

World Journal of *Clinical Cases*

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Contents

Thrice Monthly Volume 9 Number 19 July 6, 2021

OPINION REVIEW

- 4881** Fear of missing out: A brief overview of origin, theoretical underpinnings and relationship with mental health
Gupta M, Sharma A

REVIEW

- 4890** Molecular pathways in viral hepatitis-associated liver carcinogenesis: An update
Elpek GO
- 4918** Gastroenterology and liver disease during COVID-19 and in anticipation of post-COVID-19 era: Current practice and future directions
Oikonomou KG, Papamichalis P, Zafeiridis T, Xanthoudaki M, Papapostolou E, Valsamaki A, Bouliaris K, Papamichalis M, Karvouniaris M, Vlachostergios PJ, Skoura AL, Komnos A
- 4939** Enhancing oxygenation of patients with coronavirus disease 2019: Effects on immunity and other health-related conditions
Mohamed A, Alawna M

MINIREVIEWS

- 4959** Clinical potentials of ginseng polysaccharide for treating gestational diabetes mellitus
Zhao XY, Zhang F, Pan W, Yang YF, Jiang XY
- 4969** Remarkable gastrointestinal and liver manifestations of COVID-19: A clinical and radiologic overview
Fang LG, Zhou Q
- 4980** Liver injury in COVID-19: Known and unknown
Zhou F, Xia J, Yuan HX, Sun Y, Zhang Y
- 4990** COVID-19 and gastroenteric manifestations
Chen ZR, Liu J, Liao ZG, Zhou J, Peng HW, Gong F, Hu JF, Zhou Y
- 4998** Role of epithelial-mesenchymal transition in chemoresistance in pancreatic ductal adenocarcinoma
Hu X, Chen W
- 5007** Insights into the virologic and immunologic features of SARS-COV-2
Polat C, Ergunay K

ORIGINAL ARTICLE

Basic Study

- 5019 SMAC exhibits anti-tumor effects in ECA109 cells by regulating expression of inhibitor of apoptosis protein family

Jiang N, Zhang WQ, Dong H, Hao YT, Zhang LM, Shan L, Yang XD, Peng CL

Case Control Study

- 5028 Efficacy of Solitaire AB stent-release angioplasty in acute middle cerebral artery atherosclerosis obliterative cerebral infarction

Wang XF, Wang M, Li G, Xu XY, Shen W, Liu J, Xiao SS, Zhou JH

Retrospective Study

- 5037 Diagnostic value of different color ultrasound diagnostic method in endometrial lesions

Lin XL, Zhang DS, Ju ZY, Li XM, Zhang YZ

- 5046 Clinical and pathological features and risk factors for primary breast cancer patients

Lei YY, Bai S, Chen QQ, Luo XJ, Li DM

- 5054 Outcomes of high-grade aneurysmal subarachnoid hemorrhage patients treated with coiling and ventricular intracranial pressure monitoring

Wen LL, Zhou XM, Lv SY, Shao J, Wang HD, Zhang X

- 5064 Microwave ablation combined with hepatectomy for treatment of neuroendocrine tumor liver metastases

Zhang JZ, Li S, Zhu WH, Zhang DF

- 5073 Clinical application of individualized total arterial coronary artery bypass grafting in coronary artery surgery

Chen WG, Wang BC, Jiang YR, Wang YY, Lou Y

Observational Study

- 5082 Early diagnosis, treatment, and outcomes of five patients with acute thallium poisoning

Wang TT, Wen B, Yu XN, Ji ZG, Sun YY, Li Y, Zhu SL, Cao YL, Wang M, Jian XD, Wang T

- 5092 Sarcopenia in geriatric patients from the plateau region of Qinghai-Tibet: A cross-sectional study

Pan SQ, Li YM, Li XF, Xiong R

- 5102 Medium-term efficacy of arthroscopic debridement *vs* conservative treatment for knee osteoarthritis of Kellgren-Lawrence grades I-III

Lv B, Huang K, Chen J, Wu ZY, Wang H

Prospective Study

- 5112 Impact of continuous positive airway pressure therapy for nonalcoholic fatty liver disease in patients with obstructive sleep apnea

Hirono H, Watanabe K, Hasegawa K, Kohno M, Terai S, Ohkoshi S

Randomized Controlled Trial

- 5126** Erector spinae plane block at lower thoracic level for analgesia in lumbar spine surgery: A randomized controlled trial
Zhang JJ, Zhang TJ, Qu ZY, Qiu Y, Hua Z

SYSTEMATIC REVIEWS

- 5135** Controversies' clarification regarding ribavirin efficacy in measles and coronaviruses: Comprehensive therapeutic approach strictly tailored to COVID-19 disease stages
Liatsos GD
- 5179** Systematic review and meta-analysis of trans-jugular intrahepatic portosystemic shunt for cirrhotic patients with portal vein thrombosis
Zhang JB, Chen J, Zhou J, Wang XM, Chen S, Chu JG, Liu P, Ye ZD

CASE REPORT

- 5191** Myelodysplastic syndrome transformed into B-lineage acute lymphoblastic leukemia: A case report
Zhu YJ, Ma XY, Hao YL, Guan Y
- 5197** Imaging presentation and postoperative recurrence of peliosis hepatis: A case report
Ren SX, Li PP, Shi HP, Chen JH, Deng ZP, Zhang XE
- 5203** Delayed retroperitoneal hemorrhage during extracorporeal membrane oxygenation in COVID-19 patients: A case report and literature review
Zhang JC, Li T
- 5211** Autologous tenon capsule packing to treat posterior exit wound of penetrating injury: A case report
Yi QY, Wang SS, Gui Q, Chen LS, Li WD
- 5217** Treatment of leiomyomatosis peritonealis disseminata with goserelin acetate: A case report and review of the literature
Yang JW, Hua Y, Xu H, He L, Huo HZ, Zhu CF
- 5226** Homozygous deletion, c. 1114-1116del, in exon 8 of the *CRPPA* gene causes congenital muscular dystrophy in Chinese family: A case report
Yang M, Xing RX
- 5232** Successful diagnosis and treatment of jejunal diverticular haemorrhage by full-thickness enterotomy: A case report
Ma HC, Xiao H, Qu H, Wang ZJ
- 5238** Liver metastasis as the initial clinical manifestation of sublingual gland adenoid cystic carcinoma: A case report
Li XH, Zhang YT, Feng H
- 5245** Severe hyperbilirubinemia in a neonate with hereditary spherocytosis due to a *de novo* ankyrin mutation: A case report
Wang JF, Ma L, Gong XH, Cai C, Sun JJ

- 5252** Long-term outcome of indwelling colon observed seven years after radical resection for rectosigmoid cancer: A case report
Zhuang ZX, Wei MT, Yang XY, Zhang Y, Zhuang W, Wang ZQ
- 5259** Diffuse xanthoma in early esophageal cancer: A case report
Yang XY, Fu KI, Chen YP, Chen ZW, Ding J
- 5266** COVID-19 or treatment associated immunosuppression may trigger hepatitis B virus reactivation: A case report
Wu YF, Yu WJ, Jiang YH, Chen Y, Zhang B, Zhen RB, Zhang JT, Wang YP, Li Q, Xu F, Shi YJ, Li XP
- 5270** Maintenance treatment with infliximab for ulcerative ileitis after intestinal transplantation: A case report
Fujimura T, Yamada Y, Umeyama T, Kudo Y, Kanamori H, Mori T, Shimizu T, Kato M, Kawaida M, Hosoe N, Hasegawa Y, Matsubara K, Shimojima N, Shinoda M, Obara H, Naganuma M, Kitagawa Y, Hoshino K, Kuroda T
- 5280** Infliximab treatment of glycogenosis Ib with Crohn's-like enterocolitis: A case report
Gong YZ, Zhong XM, Zou JZ
- 5287** Hemichorea due to ipsilateral thalamic infarction: A case report
Li ZS, Fang JJ, Xiang XH, Zhao GH
- 5294** Intestinal gangrene secondary to congenital transmesenteric hernia in a child misdiagnosed with gastrointestinal bleeding: A case report
Zheng XX, Wang KP, Xiang CM, Jin C, Zhu PF, Jiang T, Li SH, Lin YZ
- 5302** Collagen VI-related myopathy with scoliosis alone: A case report and literature review
Li JY, Liu SZ, Zheng DF, Zhang YS, Yu M
- 5313** Neuromuscular electrical stimulation for a dysphagic stroke patient with cardiac pacemaker using magnet mode change: A case report
Kim M, Park JK, Lee JY, Kim MJ
- 5319** Four-year-old anti-N-methyl-D-aspartate receptor encephalitis patient with ovarian teratoma: A case report
Xue CY, Dong H, Yang HX, Jiang YW, Yin L
- 5325** Glutamic acid decarboxylase 65-positive autoimmune encephalitis presenting with gelastic seizure, responsive to steroid: A case report
Yang CY, Tsai ST
- 5332** Ectopic opening of the common bile duct into the duodenal bulb with recurrent choledocholithiasis: A case report
Xu H, Li X, Zhu KX, Zhou WC
- 5339** Small bowel obstruction caused by secondary jejunal tumor from renal cell carcinoma: A case report
Bai GC, Mi Y, Song Y, Hao JR, He ZS, Jin J
- 5345** Brugada syndrome associated with out-of-hospital cardiac arrest: A case report
Ni GH, Jiang H, Men L, Wei YY, A D, Ma X

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COVID-19 and gastroenteric manifestations

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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, C2BBE1, 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].

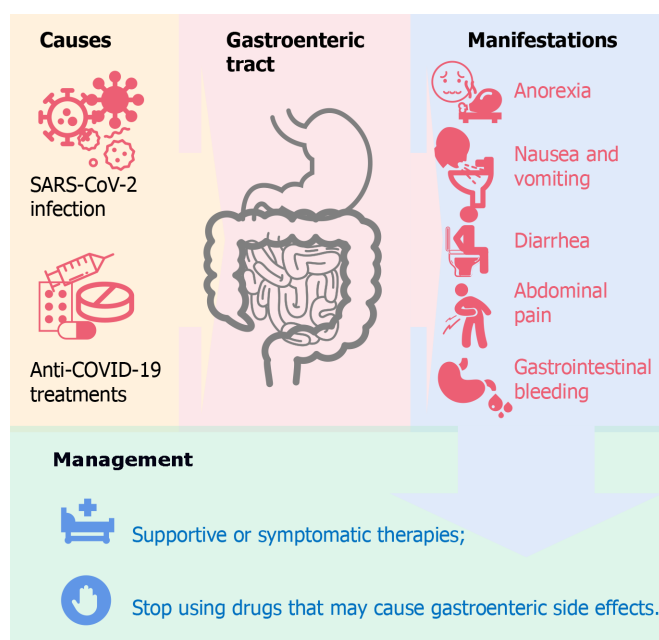


Figure 1 The causes, symptoms, and management of coronavirus disease 2019 patients with gastroenteric manifestations. Both the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the treatments of coronavirus disease 2019 (COVID-19) can induce gastroenteric manifestations. Those 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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