatti A, Gupta A, et al. COVID-19 presenting as acute pancreatitis. Pancreatology. 2020;20(5):1026–7.

58 Coccolini F, Tartaglia D, Puglisi A, et al. SARS-CoV-2 is present in peritoneal fluid in COVID-19 patients. Ann Surg. 2020;272(3):e240.

59 Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929–36.

60 Hosoda T, Sakamoto M, Shimizu H, et al. SARS-CoV-2 enterocolitis with persisting to excrete the virus for approximately two weeks after recovering from diarrhea: a case report. Infect Control Hosp Epidemiol. 2020;41(6):753–4.

61 Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology. 2020;159(1):81–95.

62 D'Amico F, Baumgart DC, Danese S, et al. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention, and management. Clin Gastroenterol Hepatol. 2020;18(8):1663–72.

63 Wang J, Wang D, Chen GC, et al. [SARS-CoV-2 infection with gastrointestinal symptoms as the first manifestation in a neonate]. Zhongguo Dang Dai Er Ke Za Zhi. 2020;22(3):211–4.

64 Aguila EJT, Cua IHY, Fontanilla JAC, et al. Gastrointestinal manifestations of COVID-19: impact on nutrition practices. Nutr Clin Pract. 2020;35(5):800–5.

65 Carvalho A, Alqusairi R, Adams A, et al. SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis: implications for detection and transmission of COVID-19 disease. Am J Gastroenterol. 2020;115(6):942–6.

66 Wang Z, Chen X, Lu Y, et al. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends. 2020;14(1):64–8.

67 Chen Y, Chen L, Deng Q, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020;92(7):833–40.

68 Liang W, Feng Z, Rao S, et al. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. Gut. 2020;69(6):1141–3.

69 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell entry depends on aCE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–80.e8.

70 Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci USA. 2020;117(21):11727–34.

71 Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. BioRxiv. 2020; https://doi.org/10.1101/2020.01.30.927806.

72 Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science. 2020;369(6499):50–4.

73 Zhang H, Kang Z, Gong H, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. Gut. 2020;69(6):1010–8.

74 To KK, Tsang OT, Yip CC, et al. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis. 2020;71(15):841–3.

75 Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021;93(1):250–6.

76 Wu J, Liu J, Li S, et al. Detection and analysis of nucleic acid in various biological samples of COVID-19 patients. Travel Med Infect Dis. 2020;37:101673.

77 Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol. 2020;33(6):1007–14.

78 Yao X, Li T, He Z, et al. [A pathological report of three COVID-19 cases by minimally invasive autopsies]. Zhonghua Bing Li Xue Za Zhi. 2020;49(5):411–7.

79 Deshmukh V, Motwani R, Kumar A, et al. Histopathological observations in COVID-19: a systematic review. J Clin Pathol. 2021;74(2):76–83.

80 Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of mul-

tiple shedding routes. Emerg Microbes Infect. 2020;9(1): 386–9.

81 Ling Y, Xu SB, Lin YX, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl). 2020;133(9):1039–43.

82 Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology. 2020;158(6):1518–9.

83 Joynt GM, Wu WK. Understanding COVID-19: what does viral RNA load really mean? Lancet Infect Dis. 2020;20(6):635–6.

84 Dhar D, Mohanty A. Gut microbiota and Covid-19– possible link and implications. Virus Res. 2020;285:198018.

85 Villapol S. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. Transl Res. 2020;226:57–69.

86 Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020; doi: 10.1002/dmrr.3319.

87 Zuo T, Zhan H, Zhang F, et al. Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until discharge. Gastroenterology. 2020;159(4): 1302–10.e5.

88 Baud D, Dimopoulou Agri V, Gibson GR, et al. Using probiotics to flatten the curve of coronavirus disease COVID-2019 pandemic. Front Public Health. 2020;8:186.

89 Segal JP, Mak JWY, Mullish BH, et al. The gut microbiome: an underrecognised contributor to the COVID-19 pandemic? Therap Adv Gastroenterol. 2020;13:1756284820974914.

90 Rishi P, Thakur K, Vij S, et al. Diet, gut microbiota and COVID-19. Indian J Microbiol. 2020;60(4):1–10.

91 van der Lelie D, Taghavi S. COVID-19 and the gut microbiome: more than a gut feeling. mSystems. 2020;5(4):e00453–20.

92 Donati Zeppa S, Agostini D, Piccoli G, et al. Gut microbiota status in COVID-19: an unrecognized player? Front Cell Infect Microbiol. 2020;10:576551.

93 Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. J Clin Med. 2020;9(4):941.

94 Lui RN, Wong SH, Sánchez-Luna SA, et al. Overview of guidance for endoscopy during the coronavirus disease 2019 pandemic. J Gastroenterol Hepatol. 2020;35(5):749–59.

95 Minodier L, Charrel RN, Ceccaldi P-E, et al. Prevalence of gastrointestinal symptoms in patients with influenza, clinical significance, and pathophysiology of human influenza viruses in faecal samples: what do we know? Virol J. 2015;12(1):215.

96 Jayarajah U, Silva PK, Jayawardana P, et al. Pattern of dengue virus infections in adult patients from Sri Lanka. Trans R Soc Trop Med Hyg. 2018;112(3):144–53.

97 Jayarajah U, Madarasinghe M, Hapugoda D, et al. Clinical and biochemical characteristics of dengue infections in children from Sri Lanka. Glob Pediatr Health. 2020;7: 2333794X20974207.

98 Jayarajah U, Lahiru M, De Zoysa I, et al. Dengue infections and the surgical patient. Am J Trop Med Hyg. 2020;104(1):52–9.

99 Borges do Nascimento IJ, von Groote TC, O'Mathúna DP, et al. Clinical, laboratory and radiological characteristics and outcomes of novel coronavirus (SARS-CoV-2) infection in humans: a systematic review and series of meta-analyses. PLoS One. 2020;15(9):e0239235.

100 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704.

101 Ye Q, Wang B, Zhang T, et al. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. Am J Physiol Gastrointest Liver Physiol. 2020;319(2):G245–52.

102 Wei PF. Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7). Chin Med J. 2020;133(9):1087–95.

103 Shah R, Klumpp LC, Syed N, et al. Abdominal compartment syndrome in a patient suspected of coronavirus 2019 (COVID-19). J Infect Dis Epidemiol. 2020;6(4):139.

104 Rahman A, Niloofa R, Jayarajah U, et al. Haematological abnormalities in COVID-19: a narrative review. Am J Trop Med Hyg. 2021; doi: 10.4269/ajtmh.20-1536.

105 Jayasinghe R, Jayarajah U, Seneviratne S. Consensus in surgical practice during the COVID-19 pandemic: an appraisal of the literature. Preprints. 2020; doi: 10.20944/preprints202006.0109.v1.

106 Collaborative C. Preoperative nasopharyngeal swab testing and postoperative pulmonary complications in patients undergoing elective surgery during the SARS-CoV-2 pandemic. Br J Surg. 2021;108(1):88–96.

107 Jayasinghe R, Jayarajah U, Seneviratne S. Consensus on perioperative surgical practice during the COVID-19 pandemic: an appraisal of the literature. Sri Lanka J Surg. 2020;38(2): 57–61.

108 Barlow A, Landolf KM, Barlow B, et al. Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019. Pharmacotherapy. 2020;40(5):416–37.

109 Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.

110 A trial of remdesivir in adults with severe COVID-19. NCT04257656. Available from: https://clinicaltrials.gov/ct2/show/NCT04257656 [accessed 29 July 2020].

111 A trial of remdesivir in adults with mild and moderate COVID-19. NCT04252664. Available from: https://clinicaltrials.gov/ct2/show/NCT04252664 [accessed 29 July 2020].

112 MERS-CoV infection treated with a combination of lopinavir/ritonavir and interferon beta-1b (MIRACLE). NCT02845843. Available from: https://clinicaltrials.gov/ct2/show/NCT02845843 [accessed 18 March 2020].

113 Deng L, Li C, Zeng Q, et al. Arbidol combined with LPV/r versus LPV/r alone against corona virus disease 2019: a retrospective cohort study. J Infect. 2020;81(1):e1–5.

114 Lopinavir/ritonavir, ribavirin and IFN-beta combination for nCoV treatment. NCT04276688. Available from: https://clinicaltrials.gov/ct2/show/NCT04276688 [accessed 29 July 2020].

115 Control of COVID-19 outbreaks in long term care. NCT04448119. Available from: https://clinicaltrials.gov/ct2/show/NCT04448119 [accessed 29 July 2020].

116 Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2020;102:501–8.

117 Tan Q, Duan L, Ma Y, et al. Is oseltamivir suitable for fighting against COVID-19: in silico assessment, in vitro and retrospective study. Bioorg Chem. 2020;104:104257.

118 Yang C, Ke C, Yue D, et al. Effectiveness of arbidol for COVID-19 prevention in health professionals. Front Public Health. 2020;8:249.

119 Della-Torre E, Campochiaro C, Cavalli G, et al. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. Ann Rheum Dis. 2020;79(10):1277–85.

120 Baricitinib therapy in COVID-19. NCT04358614. Available from: https://clinicaltrials.gov/ct2/show/NCT04358614?term=NCT04358614&draw=2&rank=1 [accessed 2 March 2021].

121 Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10223):e30–1.

122 COVID-19-associated ARDS treated with dexamethasone: alliance Covid-19 Brasil III (CoDEX). NCT04327401. Available from: https://clinicaltrials.gov/ct2/show/NCT04327401 [accessed 29 July 2020].

123 Efficacy of dexamethasone treatment for patients with ARDS caused by COVID-19 (DEXA-COVID19). NCT04325061. Available from: https://clinicaltrials.gov/ct2/show/NCT04325061 [accessed 29 July 2020].

124 Ferner RE, DeVito N, Aronson JK. Drug vignettes: dexamethasone. Available from: https://www.cebm.net/covid-19/dexamethasone/ [accessed 2 March 2021].

125 Glucocorticoid therapy for COVID-19 critically ill patients with severe acute respiratory failure. NCT04244591. Available from: https://clinicaltrials.gov/ct2/show/NCT04244591 [accessed 29 July 2020].

126 The efficacy of different hormone doses in 2019-nCoV severe pneumonia. NCT04263402. Available from: https://clinicaltrials.gov/ct2/show/NCT04263402 [accessed 29 July 2020].

127 Fu H-Y, Luo Y, Gao J-P, et al. Effects of short-term low-dose glucocorticoids for patients with mild COVID-19. BioMed Res Int. 2020;2020:2854186.

128 Evaluation of efficacy of levamisole and formoterol+budesonide in treatment of COVID-19. NCT04331470. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04331470 [accessed 29 July 2020].

129 Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis. 2020;7(3):ofaa102.

130 Pourahmad R, Moazzami B, Rezaei N. Efficacy of plasmapheresis and immunoglobulin replacement therapy (IVIG) on patients with COVID-19. SN Compr Clin Med. 2020; doi: 10.1007/s42399-020-00438-2.

131 Song Y, Liu P, Shi XL, et al. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. Gut. 2020;69(6):1143–4.

132 Kujawski SA, Wong KK, Collins JP, et al. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Nat Med. 2020;26(6):861–8.

133 Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020;382(24):2327–36.

134 Sulkowski MS, Cooper C, Hunyady B, et al. Management of adverse effects of Peg-IFN and ribavirin therapy for hepatitis C. Nat Rev Gastroenterol Hepatol. 2011;8(4):212–23.

135 Charpiat B, Bleyzac N, Tod M. Proton pump inhibitors are risk factors for viral infections: even for COVID-19? Clin Drug Invest. 2020;40(10):897–9.

136 Almario CV, Chey WD, Spiegel BM. Increased risk of COVID-19 among users of proton pump inhibitors. Am J Gastroenterol. 2020;115(10):1707–15.

137 Lee SW, Ha EK, Yeniova AÖ, et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. Gut. 2020;70(1):76–84.

138 Taştemur Ş, Ataseven H. Is it possible to use proton pump inhibitors in COVID-19 treatment and prophylaxis? Med Hypotheses. 2020;143:110018.

139 Rodríguez-Lago I, Ramírez de la Piscina P, Elorza A, et al. Characteristics and prognosis of patients with inflammatory bowel disease during the SARS-CoV-2 pandemic in the Basque Country (Spain). Gastroenterology. 2020;159(2):781–3.

140 Rubin DT, Feuerstein JD, Wang AY, et al. AGA clinical practice update on management of inflammatory bowel disease during the COVID-19 pandemic: expert commentary. Gastroenterology. 2020;159(1):350–7.

141 Bezzio C, Saibeni S, Variola A, et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. Gut. 2020;69(7):1213–7.

142 Kennedy NA, Jones GR, Lamb CA, et al. British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic. Gut. 2020;69(6):984–90.

143 Rosen MH, Axelrad J, Hudesman D, et al. Management of acute severe ulcerative colitis in a pregnant woman with COVID-19 infection: a case report and review of the literature. Inflamm Bowel Dis. 2020;26(7):971–3.

144 Divizia A, Sensi B, Sica GS. Ambulatory management of perianal Crohn's disease during the COVID-19 pandemic. Colorectal Dis. 2020;22(6):645–6.

145 COVIDSurg Collaborative. Outcomes from elective colorectal cancer surgery during the SARS-CoV-2 pandemic. Colorectal Dis. 2020; doi: 10.1111/codi.15431.

146 Glasbey JC, Nepogodiev D, Simoes JFF, et al. Elective cancer surgery in COVID-19-free surgical pathways during the SARS-CoV-2 pandemic: an international, multicenter, comparative cohort study. J Clin Oncol. 2021;39(1):66–78.

147 Bhat PKR, Santosh Kumar KY, Sorake C, et al. Gastrointestinal malignancies and the COVID-19 pandemic: evidence-based triage to surgery. J Gastrointest Surg. 2020;24(11):2698–9.

148 HO Al-Shamsi, Alhazzani W, Alhuraiji A, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group. Oncologist. 2020;25(6):e936–45.

149 COVIDSurg Collaborative. Delaying surgery for patients with a previous SARS-CoV-2 infection. Br J Surg. 2020;107(12):e601–2.

150 Fligor SC, Wang S, Allar BG, et al. Gastrointestinal malignancies and the COVID-19 pandemic: evidence-based triage to surgery. J Gastrointest Surg. 2020;24(10):2357–73.

151 Yu J, Ouyang W, Chua MLK, et al. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol. 2020;6(7):1108–10.