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Editorial Board Member of *World Journal of Clinical Cases*, Fan-Bo Meng, MD, PhD, Chief Doctor, Deputy Director, Professor, Department of Cardiology, China-Japan Union Hospital of Jilin University, Changchun 130000, Jilin Province, China. mengfb@jlu.edu.cn

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COVID-19 and gastroenteric manifestations

Zhang-Ren Chen, Jing Liu, Zhi-Guo Liao, Jian Zhou, Hong-Wei Peng, Fei Gong, Jin-Fang Hu, Ying Zhou

ORCID number: Zhang-Ren Chen 0000-0002-1520-3519; Jing Liu 0000-0002-1520-0000; Zhi-Guo Liao 0000-0002-1520-0001; Jian Zhou 0000-0002-1520-0002; Hong-Wei Peng 0000-0002-1520-0011; Fei Gong 0000-0002-1520-3523; Jin-Fang Hu 0000-0002-1520-3578; Ying Zhou 0000-0001-5311-9070.

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Zhang-Ren Chen, Jing Liu, Zhi-Guo Liao, Jian Zhou, Hong-Wei Peng, Fei Gong, Jin-Fang Hu, Ying Zhou, Department of Pharmacy, The First Affiliated Hospital of Nanchang University, Nanchang 330100, Jiangxi Province, China

Corresponding author: Ying Zhou, PhD, Associate Chief Pharmacist, Research Assistant Professor, Research Scientist, Department of Pharmacy, The First Affiliated Hospital of Nanchang University, No. 17 Yongwaizhengjie, Donghu District, Nanchang 330100, Jiangxi Province, China. zyyiva@163.com

Abstract

Coronavirus disease 2019 (COVID-19), caused by the infection of a novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], has become a pandemic. The infection has resulted in about one hundred million COVID-19 cases and millions of deaths. Although SARS-CoV-2 mainly spreads through the air and impairs the function of the respiratory system, it also attacks the gastrointestinal epithelial cells through the same receptor, angiotensin converting enzyme 2 receptor, which results in gastroenteric symptoms and potential fecal-oral transmission. Besides the infection of SARS-CoV-2, the treatments of COVID-19 also contribute to the gastroenteric manifestations due to the adverse drug reactions of anti-COVID-19 drugs. In this review, we update the clinical features, basic studies, and clinical practices of COVID-19-associated gastroenteric manifestations.

Key Words: COVID-19; SARS-CoV-2; Gastroenteric manifestations; Adverse drug reaction; Management

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Core Tip: Gastroenteric manifestations, including anorexia, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding, can worsen the situation of patients with coronavirus disease 2019 (COVID-19). More efforts should be spared to understand its pathology and mechanism. Besides the infection of severe acute respiratory syndrome coronavirus 2 virus, the treatments of COVID-19 also contribute to the gastroenteric manifestations due to the adverse drug reactions of anti-COVID-19 drugs. Timely supportive or symptomatic treatment and withdrawal of adverse drug reaction-inducing drugs can help to manage COVID-19-associated gastroenteric manifestations.

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INTRODUCTION

The Coronaviridae family can infect both humans and animals, of which seven types of coronaviruses (CoVs) can infect humans[1]. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-CoV emerged in the 21st century and were endemic locally[2,3]. Since late 2019 through January 2021, SARS-CoV-2 has accounted for over one hundred million confirmed cases and over two million deaths in all countries and all seven continents (<https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6>). SARS-CoV-2 is a beta coronavirus that originated in bats[4]. It is still poorly understood how those zoonotic coronaviruses were transmitted from bats to humans despite some clues[5,6].

The RNA of SARS-CoV-2 can be detected in the blood, kidneys, liver, heart, brain, and other organs of infected patients[7]. The infection of SARS-CoV-2 mainly occurs in the respiratory tract. The clinical manifestations of the SARS-CoV-2 infection range from asymptomatic infection, mild influenza-like symptoms (mainly fever, cough, and fatigue), severe pneumonia, multiorgan failure, and even death[8]. Some of the COVID-19 patients who suffer from the disease induced by the infection of SARS-CoV-2 have gastroenteric manifestations, mainly manifested as anorexia, nausea, vomiting, diarrhea, and abdominal pain[9,10]. The mechanism of COVID-19-associated gastroenteric manifestations has not been fully demonstrated. Also, the anti-COVID-19 treatments can induce gastroenteric side effects that may confuse with or superimpose with the COVID-19-associated gastroenteric manifestations. This review introduces the clinical features, mechanism, and management of COVID-19-associated gastroenteric manifestations.

GASTROENTERIC MANIFESTATIONS OF COVID-19 PATIENTS

Respiratory symptoms, including fever, fatigue, and dry cough, are the most common manifestations among COVID-19 patients. In addition, some patients suffered gastrointestinal tract disorders, including anorexia, nausea, vomiting, diarrhea, and abdominal pain[8]. The incidence of gastroenteric manifestations among COVID-19 patients varied between initial reports and subsequent studies[11]. Guan *et al*[12] and Wang *et al*[13] reported that gastroenteric manifestations can be found among 2% to 10% of COVID-19 patients. However, some meta-analyses found that the prevalence can be 9.8%, 33.4%, and 50.5%[14-16]. This divergence can be explained partly by the difference of included patients, which consist of outpatients and hospitalized patients. The RNA of SARS-CoV-2 can be detected in the stools of infected people, and the fecal viral shedding duration and positive viral rectal swabs can last for a long time after the respiratory specimens or nasopharyngeal swabs turned negative in both adults and children[17]. Those findings proposed the potential fecal-oral transmission. But the viral RNA detected in stools does not fully equate to live viruses, and further studies need to be done.

Typical gastrointestinal symptoms of COVID-19 patients consist of anorexia, nausea and vomiting, diarrhea, and abdominal pain[18]. In addition to the above-mentioned typical symptoms, some specific symptoms can be observed, such as gastrointestinal bleeding[18,19]. Noteworthy, the above-mentioned gastroenteric manifestations were observed before fever in 14 (10.1%) patients in a study[13]. Most typical gastrointestinal symptoms are mild and common[20]. The diagnosis of gastrointestinal manifestations related to COVID-19 is essential but difficult due to the atypical features in the clinic[21]. Some COVID-19 patients may not exhibit respiratory symptoms but gastrointestinal or other such atypical symptoms[21].

Anorexia, which manifests as loss of appetite, is the most common gastroenteric manifestations, and the prevalence ranged from 1.0% to 79%[22,23]. The mechanism of COVID-19 associated anorexia is still poorly understood. Gustatory dysfunction of COVID-19 patients may explain it partly[23]. Gustatory dysfunction was markedly associated with olfactory dysfunction, which is a specific feature of early SARS-CoV-2

infection[24].

Nausea and vomiting, as a symptom of COVID-19, may result from the SARS-CoV-2 impact on the digestive system and/or central nervous system[22]. The prevalence of nausea and vomiting ranged from 7.8% to 22.7%[22]. Some anti-COVID-19 treatments can also induce nausea and vomiting, which is independent of the viral infection. In addition, treatment-induced nausea and vomiting may be merged with disease-induced nausea and vomiting and worsen the clinical status of COVID-19 patients.

Diarrhea, a common disorder of COVID-19 patients, can be induced by the intestinal SARS-CoV-2 infection itself, the disturbance of gut microbiota, and some anti-COVID-19 treatments (such as oseltamivir and abidol hydrochloride). The prevalence has been reported as 5%-10%, 2%-50%, and 22.1% in three independent reports[14,15,25]. Twenty-two percent of COVID-19-associated diarrhea were not treatment-induced[22]. Considering the potential fecal-oral transmission of SARS-CoV-2, more attention should be paid to COVID-19-associated diarrhea as a public health issue that could lead to the community transmission of COVID-19.

Abdominal pain was less common among COVID-19 patients compared with the above-mentioned gastrointestinal symptoms[22]. The mechanism of COVID-19 associated abdominal pain has also not been well elucidated yet. The SARS-CoV-2 infection-induced visceral pain and/or the involvement of the peritoneum may contribute to COVID-19 associated abdominal pain[22].

Gastrointestinal bleeding is a rare specific manifestation of COVID-19 patients and causes hematemesis or melena. Several gastrointestinal bleeding cases of COVID-19 patients have been reported, and it is more fatal than general gastrointestinal manifestations[18,19,26]. Cavaliere *et al*[19] reported 6 COVID-19 patients with upper gastrointestinal bleeding and concluded that COVID-19 patients with upper gastrointestinal bleeding should be treated without endoscopy. But there are still some controversies because some disorders (pulmonary embolism, myocardial infarction, and renal failure) and the intake of substances (iron supplements, bismuth subsalicylate, and foods such as blood soup) can lead to coffee-ground hematemesis episodes or black stools similar to melena[27]. Thus, despite those patients' responses to conservative treatment in 24 h[19], Duan *et al*[27] states that endoscopy is still essential to find the cause of hematemesis or melena.

PATHOLOGY AND MECHANISM OF SARS-COV-2 INFECTING THE GASTROENTERIC TRACT

Pathological research confirmed that SARS-CoV-2 mainly targets the respiratory system and causes the impairment of pulmonary function. COVID-19 has similar pathological features of SARS and Middle East respiratory syndrome[20]. In addition, autopsy and endoscopy studies demonstrated that the infection of SARS-CoV-2 also causes lesions in the gastroenteric tract. Some researchers analyzed 28 autopsy studies that include 341 COVID-19 cases, and concluded that most studies focused on pulmonary alterations, and only a few pieces of information are given about the features of other organs and systemic findings[28-30]. Elsoukkary *et al*[29] found that the color of the stomach mucosa turned crimson, and some bleeding points can be seen on the stomach mucosa *via* the gross examination of a COVID-19 death autopsy, while the color of the intestine has not changed[31]. In the intestine autopsy of an 85-year-old man with COVID-19, segmental dilatation and stenosis alternating was found. However, it is still not clear whether it is induced by the infection of SARS-CoV-2[31]. Furthermore, viral particles were found in enterocytes in the large intestine after COVID-19 death autopsy through electron microscope[32]. Those findings provide further evidence of the possibility of the fecal-oral transmission of SARS-CoV-2.

Efforts to discover the mechanism of SARS-CoV-2 infecting gastroenteric tract cells led to studies involving cell lines, animals, and organoids[33,34]. Four human intestinal epithelial cell lines are permissive to SARS-CoV-2 infection, including T84, C2BBel, Caco-2, and CL14[8]. Human organoids and bat intestinal organoids also support the infection of SARS-CoV-2[35,36]. Organoids are self-assembled, differentiated, nontransformed, and three-dimensional microphysiologically culture systems that contain multiple cell types similar to the cells in a specific tissue[37]. Organoids can model niche-mimicking and form similar architectures of original organs[37]. There are unique advantages for the utilization of organoids in medical research, especially infectious diseases, cancer, genetic diseases, and novel drug discovery. Human intestinal organoids are the most advanced accessible tool for the simulation of SARS-CoV-2 infection of gastroenteric tract cells[37]. Multiple intestinal epithelial

cell types, such as enterocytes, goblet cells, tuft cells, enteroendocrine cells, and Paneth cells, can be found in human intestinal organoids.

Studies with the above-mentioned models have demonstrated the process that SARS-CoV-2 infects gastroenteric tract cells. There are four structural proteins in SARS-CoV-2: spike, envelope, membrane, and nucleocapsid. The spike protein binds to the adhesion receptor of hosts first, then binds to the entry receptor and activates a fusion of the viral and cellular membranes. Angiotensin converting enzyme 2 (ACE2) is the entry receptor for SARS-CoV-2, and transmembrane protease serine 2 is a spike priming protease[8,20]. There is a higher expression of ACE2 in the gastroenteric tract than in the respiratory tract[38]. Generally, the higher expression of ACE2 in a tissue, the more likely it was infected by SARS-CoV-2. The human colon expressed ACE2 much lower than stomach epithelial cells and enterocytes from the small intestine[39]. Consequently, human colon organoids are affected to a lesser extent than small intestine organoids, and SARS-CoV-2 infects only enterocytes, not goblet cells, enteroendocrine cells, tuft cells, or Paneth cells[36].

The infection of SARS-CoV-2 can induce alterations in gut microbiota[40]. The alterations in gut microbiota, the increase of opportunistic pathogens, and the loss of salutary bacteria contribute to the gastroenteric manifestations[41]. Bacterial species *Collinsella aerofaciens*, *Collinsella tanaka*, *Streptococcus infantis*, and *Morganella morganii* are enriched in the stools of COVID-19 patients with higher SARS-CoV-2 infectivity[41]. In another study, the reduction of an anti-inflammatory bacterium, *Faecalibacterium prausnitzii*, and the increase of *Coproccillus*, *Clostridium ramosum*, and *Clostridium hathewayi* were found to be correlated with the severity of COVID-19[42]. Management to alter the gut microbiota, such as the utilization of intestinal microecological preparations, may help to relieve disease symptoms[42,43].

COVID-19 TREATMENT-ASSOCIATED GASTROENTERIC MANIFESTATIONS

Gastroenteric disorders were the most frequent adverse drug reactions (ADRs) for the patients with COVID-19[44]. There is still a lack of specific treatment for COVID-19. Most anti-COVID-19 therapies are supportive and symptomatic treatments. Numerous drugs and chemical or biological entities have been reported as inhibitors of SARS-CoV-2 or the cures of COVID-19. Those drugs, including interferon, ribavirin, arbidol (umifenovir), lopinavir/ritonavir, hydroxychloroquine/chloroquine, azithromycin, remdesivir, *etc.* are controversial for their unproven and contradictory anti-COVID-19 effects[45]. Nevertheless, those drugs have been associated with many ADRs, of which gastrointestinal reaction are the most common[46]. Some researchers analyzed 1452 ADRs caused by antiviral agents named ribavirin, chloroquine phosphate, arbidol, and lopinavir/ritonavir and revealed that all four drugs can induce gastroenteric manifestations[47]. Gastroenteric ADRs are very common among lopinavir/ritonavir or arbidol treated patients (46.50% and 45.71%, respectively)[47,48] and less common among ribavirin or chloroquine phosphate treated patients (17.63% and 2.99%, respectively)[47]. Remdesivir can induce diarrhea, nausea, and vomiting in 3% to 9% and 3% to 5% of patients with COVID-19[49,50]. The pathology and mechanism of COVID-19 treatment-associated gastroenteric manifestations are still not revealed. Hydroxychloroquine can alter gut microbiota[51], but its correlation with gastroenteric symptoms is still not clear.

MANAGEMENT OF COVID-19-ASSOCIATED GASTROENTERIC MANIFESTATIONS

There is still no report or guideline on the treatment of COVID-19-associated gastroenteric manifestations[20]. Supportive and symptomatic therapies are suggested for the management of COVID-19-associated gastroenteric manifestations. Supportive care includes the intake of nutrients, calories, fluid, and salt to maintain balance. For patients with mild dehydration, oral rehydration is enough. But for patients with severe dehydration, intravenous rehydration should be considered. For symptomatic treatments, antiemetic drugs, such as metoclopramide and ondansetron, are suggested for patients with nausea and vomiting. Antidiarrheal medicines, like loperamide, are suggested for patients with diarrhea[20]. Intestinal microecological agents may help to mitigate the symptoms induced by the disorder of intestinal bacteria[52-54].

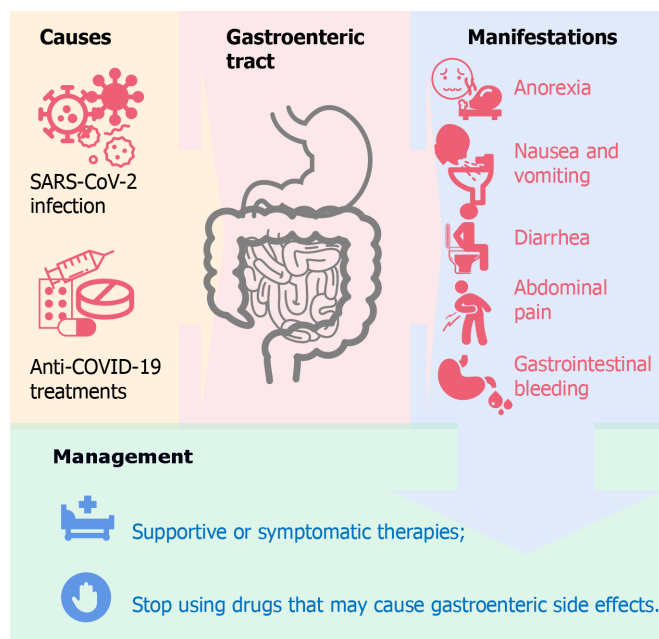


Figure 1 The causes, symptoms, and management of coronavirus disease 2019 patients with gastroenteric manifestations. Both the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the treatments of coronavirus disease 2019 (COVID-19) can induce gastroenteric manifestations. Those symptoms include anorexia, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding. Supportive or symptomatic treatments should be considered for patients with the above-mentioned disorders. The administration of drugs, which may cause those adverse drug reactions, should be discontinued.

CONCLUSION

Gastroenteric manifestations, including anorexia, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding, can be found in most COVID-19 patients, which appears to be associated with worse clinical outcomes. More patients with gastrointestinal symptoms were hospitalized compared with patients without gastrointestinal symptoms[55]. Because most gastroenteric symptoms are milder than respiratory symptoms, physicians may underestimate the risk of it. In addition, anti-COVID-19 treatments can induce gastroenteric disorders independently. The merging of SARS-CoV-2 infection-induced manifestations and COVID-19 treatment-induced manifestations may worsen the situation of patients with COVID-19. Timely supportive or symptomatic treatment and withdrawal of ADR-inducing drugs should be considered (Figure 1).

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REFERENCES

- 1 Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, Viazis N, Liatsos C, Mantzaris GJ. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. *World J Gastroenterol* 2020; **26**: 4579-4588 [PMID: 32884218 DOI: 10.3748/wjg.v26.i31.4579]
- 2 Peng H, Chen Z, Wang Y, Ren S, Xu T, Lai X, Wen J, Zhao M, Zeng C, Du L, Zhang Y, Cao L, Hu J, Wei X, Hong T. Systematic Review and Pharmacological Considerations for Chloroquine and Its Analogs in the Treatment for COVID-19. *Front Pharmacol* 2020; **11**: 554172 [PMID: 33192503 DOI: 10.3389/fphar.2020.554172]
- 3 Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, Singh KP, Chaicumpa W, Bonilla-Aldana DK, Rodriguez-Morales AJ. Coronavirus Disease 2019-COVID-19. *Clin Microbiol Rev* 2020; **33** [PMID: 32580969 DOI: 10.1128/CMR.00028-20]
- 4 Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD,

- Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: [32015507](#) DOI: [10.1038/s41586-020-2012-7](#)]
- 5 **Lam TT**, Jia N, Zhang YW, Shum MH, Jiang JF, Zhu HC, Tong YG, Shi YX, Ni XB, Liao YS, Li WJ, Jiang BG, Wei W, Yuan TT, Zheng K, Cui XM, Li J, Pei GQ, Qiang X, Cheung WY, Li LF, Sun FF, Qin S, Huang JC, Leung GM, Holmes EC, Hu YL, Guan Y, Cao WC. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* 2020; **583**: 282-285 [PMID: [32218527](#) DOI: [10.1038/s41586-020-2169-0](#)]
 - 6 **Xiao K**, Zhai J, Feng Y, Zhou N, Zhang X, Zou JJ, Li N, Guo Y, Li X, Shen X, Zhang Z, Shu F, Huang W, Li Y, Chen RA, Wu YJ, Peng SM, Huang M, Xie WJ, Cai QH, Hou FH, Chen W, Xiao L, Shen Y. Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins. *Nature* 2020; **583**: 286-289 [PMID: [32380510](#) DOI: [10.1038/s41586-020-2313-x](#)]
 - 7 **Puelles VG**, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, Chilla S, Heinemann A, Wanner N, Liu S, Braun F, Lu S, Pfefferle S, Schröder AS, Edler C, Gross O, Glatzel M, Wichmann D, Wiecek T, Kluge S, Püschel K, Aepfelbacher M, Huber TB. Multiorgan and Renal Tropism of SARS-CoV-2. *N Engl J Med* 2020; **383**: 590-592 [PMID: [32402155](#) DOI: [10.1056/NEJMc2011400](#)]
 - 8 **Synowiec A**, Szczepański A, Barreto-Duran E, Lie LK, Pyrc K. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection. *Clin Microbiol Rev* 2021; **34** [PMID: [33441314](#) DOI: [10.1128/CMR.00133-20](#)]
 - 9 **Cha MH**, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. *World J Gastroenterol* 2020; **26**: 2323-2332 [PMID: [32476796](#) DOI: [10.3748/wjg.v26.i19.2323](#)]
 - 10 **Ai JW**, Zi H, Wang Y, Huang Q, Wang N, Li LY, Pei B, Ji J, Zeng XT. Clinical Characteristics of COVID-19 Patients With Gastrointestinal Symptoms: An Analysis of Seven Patients in China. *Front Med (Lausanne)* 2020; **7**: 308 [PMID: [32656221](#) DOI: [10.3389/fmed.2020.00308](#)]
 - 11 **El Ouali S**, Achkar JP, Lashner B, Regueiro M. Gastrointestinal manifestations of COVID-19. *Cleve Clin J Med* 2021 [PMID: [32554734](#) DOI: [10.3949/ccjm.87a.ccc049](#)]
 - 12 **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: [32109013](#) DOI: [10.1056/NEJMoa2002032](#)]
 - 13 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: [32031570](#) DOI: [10.1001/jama.2020.1585](#)]
 - 14 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. 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**: 81-95 [PMID: [32251668](#) DOI: [10.1053/j.gastro.2020.03.065](#)]
 - 15 **Sultan S**, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK, Falck-Ytter Y, El-Serag HB; AGA Institute. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. *Gastroenterology* 2020; **159**: 320-334. e27 [PMID: [32407808](#) DOI: [10.1053/j.gastro.2020.05.001](#)]
 - 16 **Rokkas T**. Gastrointestinal involvement in COVID-19: a systematic review and meta-analysis. *Ann Gastroenterol* 2020; **33**: 355-365 [PMID: [32624655](#) DOI: [10.20524/aog.2020.0506](#)]
 - 17 **Wu Y**, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020; **5**: 434-435 [PMID: [32199469](#) DOI: [10.1016/S2468-1253\(20\)30083-2](#)]
 - 18 **Li X**, Huang S, Lu J, Lai R, Zhang Z, Lin X, Zheng X, Shan H. Upper Gastrointestinal Bleeding Caused by SARS-CoV-2 Infection. *Am J Gastroenterol* 2020; **115**: 1541-1542 [PMID: [32694288](#) DOI: [10.14309/ajg.0000000000000757](#)]
 - 19 **Cavaliere K**, Levine C, Wander P, Sejpal DV, Trindade AJ. Management of upper GI bleeding in patients with COVID-19 pneumonia. *Gastrointest Endosc* 2020; **92**: 454-455 [PMID: [32325065](#) DOI: [10.1016/j.gie.2020.04.028](#)]
 - 20 **Su S**, Shen J, Zhu L, Qiu Y, He JS, Tan JY, Iacucci M, Ng SC, Ghosh S, Mao R, Liang J. Involvement of digestive system in COVID-19: manifestations, pathology, management and challenges. *Therap Adv Gastroenterol* 2020; **13**: 1756284820934626 [PMID: [32595762](#) DOI: [10.1177/1756284820934626](#)]
 - 21 **Saito H**, Ozaki A, Mizuno Y, Todo K. Difficulty in diagnosing mild cases of COVID-19 without respiratory symptoms during the Novel Coronavirus Pandemic: Careful monitoring needed for patients with persistent upper gastrointestinal symptoms. *Clin Case Rep* 2020; **8**: 2787-2790 [PMID: [33363823](#) DOI: [10.1002/ccr3.3248](#)]

- 22 **Perisetti A**, Goyal H, Gajendran M, Boregowda U, Mann R, Sharma N. Prevalence, Mechanisms, and Implications of Gastrointestinal Symptoms in COVID-19. *Front Med (Lausanne)* 2020; **7**: 588711 [PMID: [33195352](#) DOI: [10.3389/fmed.2020.588711](#)]
- 23 **Yang L**, Tu L. Implications of gastrointestinal manifestations of COVID-19. *Lancet Gastroenterol Hepatol* 2020; **5**: 629-630 [PMID: [32405602](#) DOI: [10.1016/S2468-1253\(20\)30132-1](#)]
- 24 **Lechien JR**, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, Chekkoury-Idrissi Y, Hans S, Delgado IL, Calvo-Henriquez C, Lavigne P, Falanga C, Barillari MR, Cammaroto G, Khalife M, Leich P, Souchay C, Rossi C, Journe F, Hsieh J, Edjlali M, Carlier R, Ris L, Lovato A, De Filippis C, Coppee F, Fakhry N, Ayad T, Saussez S. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020; **277**: 2251-2261 [PMID: [32253535](#) DOI: [10.1007/s00405-020-05965-1](#)]
- 25 **Hajifathalian K**, Krisko T, Mehta A, Kumar S, Schwartz R, Fortune B, Sharaiha RZ; WCM-GI research group*. Gastrointestinal and Hepatic Manifestations of 2019 Novel Coronavirus Disease in a Large Cohort of Infected Patients From New York: Clinical Implications. *Gastroenterology* 2020; **159**: 1137-1140. e2 [PMID: [32389667](#) DOI: [10.1053/j.gastro.2020.05.010](#)]
- 26 **Barrett LF**, Lo KB, Stanek SR, Walter JW. Self-limited gastrointestinal bleeding in COVID-19. *Clin Res Hepatol Gastroenterol* 2020; **44**: e77-e80 [PMID: [32753264](#) DOI: [10.1016/j.clinre.2020.06.015](#)]
- 27 **Duan Z**, Liu K, Zhou S. The dilemma in the management of suspected upper GI bleeding in patients with COVID-19 pneumonia. *Gastrointest Endosc* 2020; **92**: 1273-1274 [PMID: [33236998](#) DOI: [10.1016/j.gie.2020.07.006](#)]
- 28 **Xiao F**, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* 2020; **158**: 1831-1833. e3 [PMID: [32142773](#) DOI: [10.1053/j.gastro.2020.02.055](#)]
- 29 **Elsoukkary SS**, Mostyka M, Dillard A, Berman DR, Ma LX, Chadburn A, Yantiss RK, Jessurun J, Seshan SV, Borczuk AC, Salvatore SP. Autopsy Findings in 32 Patients with COVID-19: A Single-Institution Experience. *Pathobiology* 2021; **88**: 56-68 [PMID: [32942274](#) DOI: [10.1159/000511325](#)]
- 30 **Maiese A**, Manetti AC, La Russa R, Di Paolo M, Turillazzi E, Frati P, Fineschi V. Autopsy findings in COVID-19-related deaths: a literature review. *Forensic Sci Med Pathol* 2020 [PMID: [33026628](#) DOI: [10.1007/s12024-020-00310-8](#)]
- 31 **Liu Q**, Wang RS, Qu GQ, Wang YY, Liu P, Zhu YZ, Fei G, Ren L, Zhou YW, Liu L. Gross examination report of a COVID-19 death autopsy. *Fa Yi Xue Za Zhi* 2020; **36**: 21-23 [PMID: [32198987](#) DOI: [10.12116/j.issn.1004-5619.2020.01.005](#)]
- 32 **Bradley BT**, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, Najafian B, Deutsch G, Lacy JM, Williams T, Yarid N, Marshall DA. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 2020; **396**: 320-332 [PMID: [32682491](#) DOI: [10.1016/S0140-6736\(20\)31305-2](#)]
- 33 **Dickson I**. Organoids demonstrate gut infection by SARS-CoV-2. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 383 [PMID: [32427981](#) DOI: [10.1038/s41575-020-0317-5](#)]
- 34 **Jurado-Gomez A**, Giraldez MD. Novel Coronavirus Disease-2019 and the Gastrointestinal Tract: Lessons Learned from Human Organoids. *Gastroenterology* 2020; **159**: 2245-2247 [PMID: [33010249](#) DOI: [10.1053/j.gastro.2020.09.039](#)]
- 35 **Zhou J**, Li C, Liu X, Chiu MC, Zhao X, Wang D, Wei Y, Lee A, Zhang AJ, Chu H, Cai JP, Yip CC, Chan IH, Wong KK, Tsang OT, Chan KH, Chan JF, To KK, Chen H, Yuen KY. Infection of bat and human intestinal organoids by SARS-CoV-2. *Nat Med* 2020; **26**: 1077-1083 [PMID: [32405028](#) DOI: [10.1038/s41591-020-0912-6](#)]
- 36 **Lamers MM**, Beumer J, van der Vaart J, Knoop K, Puschhof J, Breugem TI, Ravelli RBG, Paul van Schayck J, Mykytyn AZ, Duimel HQ, van Donselaar E, Riesebosch S, Kuijpers HJH, Schipper D, van de Wetering WJ, de Graaf M, Koopmans M, Cuppen E, Peters PJ, Haagmans BL, Clevers H. SARS-CoV-2 productively infects human gut enterocytes. *Science* 2020; **369**: 50-54 [PMID: [32358202](#) DOI: [10.1126/science.abc1669](#)]
- 37 **Li M**, Izpisua Belmonte JC. Organoids - Preclinical Models of Human Disease. *N Engl J Med* 2019; **380**: 569-579 [PMID: [30726695](#) DOI: [10.1056/NEJMr1806175](#)]
- 38 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: [31986264](#) DOI: [10.1016/S0140-6736\(20\)30183-5](#)]
- 39 **Hamming I**, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; **203**: 631-637 [PMID: [15141377](#) DOI: [10.1002/path.1570](#)]
- 40 **Zuo T**, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung ACK, Cheung CP, Chen N, Lai CKC, Chen Z, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology* 2020; **159**: 944-955. e8 [PMID: [32442562](#) DOI: [10.1053/j.gastro.2020.05.048](#)]
- 41 **Zuo T**, Liu Q, Zhang F, Lui GC, Tso EY, Yeoh YK, Chen Z, Boon SS, Chan FK, Chan PK, Ng SC. Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19. *Gut* 2021; **70**: 276-284 [PMID: [32690600](#) DOI: [10.1136/gutjnl-2020-322294](#)]
- 42 **Akour A**. Probiotics and COVID-19: is there any link? *Lett Appl Microbiol* 2020; **71**: 229-234

- [PMID: 32495940 DOI: 10.1111/Lam.13334]
- 43 **Mak JWY**, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterol Hepatol* 2020; **5**: 644-645 [PMID: 32339473 DOI: 10.1016/S2468-1253(20)30122-9]
 - 44 **Sun J**, Deng X, Chen X, Huang J, Huang S, Li Y, Feng J, Liu J, He G. Incidence of Adverse Drug Reactions in COVID-19 Patients in China: An Active Monitoring Study by Hospital Pharmacovigilance System. *Clin Pharmacol Ther* 2020; **108**: 791-797 [PMID: 32324898 DOI: 10.1002/cpt.1866]
 - 45 **Chen ZR**, Zhou Y, Liu J, Peng HW, Zhou J, Zhong HL, Liu LL, Lai MF, Wei XH, Wen JH. Pharmacotherapeutics Advice in Guidelines for COVID-19. *Front Pharmacol* 2020; **11**: 950 [PMID: 32670066 DOI: 10.3389/fphar.2020.00950]
 - 46 **Javorac D**, Grahovac L, Manić L, Stojilković N, Anđelković M, Bulat Z, Đukić-Čosić D, Curčić M, Djordjević AB. An overview of the safety assessment of medicines currently used in the COVID-19 disease treatment. *Food Chem Toxicol* 2020; **144**: 111639 [PMID: 32707160 DOI: 10.1016/j.fct.2020.111639]
 - 47 **Ying L**, Jiong T. Literature Analysis of Antiviral Agent Adverse Drug Reactions in the Treatment of COVID-19. *World Notes on Antibiotics* 2020; **42**: 101-105
 - 48 **Wen CY**, Xie ZW, Li YP, Deng XL, Chen XT, Cao Y, Ou X, Lin WY, Li F, Cai WP, Li LH. [Real-world efficacy and safety of lopinavir/ritonavir and arbidol in treating with COVID-19 : an observational cohort study]. *Zhonghua Nei Ke Za Zhi* 2020; **59**: E012 [PMID: 32388937 DOI: 10.3760/cma.j.cn112138-20200227-00147]
 - 49 **Wang Y**, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395**: 1569-1578 [PMID: 32423584 DOI: 10.1016/S0140-6736(20)31022-9]
 - 50 **Grein J**, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E, Oda R, Yo K, Quiros-Roldan E, Studemeister A, Redinski J, Ahmed S, Bernetti J, Chelliah D, Chen D, Chihara S, Cohen SH, Cunningham J, D'Arminio Monforte A, Ismail S, Kato H, Lapadula G, L'Her E, Maeno T, Majumder S, Massari M, Mora-Rillo M, Mutoh Y, Nguyen D, Verweij E, Zoufaly A, Osinusi AO, DeZure A, Zhao Y, Zhong L, Chokkalingam A, Elboudwarej E, Telep L, Timbs L, Henne I, Sellers S, Cao H, Tan SK, Winterbourne L, Desai P, Mera R, Gaggar A, Myers RP, Brainard DM, Childs R, Flanagan T. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med* 2020; **382**: 2327-2336 [PMID: 32275812 DOI: 10.1056/NEJMoa2007016]
 - 51 **Pan ZY**, Chang YX, Han N, Hou FY, Lee BJJ, Zhi FC, Yang RF, Bi YJ. Short-term high-dose gavage of hydroxychloroquine changes gut microbiota but not the intestinal integrity and immunological responses in mice. *Life Sci* 2021; **264**: 118450 [PMID: 33131749 DOI: 10.1016/j.lfs.2020.118450]
 - 52 **Trottein F**, Sokol H. Potential Causes and Consequences of Gastrointestinal Disorders during a SARS-CoV-2 Infection. *Cell Rep* 2020; **32**: 107915 [PMID: 32649864 DOI: 10.1016/j.celrep.2020.107915]
 - 53 **Villapol S**. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. *Transl Res* 2020; **226**: 57-69 [PMID: 32827705 DOI: 10.1016/j.trsl.2020.08.004]
 - 54 **Bozkurt HS**, Quigley EM. The probiotic *Bifidobacterium* in the management of Coronavirus: A theoretical basis. *Int J Immunopathol Pharmacol* 2020; **34**: 2058738420961304 [PMID: 33103512 DOI: 10.1177/2058738420961304]
 - 55 **Cholankeril G**, Podboy A, Aivaliotis VI, Pham EA, Spencer SP, Kim D, Ahmed A. Association of Digestive Symptoms and Hospitalization in Patients With SARS-CoV-2 Infection. *Am J Gastroenterol* 2020; **115**: 1129-1132 [PMID: 32618665 DOI: 10.14309/ajg.0000000000000712]



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