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Diarrhoea and the COVID-19 pandemic

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The new COVID-19 pandemic has been initially linked to respiratory manifestations. However, there is increasing evidence that other systems are affected by SARS-CoV2, one of which is the gastrointestinal system with several organ-related symptoms and possible implications on prognosis and spread. Diarrhoea is one of the main symptoms of gastrointestinal involvement. In this review the mechanisms, characteristics, prognostic significance and management of of COVID-19 related diarrhoea are discussed. The possibility of faecal transmission of disease is reviewed.

Introduction

Coronavirus disease 2019 (COVID-19) which is caused by a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has emerged as a new pandemic. COVID-19 has been initially described to be mainly a respiratory illness. Infection can be asymptomatic or associated with a spectrum of respiratory symptoms [1,2]. However, the disease is not limited to the respiratory system and other organs can be affected [3]. Gastrointestinal (GI) symptoms and shedding of SARS-CoV-2 RNA in faeces have been frequently documented in COVID-19 [4]. Patients with COVID-19 presenting with diarrhoea are increasingly reported, with cases presenting with GI symptoms as the only presentation of COVID-19 without any respiratory symptoms [2,5].

Epidemiology

Incidence rate of diarrhoea due to SARS-CoV-2 infection in clinical studies is ranging from 2% to 50% of cases, and in a pooled analysis based on 24 publications including 3042 patients the overall diarrhoea rate was 10.4% [2]. A study showed that 3.8% of 1099 Chinese patients with COVID-19 had diarrhoea [6]. In another study diarrhoea developed in 9% of patients who had symptoms more than 10 days, however patients with shorter duration of disease course did not develop diarrhoea [7]. Regarding children, epidemiologic data on COVID-19 are flawed; however in 171 children with a median age of 6.7 years diarrhoea was reported in 8.8% of cases [8].

Diarrhoea was reported in 4.8% of patients with COVID-19 in a systematic review describing the epidemiologic aspects of 1995 patients with SARS-CoV-2 infection [9].

Diarrhoea was a major symptom in 48% of patients with SARS-CoV-2 infection in a retrospective study done at the Nord Franche-Comté hospital, and was the fifth most common symptom. The median age of patients was 56 years (±18) and 58% were female. It started 4.5 days (±1.8) after the onset of first other symptoms, and around half of patients had at least one simultaneous GI symptom other than diarrhoea. It is worth mentioning that 3.6% of patients were previously diagnosed as inflammatory bowel disease [10].

The American Gastroenterological Association (AGA) has published new expert recommendations in gastroenterology and stated that, diarrhoea can be the first presentation in COVID-19, however GI symptoms are not as common in COVID-19 as previously estimated, with an overall prevalence of 7.7% (95% CI 7.4 to 8.6%) for diarrhoea, and pooled prevalence of 7.9% across 35 studies, encompassing 9,717 patients [11]. However, with the spread of the pandemic and further collection of data from different parts of the world these figure may need to be revisited.

A more recent meta-analysis was performed and included 3024 patients with COVID-19 from 21 studies, and results showed that the prevalence of diarrhoea in those patients was 9.1% [12] (Table 1).

Mechanism of diarrhoea in COVID-19

Viral structure

SARS-CoV-2 belongs to a large family of coronaviruses (CoVs), it is containing single-stranded (positive-sense) RNA with a nucleo-
protein within a capsid comprised of matrix protein, and outer envelope that carries glycoprotein projections. It is formed of four main structural proteins, envelope, spike, membrane, and nucleocapsid proteins that are encoded by open reading frames (ORFs) 10, 11 [13,14]. Entry of SARS-CoV into a host cell is mediated through the interaction between the viral spike (S) protein and the angiotensin-converting enzyme 2 (ACE2) cell receptor. The S protein is composed of 2 subunits, S1 allows attachment of the viral particles to the cell membrane, and S2 aids in the fusion of the both cell membranes [2,15]. Continuation of this process is done by cellular serine proteases (TMPRSS2), which promotes spike protein cleavage, priming and regulating the entire process [16]. Besides TMPRSS2, Zang et al found that TMPRSS4 increases SARS-CoV-2 infectivity, at least in gut epithelial cells [4] (Fig. 1).

ACE2 is expressed in lung alveolar type II cells, upper oesophagus, and in absorptive enterocytes in the ileum and the colon as shown by bioinformatic analysis of single-cell transcriptomes [17]. There is high expression of both ACE2 and TMPRSS2 in the intestinal epithelial cells of the GI tract. These latter cells also represent targets for many human enteric viruses. Several animal CoVs are natural enteric pathogens, cause GI diseases, and spread by the faecal-oral route [18]. The binding affinity of viral particles to ACE2 receptors represents a major determinant of infectivity. SARS-CoV-2 seems to use human ACE2 more efficiently than the 2003 strain of SARS-CoV [19,20] The accurate mechanisms of diarrhoea in these viral infections are not entirely known and more studies are needed in that respect and also to investigate the correlation between respiratory and GI symptoms [21]. It should be noted that intestinal ACE2 is regulating the expression and uptake of dietary amino acids, antimicrobial peptides and enhances the homeostasis of the gut microbiome [22], and viral infection cause alteration of intestinal permeability enterocyte leading to malabsorption [23].

Cytokines

Cytokines such as interleukin-1 (IL-1), IL-6, IL-36, IL-33, tumor necrosis factor-α (TNF-α) and TNF-like have a role in maintaining the GI integrity [24]. The cytokine storm which occurs with SARS-CoV-2 infection leads to elevation of different cytokines, including IL-2, IL-7, IL1-β, IL-1RA, IL-7, IL-8, IL-9, IL-10, granulocyte colony-stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and tumour necrosis factor-α [25,26]. Some of these cytokines are suggested to maintain GI health and can be also responsible for GI disease. IL-2, for example, is a potent cytokine which preserves intestinal epithelium after injury by mechanical stress, infections or viruses, through binding to lymphocytes and macrophages [27]. Moreover, IL-10 and TNFα allow termination of excess inflammatory responses after infections or cell death so maintaining integrity of gut barrier [28–30]. These effects imply an increased protective response to COVID-19 infection and damage to the GI tract. However, we need more studies to show how cytokines affect the integrity of the GI and respiratory tract through alterations in expression and secretion [30].
Faecal transmission of COVID-19

SARS-CoV-2 was isolated from whole blood, serum, urine, and faecal samples [35]. Zhang et al suggested faecal-oral transmission is a route for COVID-19 spread, through detection of the viral nucleic acid in anal swabs and faecal samples of hospitalized patients [36]. Cai et al. demonstrated prolonged viral RNA shedding in faeces for up to one month or more, suggesting the gastrointestinal tract as a possible site for viral replication [37]. In China 53.42% of 73 COVID-19 patients with ages ranging from 10 months to 78 years old tested positive for SARS-CoV-2 RNA in stool samples, whereas 23.29% continued to test positive in stool even after having negative samples from the respiratory tract [32]. Also SARS-CoV-2 RNA was detected with positive staining of the viral nucleocapsid protein in gastric, duodenal, and rectal biopsies taken by endoscopy. These results support the evidence of viral replication within the gastrointestinal tract [32]. Accordingly, faecal-oral transmission should be considered. Furthermore, it should be underlined that viral RNA in faeces can remain even after clearance of viral RNA from respiratory tract clears, which may imply a threat for spread through this route. Testing of viral RNA in faeces by rRT-PCR can be considered to monitor for adequate infection control [32,38].

In children SARS-CoV-2 may exist in the GI tract for a longer time than the respiratory system, viral RNA remained detectable in stools of paediatric patients for longer than 4 weeks [39].

All major American gastroenterological societies including American Association for the Study of Liver Diseases (AASLD), American Gastroenterological Association (AGA), American College of Gastroenterology (ACG) and American Society of Gastrointestinal Endoscopy (ASGE) have made recommendations for managing COVID-19 in the patients both in outpatient and endoscopy settings taking in consideration the potential risk of spread of infection via faecal–oral transmission [40–42]. We need to highlight different points of research on the possibility of faecal–oral route of transmission of SARS-CoV-2, that should include environmental studies to determine the viability of the virus in conditions that would favour such transmission, whether severity of the disease and presence or absence of GI symptoms correlate with the concentrations of SARS-CoV-2 RNA in faeces, and detection of fecal SARS-CoV-2 RNA in the incubation or convalescence phases of COVID-19 [20].

Features of diarrhoea due to COVID-19

In COVID-19 diarrhoea may be an isolated symptom, develop in conjunction with other GI symptoms without respiratory symptoms or develop prior to respiratory affection [11,43]. However, few reports exist on the features of diarrhoea caused by SARS-CoV-2 [11]. Lin et al, described it as loose or watery stools with 2–10 bowel movements per day in 24% of patients (23 /95); but, a small number of patients (5.2%) had diarrhoea at admission. Most patients developed diarrhoea during the course of hospitalization, and may be also related to drugs [44]. Jin et al described diarrhoea as more than 3 loose stools per day in 8.6% of 651 patients on hospital admission, before starting any medications, with median duration of 4 days (range, 1–9 days). Stool cultures were negative (including Clostridium difficile) in all patients [45].

Prognostic significance of diarrhoea in COVID-19

Data from 35 studies, including 6686 patients with COVID-19 demonstrated a relative delay in diagnosis in patients with GI symptoms with subsequent negative impact on patients themselves and their contacts [46]. A systematic review showed that no difference in the prevalence of diarrhoea between severe and non-severe patients (OR, 1.24; 95%CI, 0.90 to 1.72; I² = 0%, P = 0.19). Furthermore, diarrhoea was not related to prognosis (OR, 1.22; 95%CI, 0.50 to 2.98; I² = 0%, P = 0.66) [12].

Wei et al., reported that 26 (31%) of 84 patients with SARS-CoV-2 pneumonia, had diarrhoea. The duration of fever and dyspnoea in patients with diarrhoea was significantly longer than in those without diarrhoea (10.5 ± 4.7 vs 7.6 ± 3.4 days, P = 0.005; 8.1 ± 3.2 vs 4.7 ± 2.3 days, P = 0.002, respectively) [47].

A systematic review of data from 78 studies, including 12,797 patients with SARS-CoV-2 infection showed that, mortality among patients with GI symptoms was 0.4% (95% CI, 0%-1.1%) which was similar to overall mortality [2.1% (95% CI, 0.2%-4.7% )], p = 0.15 [48].

Management of diarrhoea in COVID-19

Till now no specific antiviral treatment is confirmed to be effective in the treatment of COVID-19 nor is there a vaccine available. Management is mainly based on supportive care. However, clinical trials are in effect with medications such as lopinavir/ritonavir,
hydroxylchloroquine, aerosolized alpha-interferon, tocilizumab and remdesivir [38,53]. There are reports on a noticeable improvement in diarrhea after starting antiviral therapy [54].

Most patients with acute diarrhea can compensate the loss in fluids and electrolytes via the oral route. Balanced electrolyte rehydration over other oral rehydration options particularly in the elderly with severe diarrhea or cholera-like watery diarrhea is recommended [55].

It is known that antibiotics and antivirals can lead to gut dysbiosis, causing diarrhea. These are often used during the course of COVID-19 disease [2,56]. Gut microbiota could, therefore, be a new therapeutic target. Probiotics may have a role in the management of diarrhea due to COVID-19 [23,33]. It should be taken into consideration to exclude other agents before initiating supportive care. Clostridium difficile toxin assay, for example, may be needed as well as other gastrointestinal pathogen panel. The use of antibiotics is controversial but recommended only if coinfection is noted [38].

Probiotics have been recommended in patients with severe COVID-19 by China’s National Health Commission to maintain intestinal integrity and prevent secondary bacterial infections [2,23].

Several molecules may have beneficial effects, at least theoretically. Some monoclonal antibodies can target the receptor-binding domain of the spike protein and inhibit the contact between the virus and ACE2 [57]. Another target can be the TMPRSS2 protease, which plays a crucial role in pathogenesis of the disease [2,4,24].

Camostat mesylate is a TMPRSS2 inhibitor and is approved in Japan for management of noninfectious conditions, such as chronic pancreatitis and reflux esophagitis. There are suggestions that it can be effective in COVID-19 treatment [25,8].

Baricitinib is a JAK kinase inhibitor which was proposed for of COVID-19 treatment. It acts on cellular endocytosis, with subsequent possible reduction of viral passage into host cells. Both anti-inflammatory and antiangiogenic activities of the drug could be effective in diarrhea and deserve further studies [2,59].

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