Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Arab Journal of Gastroenterology 21 (2020) 146–150

Contents lists available at ScienceDirect

Arab Journal of Gastroenterology

journal homepage: www.elsevier.com/locate/ajg

Review article

Diarrhoea and the COVID-19 pandemic

Yasmine Gaber *

Endemic Medicine Department, Kasr Al-Aini Faculty of Medicine, Cairo University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 23 June 2020
Accepted 23 June 2020

ABSTRACT

The new COVID-19 pandemic has been initially linked to respiratory manisfestations. 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 managment 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-

* Corresponding author.
E-mail address: yasmin.mohamed@cu.edu.eg

https://doi.org/10.1016/j.ajg.2020.06.001
1687-1979/

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].

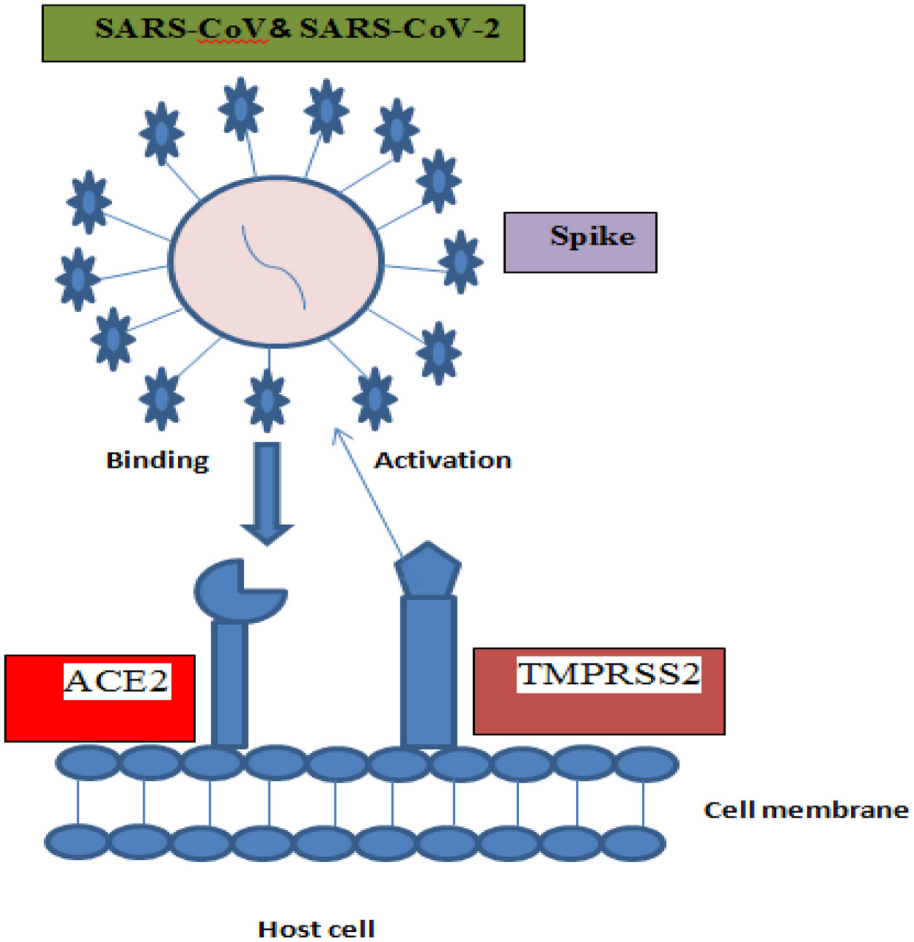

Fig. 1. The interaction of SARS-CoV to ACE2 and cellular serine protease TMPRSS2 [14].

Table 1
Systematic reviews and meta-analysis on gastrointestinal symptoms of COVID-19, including diarrhoea.

	Total number of studies	Total number of patients	Pooled estimates (%) of GI symptoms	Pooled estimates (%) of diarrhoea	Viral RNA Fecal shedding (% of patients)
Parasa et al. [49]	23 published and 6 preprint	4805	12%	7.4%	40.5%
Tariq [48]	78	12,797		12%	
Mao et al. [46]	35, (only 29 studies reported GI symptoms)	6686 (6064 reported GI symptoms)	15%	9%	54%
Rokkas [50]	37	5601	9.8%	10.4%	30.3%
Kumar et al. [51]	17	2477	13%	7.8%	
Sultan et al.[11]	47	10,890		7.7%	
Cheung et al. [52]	60	4243	17.6%	12.5%	48.1%

Abbreviations: GI: gastrointestinal.

Gut microbiota

There is growing evidence that gut dysbiosis is involved in the pathogenesis of both intestinal and extra-intestinal disorders [31]. It is supposed that despite resolution of respiratory infection, COVID-19 might produce changes in the GI tract structure and physiology. It is reported that 20% of COVID-19 patients have continuous faecal viral shedding even after the negative conversion of viral RNA in the respiratory tract [32]. As observed in the past with the influenza virus, gut-microbiome and gut-lung crosstalk could happen with COVID-19 genome [33]. Gut dysbiosis was observed in few patients with COVID-19 such as decreased probiotics lactobacilli and Bifidobacteria [30,34].

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; I^2 = 0%, P = 0.19). Furthermore, diarrhoea was not related to prognosis (OR, 1.22; 95%CI, 0.50 to 2.98; I^2 = 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,

hydroxychloroquine, aerosolized alpha-interferon, tocilizumab and remdesivir [38,53]. There are reports on a noticeable improvement in diarrhoea after starting antiviral therapy [54].

Most patients with acute diarrhoea 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 diarrhoea or cholera-like watery diarrhoea is recommended [55].

It is known that antibiotics and antivirals can lead to gut dysbiosis, causing diarrhoea. 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 diarrhoea 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].

Camostat mesylate is a TMPRSS2 inhibitor and is approved in Japan for management of noninfectious conditions, such as chronic pancreatitis and reflux oesophagitis. There are suggestions that it can be effective in COVID-19 treatment [2,58].

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 antiendocytic activites of the drug could be effective in diarrhoea and deserve further studies [2,59].

References

[1] Wang D, Hu B, Hu C. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. [published online ahead of print, 2020 Feb 7]. JAMA 2020. https://doi.org/10.1001/jama.2020.1585.

[2] D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. Clin Gastroenterol Hepatol 2020.

[3] Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: radiologic and clinical overview. Clin Imaging 2020.

[4] Zang R, Castro MF, McCune BT, Zeng Q, Rothlauf PW, Sonnek NM, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol 2020;5(47).

[5] Pan L, Mu M, Ren HG. 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.

[6] Guan WJ, Ni ZY, Hu Y. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.

[7] Xu X-W, Wu X-X, Jiang X-G. 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.

[8] Lu X, Zhang L, Du H. SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663–5.

[9] Li L-Q, Huang T, Wang Y-Q. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020. https://doi.org/10.1002/jmv.25757.

[10] Klopfenstein T, N'dri Juliette Kadiane-Oussou P, Royer Y, Toko L, Gendrin V, Zayet S. Diarrhea: an underestimated symptom in coronavirus disease 2019. Clinics and Research in Hepatology and Gastroenterology. 2020 Apr 27.

[11] Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK, et al. AGA Institute Rapid Review of the GI and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. Gastroenterology 2020.

[12] Wang H, Qiu P, Liu J, Wang F, Zhao Q. The liver injury and gastrointestinal symptoms in patients with Coronavirus Disease 19: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2020.

[13] Van Boheemen S, de Graaf M, Lauber C, Bestebroer TM, Raj VS, Zaki AM, et al. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. mBio, 3 (6) (2012).e00473–12.

[14] Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID- 19: Their roles in pathogenesis. J Microbiol Immunol Infect 2020;31.

[15] Cui J, Li F, Shi Z-L. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019;17:181–92.

[16] Hoffmann M., Kleine-Weber H., Schroeder S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. [published online ahead of print, 2020 Mar 4] Cell. 2020 S0092-8674(20) 30229-4. doi:10.1016/j.cell.2020.02.052

[17] Zhang H, Kang Z, Gong H. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. bioRxiv. 2020:2020. 01.30.927806.

[18] Weiss SR, Leibowitz JL. Coronavirus pathogenesis. In Advances in virus research 2011 Jan 1 (Vol. 81, pp. 85-164). Academic Press.

[19] Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS.J Virol. 2020; (published online Jan 29.). doi: 10.1128/JVI.00127-20.

[20] Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible?. Lancet Gastroenterol Hepatol 2020 Apr 1;5(4):335–7.

[21] Gao QY, Chen YX, Fang JY. 2019 Novel coronavirus infection and gastrointestinal tract. J Dig Dis 2020;21:125–6.

[22] Hashimoto T, Perlot T, Rehman A. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 2012;487:477–81.

[23] Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. [published online ahead of print, 2020 Mar 3] Gastroenterology. 2020:S0016–S5085. (20)30281-X. doi: 10.1053/j.gastro.2020.02.054.

[24] Bamias G, Dinarello CA, Rivera-Nieves J. Innate cytokines dictate the fate of acute intestinal inflammation. Gastroenterology.2015;148:248–250. doi: 10.1053/j.gastr o.2014.11.013.

[25] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020. doi: 10.1016/s0140-6736(20)30628-0.

[26] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020. doi: 10.1016/j.jaut.2020.10243 3

[27] Dignass AU, Podolsky DK. Interleukin 2 modulates intestinal epithelial cell functionin vitro. Exp Cell Res. 1996;225:422–429.doi: 10.1006/excr.1996.0193

[28] Takada Y, Hisamatsu T, Kamada N, et al. Monocyte chemoattractant protein-1 contributes to gut homeostasis and intestinal inflammation by composition of IL-10—producing regulatory macrophage subset. J Immunol. 2010;184:2671–2676. doi: 10.4049/jimmu nol.08040 12.

[29] Ruder B, Atreya R, Becker C. Tumour necrosis factor alpha in intestinal homeostasis and gut related diseases. Int J Mol Sci.2019;20:1887. doi: 10.3390/ijms2 00818 87

[30] Kopel J, Perisetti A, Gajendran M, Boregowda U, Goyal H. Clinical Insights into the Gastrointestinal Manifestations of COVID–19.

[31] Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. Dysbiosis of the gut microbiota in disease. Microbial Ecology in Health Disease 2015;26(1):26191.

[32] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020. https://doi.org/10.1053/j.gastr o.2020.02.055.

[33] Bradley KC, Finsterbusch K, Schnepf D, et al. Microbiota driven tonic interferon signals in lung stromal cells protect from influenza virus infection. Cell Rep. 2019;28:245–256.e4. doi: 10.1016/j.celre p.2019.05.105.

[34] Xu K, Cai H, Shen Y, et al. Management of corona virus disease-19 (COVID- 19): the Zhejiang experience. J Zhejiang Univ 2020:49.

[35] Buruk K, Ozlu T. New Coronavirus: SARS-COV-2. Mucosa 2020;1–4. https://doi.org/10.33204/mucosa.706906.

[36] Zhang W., Du R.-H., Li B. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. 2020;9(1):386–389.

[37] Cai J, Xu J, Lin D, Xu L, Qu Z, Zhang Y, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin. Infect. Dis. 2020.

[38] Patel KP, Patel PA, Vunnam RR, Hewlett AT, Jain R, Jing R, et al. Gastrointestinal, hepatobiliary, and pancreatic manifestations of COVID-19. J Clin Virol 2020;29:104386.

[39] Xing YH, Ni W, Wu Q, Li WJ, Li GJ, Wang WD, et al. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. J Microbiol Immunol Infect 2020;28.

[40] American Society for Gastrointestinal Endoscopy. ASGE Releases Recommendations for Endoscopy Units in the Era of COVID-19. American Society for Gastrointestinal Endoscopy. https://www.asge.org/docs/default-source/default-document library/pressrelease_impact-of-covid-19-on-endoscopy.pdf.

[41] Bezerra JA, Pochapin MB, El-Serag HB, Vargo JJ. COVID-19 clinical insights for our community of gastroenterologists and gastroenterology care providers. Bethesda: American College of Gastroenterology; 2020.

[42] Soetikno R, Teoh AY, Kaltenbach T, et al. Considerations in performing endoscopy during the COVID-19 pandemic. Gastrointest Endosc. 2020. doi: 10.1016/j.gie.2020.03.375.
[43] Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol 2020 Jun;18 (7):1636.
[44] Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut 2020;69(6):997–1001.
[45] Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, 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.
[46] Mao R, Qiu Y, He J-S et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020; (published online May 12.) doi: 10.1016/S2468-1253(20)30126-6.
[47] Wei XS, Wang X, Niu YR, Ye LL, Peng WB, Wang ZH, et al. Diarrhea is associated with prolonged symptoms and viral carriage in COVID-19. Clin Gastroenterol Hepatol 2020.
[48] Tariq R, Saha S, Furqan F, Hassett L, Pardi D, Khanna S. Prevalence and Mortality of COVID-19 patients with Gastrointestinal Symptoms: A Systematic Review and Meta-analysis. InMayo Clinic Proceedings 2020 Jun 10. Elsevier.
[49] Parasa S, Desai M, Chandrasekar VT, Patel HK, Kennedy KF, Roesch T, Spadaccini M, Colombo M, Gabbiadini R, Artifon EL, Repici A. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. JAMA Network Open. 2020 Jun 1;3(6):e2011335.
[50] Rokkas T. Gastrointestinal involvement in COVID-19: a systematic review and meta-analysis. Ann Gastroenterol (2020) 33, 1-11. doi: 10.20524/aog.2020.0506.
[51] Kumar VC, Mukherjee S, Harne PS, Subedi A, Ganapathy MK, Patthipati VS, Sapkota B. Novelty in the gut: a systematic review and meta-analysis of the gastrointestinal manifestations of COVID-19. BMJ Open Gastroenterol 2020 May 1;7(1):e000417
[52] Cheung KS, Hung IF, Chan PP, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis. Gastroenterology 2020.
[53] Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation and Treatment Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island(FL):Stat Pearls Publishing: https://www.ncbi.nlm.nih.gov/ books/ NBK554776/ (2020).
[54] Song Y., Liu P., Shi X.L. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. [published online ahead of print, 2020 Mar 5] Gut. 2020 gutjnl-2020-320891. doi: 10.1136/gutjnl-2020-320891.
[55] Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Am J Gastroenterol 2016 May 1;111(5):602–22.
[56] Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med. 2002;346:334–9.
[57] Tian X, Li C, Huang A. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microbes Infect 2020;9:382–5.
[58] Kawase M, Shirato K, van der Hoek L. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. J Virol 2012;86:6537–45.
[59] Richardson P, Griffin I, Tucker C. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020;395:e30–1.