

CURRENT TRENDS IN THE INFLUENCE OF CORONAVIRUS INFECTION ON THE GASTROINTESTINAL TRACT IN CHILDREN

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Abstract: The high frequency of registration of gastrointestinal disorders, in many children before the start of therapy, confirms the tropism of the new coronavirus to the gastrointestinal tract. A large number of cases of discomfort in the abdomen after eating, nausea, and flatulence indicate, probably, developing fermentopathy and possible involvement of the pancreas and hepatobiliary system in the infectious and inflammatory process, which also requires further study. This review summarizes the manifestations and potential mechanisms for the development of gastrointestinal manifestations in COVID-19 in children.

Key words: coronavirus, gastrointestinal tract, diarrhea, nausea, pain, children.

Relevance. The new coronavirus infection (COVID 19), caused by the SARS-CoV 2 coronavirus, is rightfully recognized as a pandemic of the 21st century and poses a threat to the health of all humanity.

According to the World Health Organization, as of July 13, 2023, there are over 767 million cases of the disease worldwide; More than 6.9 million deaths have been confirmed [WHO, 2023], making the COVID-19 pandemic one of the deadliest in history. According to currently available data, among patients diagnosed with COVID 19, children accounted for 1 to 5% [Zuo T, Zhang F, Lui GCY, et al., 2022]. Children aged 10–18 years dominated (45.9%), and patients in the first years of life accounted for 26.1%. At the same time, over the period since the beginning of the pandemic, only a few deaths from the disease in children have been recorded in world statistics. The high contagiousness of the SARS-CoV 2 coronavirus, the ability for long-term replication, and tropism for cells of the immune system provide the virus with the possibility of almost simultaneous multiple organ damage with the rapid development of complications of both the respiratory tract and other organs and systems. The gastrointestinal tract is involved in this pathological process, representing one of the “shock organs”. In addition to common respiratory symptoms, some COVID 19 patients experience dyspeptic symptoms such as diarrhea, nausea and vomiting. Anal swab samples from COVID 19 patients test positive for SARS-CoV 2 nucleic acid, and SARS-CoV 2 has been isolated from stool samples from COVID 19 patients. Additionally, in both adults and children, there is a strong association between the lesions digestive system and SARS-CoV 2 infection.

In addition, increased liver enzyme activity with greater increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in severe COVID-19 than in mild and moderate COVID-19 indicate that there is a close relationship between digestive system damage and infection SARS-CoV-2. Data on damage to the gastrointestinal tract in patients with Covid-19 in the current state of the pandemic are considered by many authors, but given the fact that children tolerate this infection more easily, little attention is paid to the state of the digestive organs during Covid-19 in children. The main source of infection is a sick person, including those in the incubation period of the disease. The routes of transmission of the pathogen in the child population are the same as in adults - airborne droplets, airborne aerosols, household contact, fecal-oral. Children are just as susceptible to COVID-19 as adults. However, testing of the child population in outbreaks does not confirm their high infection rate. The main infection of children occurs in family centers or medical institutions (maternity hospitals). But at the same time, no evidence of intrauterine infection caused by vertical transmission from mother to fetus was found, and only cases of postnatal transmission were described in children born to women

with laboratory-confirmed COVID-19, occurring with pneumonia. The virus persists in aerosol form for about 2 hours, on plastic/metal surfaces for up to 6–8 hours, on hair for up to 3 days [Gu J, Han B, Wang J., 2020], in the room where the patient was located - several days, although some scientists doubt this and continue research. The RNA virus can be detected in nasopharyngeal washings of children until the 6th–22nd day of illness and even longer, in feces from 5 to 28 days or longer, although not always in active form. The multisystem nature of the damage to internal organs by SARS-CoV-2 is based on the structural features of the virus, which ensure the versatility of pathophysiological reactions affecting not only the respiratory but also the digestive tracts.

Gastrointestinal manifestations (anorexia, nausea, diarrhea, abdominal pain), as a rule, are not fatal and occur in 1/4 of patients with COVID-19 [Ivashkin V.T., Sheptulin A.A., Zolnikova O.Yu., et al., 2020]. They can precede the appearance of signs of damage to the respiratory tract, occupy a leading position in the clinical picture of the disease, potentiate the torpid course of a viral infection, and in some cases be associated with an unfavorable prognosis. The presence of gastrointestinal symptoms in patients with COVID-19 is associated with a delay in the diagnosis of coronavirus infection and is associated with a greater potential for disorders such as irritable bowel syndrome (IBS) and exacerbations of chronic gastrointestinal diseases in the post-infectious period [Zarifian A, Bidary MZ, Arekhi S, et al., 2020]. The possibility of damage to the digestive organs by the SARS-CoV-2 virus is due to the high expression of angiotensin-converting enzyme 2 (ACE-2) receptors on the epithelial cells of the mucous membrane. This is probably why epithelial cells of the gastrointestinal tract (along with alveocytes) can serve as the initial “entry gate” for the virus and support its stable replication. Thus, according to the results of the polymerase chain reaction, viral nucleic acid is detected in the stool of more than 50% of those infected with COVID-19, and in almost 1/4 of cases the RNA virus persists in feces for a longer time (27.9 days in stool compared to 16.7 days in the respiratory tract from the onset of the disease). This allows for the possibility of fecal-oral transmission of coronavirus infection even with negative breath tests [Gu J, Han B, Wang J., 2020]. Receptor-mediated penetration of the SARS-CoV-2 virus into the gastrointestinal epithelium modulates local immune responses, induces inflammation, changes the permeability of mucous membranes, and causes the development of microbial imbalance in the parietal mucus layer. It has been established that COVID-19 infection has not only the greatest, but also a leading effect on the intestinal microbiome compared to the effects of other factors, including the presence of pneumonia and the use of antibiotics [Saleh J, Peyssonnaux C, Singh KK, Edeas M., 2020]. Quantitative and qualitative changes in the intestinal microbial composition in patients with COVID-19 are characterized by a decrease in the proportion of beneficial representatives of the commensal microbiota, mainly butyrate-producing bacteria (*Fecalibacterium prausnitzii*, *Lachnospiraceae*, *Eubacterium rectale*, *Ruminococcus obeum*, *Blautia obeum*). Changes in the gut microbiome persist even after clearance of SARS-CoV-2 and resolution of respiratory symptoms [Zuo T, Zhang F, Lui GCY, et al., 2020].

The presence of target receptors for SARS-CoV-2, along with the respiratory system in the digestive organs, suggests the existence of an alternative route for the virus to enter the body and may explain gastrointestinal disorders in patients with COVID-19. In a study by Saleh J., et al. (2020) of a clinically important group of patients with mild COVID-19 with gastroenterological manifestations at the onset of coronavirus infection, analyzed the clinical characteristics, results of immunological testing, as well as the outcomes of patients with COVID-19 with digestive symptoms of mild severity of the disease depending on the chosen treatment tactics diarrhea syndrome. Of the examined patients with gastrointestinal manifestations of infection, 67% of sick children had a burdened premorbid background, 38.3% had a history of gastroenterological diseases (more often IBS). It is likely that patients with pre-existing chronic gastrointestinal diseases are more susceptible to intestinal damage from COVID-19, possibly due to increased expression of ACE-2 receptors on epithelial cells. In 1/3 (39.34%) of patients, digestive symptoms, especially diarrhea, dominated the clinical manifestations of COVID-19; in 66%, gastroenterological and respiratory symptoms were present simultaneously. Based on the fact that testing for COVID-19 is largely focused on patients with respiratory symptoms, it is possible that a significant cohort of patients with a predominant gastroenterological manifestation with

or without clinical symptoms of respiratory tract damage may elude medical control. Delayed etiological deciphering of gastrointestinal involvement in the early stages of COVID-19 appears to lead to unwitting spread of infection among mildly ill outpatients who remain undiagnosed and unaware of their potential to infect others. Although the study did not test for RNA in stool, the results indirectly support the possibility of fecal-oral transmission. Despite the fact that the study included patients with a mild degree of severity of the infectious disease, it was found that in patients with gastrointestinal symptoms the infection was more severe: 100% had a temperature above 37.5°C, in a larger number of patients (98.4% vs. 42.6%) showed signs of infectious intoxication (ossalgia/myalgia, general weakness) at the onset of the disease. A longer period of the acute phase of the infectious process and pronounced clinical manifestations of infectious intoxication in patients with gastroenterological manifestations of COVID-19 appear to be a reflection of a higher viral load in this group of patients. The binding of the virus to the ACE-2 receptor, its penetration and reproduction in enterocytes switches metabolic processes and energy supply to itself. This leads to a decrease in the energy supply of the epithelium. During a viral infection under conditions of energy deficiency, the processes of growth, differentiation and functional activity of colonocytes are disrupted; mitochondria modulate immune reactions, leading to increased inflammation. This unbalanced immune response can lead to dysbiosis, affecting the activity of immune, epithelial and enterochromaffin cells in the intestine [Saleh J, Peyssonnaux C, Singh KK, Edeas M., 2020].

The consequence of microecological disturbances during SARS-CoV-2 infection is not only damage to the intestinal barrier function, increased intestinal permeability, impaired absorption of water from the intestinal lumen, increased pro-inflammatory potential of intestinal contents and “toxin” load on the body. Disruption of the composition and function of the intestinal microbiome and virome leads to disruption of the interaction of the gut-lung axis. According to the results of the study by Kharitonova L.A. (2021) found that the most common gastrointestinal symptom was diarrhea (93.9%) of type 7 according to BS (72.2%). These data highlight that during a pandemic, patients who develop acute loose stools after possible exposure to COVID-19 should suspect a coronavirus cause of diarrhea, even in the absence of respiratory symptoms and fever.

In favor of COVID-19, in contrast to exacerbation of a chronic gastrointestinal disease, may be evidenced by a characteristic epidemiological history, a more rapid onset of clinical manifestations, subsequent (or simultaneous) development of respiratory symptoms, anosmia, fever, general weakness, a positive test for RNA (IgM) SARS -CoV-2. It should be borne in mind that against the background of a severe course and aggressive therapy of COVID-19, an exacerbation of a chronic gastrointestinal disease is quite possible [Grinevich V.B., Gubonina I.V., Doshchitsin V.L., et al., 2020].

Gastrointestinal tract (GIT) dysfunctions often accompany acute respiratory viral infections (ARVI). The mechanism of formation of gastrointestinal manifestations may be different. It is possible to have both a direct effect of the pathogen on the cells of the gastrointestinal tract with their direct damage and subsequent apoptosis, and an indirect effect - through disturbances in blood flow or nervous regulation. The SARS-CoV-2 virus interacts primarily with angiotensin-converting enzyme type 2 (ACE-2) receptors, which are present in various tissues, including gastrointestinal epithelial cells and the endothelium of blood vessels [1–3]. Almost from the very beginning of studying the new coronavirus infection, it became clear that, along with symptoms of respiratory tract damage and intoxication, patients often experience gastrointestinal disorders. In some cases, it is difficult to determine whether symptoms are related to the infectious agent or to the therapy being administered. However, regardless of the cause, diarrhea and vomiting can lead to dehydration with the development of hypovolemic shock, electrolyte imbalance and metabolic disorders [Popova R.V. et al., 2020].

According to the results of the study by T.A. Ruzhentsov et al. (2020) the main symptoms in all children upon admission were intoxication with loss of appetite, weakness, drowsiness, fatigue, and a rare dry cough. Body temperature was above normal in 97% of patients, with the maximum value being 38.2 °C. When analyzing the anamnesis and clinical picture over time, it was found that diarrhea was observed from the 4th–5th day of the disease in 64% of children and lasted from three to five days. The stool was liquid, mucous, and in isolated cases (14% of the total number of children)

streaked with blood. The frequency of stool in most children was up to 5 times a day, the maximum was up to 8 times. The severity and duration of abdominal pain were assessed only in the group of children over 3 years of age. Among these patients, abdominal pain syndrome was expressed in 57% of children; in most cases, the timing of appearance and duration corresponded to diarrhea syndrome. The intensity of pain ranges from slight to very severe, requiring differential diagnosis with acute appendicitis. Vomiting was not noted in any case. Nausea was observed in children who complained of abdominal pain. In most patients, the appearance of gastrointestinal symptoms was noted during therapy. However, in 22% of children, diarrhea was first reported before treatment and was one of the first symptoms of COVID-19.

Conclusions. In most cases, changes in the nature and frequency of stool are carefully monitored by parents of children of early and preschool age, while adult patients with symptoms of a respiratory infection do not always consider it necessary to inform the doctor about the existing deviations, assessing them as natural in response to changes in diet or taking medications. The severe pain syndrome noted in some patients significantly distinguishes the course of COVID-19 from other respiratory infections. In these patients, pain is likely associated with the development of mesadenitis or transient circulatory disorders of the gastrointestinal tract, which requires further research. Relief of symptoms without the exception of antiviral and antibacterial therapy indicates the direct participation of coronavirus in the pathogenesis of gastrointestinal disorders and may refute the possible influence of dysbiotic disorders with the activation of the growth of opportunistic flora, as well as dysfunction of the hepatobiliary system, which cannot be excluded when used in the first place turn, cephalosporins. The high frequency of registration of gastrointestinal disorders in many children before the start of therapy confirms the tropism of the new coronavirus to the gastrointestinal tract. A large number of cases of abdominal discomfort after eating, nausea, and flatulence indicate a likely developing fermentopathy and possible involvement of the pancreas and hepato-biliary system in the infectious-inflammatory process, which also requires further study. Gastrointestinal disorders are present in the majority of children hospitalized with community-acquired pneumonia caused by the SARS-CoV-2 virus. Diarrhea, abdominal pain syndrome, and other symptoms indicating dysfunction of the gastrointestinal tract observed in sick children infected with coronavirus infection once again emphasize the impact of this infection on the gastrointestinal tract. Symptoms are relieved by a course of primary therapy indicated for the treatment of COVID 19, and additional therapy recommended for acute intestinal infections.

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