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Covid-19 and the Digestive System

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Abstract

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

Introduction

The novel coronavirus disease (Covid-19) is causing a major pandemic. As of 23 March 2020, it has infected over 340,000 people worldwide and caused over 14,000 deaths. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense single-stranded RNA virus and is taxonomically a member of the *Betacoronavirus* genus. Patients typically present with fever and respiratory symptoms, nevertheless, some patients also have gastrointestinal manifestations with diarrhoea, vomiting and abdominal pain [1]. Studies have identified the SARS-CoV-2 RNA in anal / rectal swabs [2, 3] and stool specimens [4-6] of Covid-19 patients, even after the clearance of the virus in the upper respiratory tract [2, 3]. Furthermore, the viral receptor angiotensin converting enzyme 2 (ACE2) was found to be expressed in gastrointestinal epithelial cells [7, 8]. Together these suggest that SARS-CoV-2 can actively infect and replicate in the gastrointestinal tract. This has important implications to the disease management, transmission, and infection control. In this article, we review the important gastrointestinal aspects of the disease.

Gastrointestinal symptoms of Covid-19 patients

While Covid-19 patients typically present with a respiratory illness, some patients reported gastrointestinal symptoms including diarrhoea, vomiting and abdominal pain during course of the disease. In the first case of Covid-19 in a 35-year-old man in the United States [4], the patient presented with a 2-day history of nausea and vomiting upon hospital admission, followed by diarrhoea and abdominal discomfort on the second day of hospitalization. The SARS-CoV-2 RNA was detected in stool of the patient by reverse-transcriptase polymerase-chain-reaction (RT-PCR) on illness day 7 [4]. Similarly, in the familial cluster of Covid-19 cases during the early epidemic [9], diarrhoea was described in two young adults (aged 36 and 37 years) out of the six patients, with reported bowel openings of up to eight times a day.

Subsequent cohorts have consistently reported gastrointestinal symptoms among Covid-19 patients. In a large study that collected data from 1,099 patients from 552 hospitals in China, it reported nausea or vomiting in 55 (5.0%) and diarrhoea in 42 (3.8%) patients

[10]. Several other cohorts have reported frequencies of diarrhoea ranging 2.0-10.1%, and nausea and/or vomiting ranging 1.0-10.1% (Table 1) [11-19]. In the cohort of 140 Covid-19 patients in Wuhan, gastrointestinal symptoms were described in up to 39.6% of the patients [20], including nausea in 24 (17.3%), diarrhoea in 18 (12.9%) and vomiting in 7 (5.0%) patients. Similarly, the rate of diarrhoea was up to 35.6% in a cohort of 73 patients [7]. These rates were higher than some other cohorts, and highlighted the variability of clinical presentations. On the other hand, abdominal pain or discomfort was sparingly described [4], and was reported in 2.2-5.8% in patient cohorts [16, 20](Table 1).

Similar to adults, gastrointestinal symptoms were observed in a cohort of 171 paediatric patients with Covid-19 [14]. Diarrhoeal and vomiting were observed in 15 (8.8%) and 11 (6.4%) of these children, respectively. In another study that investigated viral shredding in paediatric Covid-19 patients, diarrhoea was observed in three out of the ten infected children [3]. Although different clinical features, such as a milder disease course [14] and less respiratory symptoms [3] have been proposed in Covid-19 children, the gastrointestinal symptoms appear to be similar, although more clinical data are needed to arrive at such a conclusion.

It is evident that patients can present with gastrointestinal symptoms early in the disease course. For example, the first Covid-19 patient in the US had nausea and vomiting two days before going to hospital, and developed diarrhoea on the second day of admission [4], whereas the two young adults in the early familial Covid-19 cluster had diarrhoea upon presentation to the hospital [9]. Diarrhoea can be one initial symptom and may even occur earlier than pyrexia or respiratory symptoms in some cases [13, 16].

Diarrhoea was a common symptom of SARS during its outbreak back in 2003. Among the SARS patients in Hong Kong, approximately 20% had with diarrhoea on disease presentation [21, 22]. The mean duration of diarrhoea was 3.7 days, and most was self-limiting [22]. There were higher rates of diarrhoea during the course of illness [22-24], up to 73% of SARS patients in one study [25] (Table 1). Gastrointestinal symptoms were also frequent in MERS [26], with cohorts reporting diarrhoea, nausea, vomiting and abdominal pain in 11.5-32% of the patients (Table 1). Comparing to these figures, the gastrointestinal symptoms in Covid-19 appeared to be less common (Table 1). This may signify the differences in viral tropism as compared with SARS-CoV and MERS-CoV.

Liver injury in Covid-19 patients

Apart from gastrointestinal symptoms, patients with Covid-19 can have liver injury with raised enzymes found in blood tests. Current data indicated that 14.8-53.1% of Covid-19 patients had abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during the course of disease, with mostly mild elevation in serum bilirubin [10-12, 15-18, 27]. In a commentary that described a cohort of 56 Covid-19 patients, gamma-glutamyl transferase (GGT) was elevated in 54% of the patients [28]. Most of the liver injuries are mild and transient, although severe liver damage can occur. The proportion of liver injury was also higher in patients with severe Covid-19 disease [10, 12]. In the cohort that described 99 patients in Wuhan, 43 patients had raised ALT or AST; one patient with critical Covid-19 had severe hepatitis with serum ALT increased up to 7590 U/L [11].

While the mechanism of liver injury is not fully understood, the injury can be due to direct viral infection of hepatocytes, immune-related injury, or drug hepatotoxicity [29]. There is also suggestion that the virus may bind to cholangiocytes through the ACE2 receptor to dysregulate the liver function [28]. Notably, histological examination of the liver biopsy from a deceased Covid-19 patient showed microvesicular steatosis and mild lobular activity [30]. These histological changes could be caused by SARS-CoV-2 infection or drug-induced liver injury. Nevertheless, no viral inclusion was observed in the liver. It remains to be studied whether SARS-CoV-2 may target the liver in a similar manner to SARS-CoV [31-33], and whether other mechanisms play an important role in the liver injury.

Mechanisms of gastrointestinal tract involvement

Evidence from previous SARS studies indicated that coronavirus has a tropism to the gastrointestinal tract. The SARS-CoV RNA could be readily detected in stool specimens of SARS patients [34], and electron microscopy on biopsy and autopsy specimens showed active viral replications in both small and large intestines [22]. Similarly, enteric infection could occur with MERS-CoV, as human intestinal epithelial cells were highly susceptible to the virus and could sustain robust viral replication [35]. This gastrointestinal tropism may explain the frequent occurrence of diarrhoea in coronavirus infection. This faecal

source can lead to fomite transmission, especially when infective aerosols are generated from the toilet plume [36].

Although at a lower frequency compared to SARS, some Covid-19 patients do develop diarrhoea during their disease course. This suggests the possible tropism of SARS-CoV-2 to the gastrointestinal tract. Genome sequences showed that SARS-CoV-2 shared 79.6% sequence identity to SARS-CoV, both encoding and expressing the spike (S) glycoproteins that could bind to the entry receptor ACE2 to enter human cells [37-39]. The receptor binding domain on SARS-CoV-2 could bind to human ACE2 with high affinity, correlating with the efficient spread of the virus among humans [40, 41]. While ACE2 is highly expressed in type II alveolar cells (AT2) in the lungs, the receptor is also abundantly expressed in the gastrointestinal tract, especially in the small and large intestines [7, 8]. Staining of viral nucleocapsid protein was visualized in cytoplasm of gastric, duodenal and rectal epithelium [27]. These data have provided valuable insights into the receptor-mediated entry into the host cells, and provided basis for its possible transmission route through the faecal contents.

Implications to patient care and infection control

The tropism of SARS-CoV-2 to the gastrointestinal tract, its positive detection in stool, and its associated gastrointestinal symptoms, have important implications to both patient care and infection control. Clinicians should be alert of the gastrointestinal symptomatology of Covid-19, especially as they may occur before the onset of pyrexia and respiratory symptoms.

More importantly, several studies have demonstrated the presence of viral RNA in stool or anal / rectal swabs of Covid-19 patients [2-6]. In a study that evaluated 73 Covid-19 patients, 39 (53.4%) were tested positive for SARS-CoV-2 RNA in stool, with a duration of positive stool ranging from 1 to 12 days. Rather of concern, 17 (23.3%) patients remained positive with stool viral RNA after showing negative in their respiratory samples [7]. In another study that followed 10 paediatric patients and evaluated their nasopharyngeal and rectal swabs, eight children were persistently tested positive on rectal swabs even after nasopharyngeal clearance of the virus [3]. Moreover, two children

had positive rectal swabs, despite after clearance with two consecutive negative rectal swabs separated by at least 24 hours apart [31]. In contrast to the cycle threshold (Ct) value of 36-38 on illness day 7 stool sample from the first US case [4], the longitudinal Ct values in the paediatric patients were mostly below 35 [3]. This suggested that viral shedding from the gastrointestinal tract may be abundant, and may last long after resolution of clinical symptoms. Indeed, a previous study of SARS-CoV indicated that viral RNA could still be detected after 30 days in stool of SARS patients [42]. Nevertheless, the viral dynamic of SARS-CoV-2 in the gastrointestinal tract is not known, and may not follow that of SARS-CoV as observed in the respiratory tract [25, 43].

The immediate implication of these data is certainly on the disease infectivity. A recent environmental study suggested that SARS-CoV-2 could remain viable in aerosols for hours, and could stay stably on plastic and stainless steel for at least 72 hours [44]. While more studies are needed to demonstrate its replication-competence, its abundance in stool and stability in environment would poise SARS-CoV-2 favourably to spread among human hosts. This faecal source can lead to viral transmission especially when aerosols are generated, as with the major outbreak caused by toilet fume in Amoy Garden during the SARS epidemics in Hong Kong [36]. The gastrointestinal involvement of Covid-19 would necessitate a need to consider several clinical policies, such as incorporation of rectal swab testing before discharging patients [45], as well as our preparedness for personal protective equipment in the endoscopy setting [46, 47]. These considerations will be important in our battle against Covid-19.

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Table 1. Presentation of gastrointestinal symptoms in coronavirus infection: a comparison of Covid-19, SARS, MERS in major clinical cohorts. Case reports, series or cohorts with less than twenty subjects are not included.

	Subject	Diarrhoea	Nausea	Vomiting	Abdominal pain
Covid-19					
Chen N et al [11]	99	2 (2.0%)	1 (1%)	1 (1%)	NA
Guan W et al [10]	1099	42 (3.8%)	55 (5.0%)	55 (5.0%)	NA
Huang C et al [12]	38	1 (2.6%)	NA	NA	NA
Liu K et al [13]	137	11 (8%)	NA	NA	NA
Lu X et al [14]	171	15 (8.8%)	NA	11 (6.4%)	NA
Shi H et al [15]	81	3 (3.7%)	NA	4 (4.9%)	NA
Wang D et al [16]	138	14 (10.1%)	14 (10.1%)	5 (3.6%)	3 (2.2%)
Xiao F et al [7]	73	26 (35.6%)	NA	NA	NA
Xu XW et al [17]	62	3 (4.8%)	NA	NA	NA
Yang X et al [18]	52	NA	NA	2 (3.8%)	NA
Zhang JJ et al [20]	139	18 (12.9%)	24 (17.3%)	7 (5.0%)	8 (5.8%)
Zhou F et al [19]	141	9 (4.7%)	7 (3.7%)	7 (3.7%)	NA
SARS					
Booth CM et al [48]	144	34 (23.6%)	28 (19.4)	28 (19.4)	5 (5.0%)
Cheng VC et al [23]	142	69 (48.6%)	NA	NA	NA
Choi KW et al [49]	267	41 (15.4%)	NA	19 (7.1%)	NA
Jang TN et al [50]	29	4 (13.8%)	5 (17.2%)	5 (17.2%)	NA
Kwan AC et al [51]	240	49 (20.4%)	NA	NA	NA
Lee N et al [21]	138	27 (19.6%)	27 (19.6%)	27 (19.6%)	NA
Leung CW et al [52]	44	9 (20.5%)	13 (29.5%)	13 (29.5%)	4 (9.1%)
Leung WK et al [22]	138	53 (38.4%)	NA	NA	NA
Liu CL et al [24]	53	35 (66.0%)	6 (11.3%)	5 (9.4%)	5 (9.4%)
Peiris JS et al [25]	75	55 (73.3%)	NA	NA	NA
MERS					
Al Ghamdi M et al [53]	51	13 (25.5%)	NA	12 (23.5%)	NA
Almekhlafi GA et al [54]	31	6 (19.4%)	NA	4 (12.9%)	9 (29.0%)
Arabi YM et al [55]	330	38 (11.5%)	58 (17.6%)	58 (17.6%)	47 (14.2%)
Assiri A et al [56]	47	12 (25.5%)	10 (21.2%)	10 (21.2%)	8 (17.0%)
Assiri A et al [57]	23	5 (21.7%)	NA	4 (17.4%)	NA
Choi WS et al [58]	186	36 (19.4%)	26 (14.0%)	26 (14.0%)	15 (8.1%)

Kim KM et al [59]	36	7 (19.4%)	5 (13.9%)	5 (13.9%)	NA
Nam HS et al [60]	25	8 (32.0%)	8 (32.0%)	8 (32.0%)	8 (32.0%)
Saad M et al [61]	70	21 (30%)	NA	21 (30%)	17 (24.3%)
Sherbini N et al [62]	29	8 (27.6%)	8 (27.6%)	8 (27.6%)	NA