To the Issue of Intoxication and Diarrhea Syndrome Treatment in the Case of Coronavirus Infection

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With coronavirus infection, gastrointestinal manifestations with diarrhea, vomiting and abdominal pain are often noted. This is due to the susceptibility of the intestinal epithelium to the virus due to the expression of ACE2 receptors. In addition, elevated liver enzymes may occur in patients with COVID-19. Presumably, this can be caused both by direct damage to the liver with damage to SARS-CoV-2 hepatocytes, and by the development of pathological immune mechanisms or hepatotoxicity of drugs. In the event of gastrointestinal symptoms and an increase in hepatic transaminases, it seems appropriate to use modern enterosorbents in the complex therapy of coronavirus infection caused by COVID-19, such as polymethylsiloxane polyhydrate. Given the mechanisms of action of this drug, its use can contribute to a more rapid relief of diarrhea, a decrease in intoxication syndrome and normalization of transaminases.

Key words: COVID-19 coronavirus infection, diarrhea, hepatitis, enterosorbents, polymethylsiloxane polyhydrate¹

¹ Translator’s note: title and author’s abstract – unmodified original publisher’s translation.
The causative agent of the new coronavirus infection COVID-19 is the single-stranded RNA virus SARS-CoV-2, which belongs to the genus Betacoronavirus. At the initial stage of infection, SARS-CoV-2 enters cells that express angiotensin-converting enzyme 2 (ACE2). The main target is the alveolar type II cells in the lungs. However ACE-2 receptors are also present on the cells of the respiratory tract, kidneys, esophagus, urinary bladder, ileum, heart and central nervous system [1, 2]. The typical clinical manifestations of COVID-19 include fever, respiratory symptoms, bilateral pneumonia, and acute respiratory distress syndrome (ARDS), which develops in 3-4% of cases. At the same time, a number of patients experience gastrointestinal manifestations with diarrhea, vomiting and abdominal pain [3].

Human intestinal epithelial cells are also susceptible to the virus and can maintain sustained viral replication [4]. For instance, electron microscopy of biopsy and autopsy specimens in a 34-year-old patient with ARDS due to coronavirus showed active virus replication in both the small and large intestine [5]. In one case of COVID-19 detected in the United States, a 35-year-old man was admitted to hospital with nausea and vomiting, and on the second day of hospitalization, he developed abdominal discomfort and diarrhea. On day 7 of the disease, RNA SARS-CoV-2 was detected in the patient’s stool [6]. In other studies, SARS-CoV-2 RNA was discovered in the anal canal or on rectal tampons [7, 8] and stool samples [6, 9, 10] even after the virus was no longer detected in the upper air passages [7, 8]. The aforementioned allows concluding that during COVID-19, the SARS-CoV-2 coronavirus is able to enter the human body, affecting the epithelial cells of the gastrointestinal tract (GIT). This affinity for the gastrointestinal tract may explain the frequent occurrence of diarrhea during the coronavirus infection. This is important for epidemiological control, tactics of diagnosis and treatment.

Based on the known pathogenetic mechanisms of COVID-19, which are common for other diseases coexistent with diarrhea, it is advisable to include modern intestinal adsorbents in the treatment regimen [11].

Using specific examples, we will consider the important gastrointestinal aspects of the novel coronavirus infection COVID-19, which have an impact on approaches to treatment and prevention of the spread of infection.

**Gastrointestinal symptoms in COVID-19 patients**

A large study of 1,099 patients at 552 hospitals in China reported nausea or vomiting in 55 (5.0%) and diarrhea in 42 (3.8%) patients [12].

The results of the study of other groups of patients showed the incidence of diarrhea, nausea and/or vomiting within 10% [13-17]. Of 140 COVID-19-positive patients in Wuhan, 39.6% had gastrointestinal symptoms [18], including nausea in 24 (17.3%), diarrhea in 18 (12.9%) and vomiting in 7 (5.0%) patients.

Similar data was obtained by F. Xiao et al. (2020): the incidence of diarrhea reached 35.6% in a group of 73 patients [1]. These rates were higher than in some other groups and indicated the variability of the clinical pattern. At the same time, abdominal pain or discomfort were rare [6] - 2.2-5.8% of cases [17-18].

On analyzing the literature data and their own data, L. Yang and L. Tu (2020) discovered only gastrointestinal symptoms in up to 10% of patients with coronavirus [19]. This complicates and delays the diagnosis, which negatively affects both patients and their social network.

Diarrhoea may be one of the first symptoms, which may occur earlier than febrile condition or respiratory symptoms [15, 17]. In some patients, gastrointestinal symptoms can be observed throughout the entire period of the disease, in some cases the virus is no longer secreted from the respiratory tract, but it is found in feces.

Similar to adults, gastrointestinal symptoms were reported in 171 children with COVID-19, diarrhea and vomiting in 15 (8.8%) and 11 (6.4%) children, respectively [16].

In a study by Y. Xu et al., diarrhea was observed in 3 out of 10 infected children [8]. Although children with COVID-19 have been described as having milder disease [16] and less severe respiratory manifestations [8], gastrointestinal symptoms appear to be the same as in adults. However, definitive conclusions require further observations. According to our data, diarrhea was observed in 28.7% of COVID-19 patients (group of 87 patients) receiving care in a newly created unit for the management of COVID-19 patients at the Federal state budgetary institution Third Central Military Clinical Hospital named after A.A. Vishnevsky of the Ministry of Defense of the Russian Federation. All of them were hospitalized with clinical symptoms of moderate to severe community-acquired pneumonia. Of them, 9.3% of patients had dyspeptic complaints (nausea, dysgeusia, anosmia, bitterness in the mouth). Dyspepsia and diarrhea may probably be caused not only by the effect of SARS-CoV-2 coronavirus on gastrointestinal epithelial cells, but also by the side effects of the therapy.

**Clinical case 1**
Patient B., born in 1957, was admitted to the department of management of patients with COVID-19 on May 2, 2020. Medical history: on 29 April 2020, he noted a fever of up to 38°C and fatigue. PCR test - COVID-19 positive, chest X-ray (CXR) from 29 April 2020 - imaging findings of viral pneumonia. The volume of the lesion of the pulmonary parenchyma is 5%. CT imaging was performed on 7 May 2020 - liquid, low-volume stool up to 10 times a day without pathological impurities. The condition was regarded as antibiotic-associated diarrhoea, but due to pneumonic infiltration, antibiotic therapy was continued. The patient was indicated diet 4, Enterosgel 3 doses per day, Linex, rehydration infusion therapy. After 8 days of treatment, the condition improved (normalization of body temperature, bowel movement episodes decreased to 2-3 times a day, consistency of stool thickened).

**Clinical case 2**

Patient L., born in 1972, fell ill on 17 April 2020 after contact with a COVID-19 patient. The patient had a fever of up to 38.5°C, fatigue, dry and rare cough, shortness of breath on minimal exertion. PCR: Positive COVID-19 RNA, CXR from 21 April 2020 - CT-1. Admitted to the department for the treatment of patients with COVID-19. Blood count: leukocytes - 4.44 thousand in μl, lymphocytes - 1.88 thousand in μl, CRP - 24 mg/l. Prescription: Plaquinil, Azithromycin, expectorants and antipyretics. Control CXR from May 30, 2020 showed negative dynamics. Severity CT-2. The therapy was intensified, the drug Kaletra was prescribed. Diarrhoea appeared (bowel movements up to 3-4 times a day). The condition was regarded as a side effect of Kaletra. The therapy was supplemented with intestinal adsorbents (Enterosgel) and probiotics (Enterol) in a standard dosage regimen. During the treatment stool normalized, a tendency towards constipation was observed.

**Liver damage in COVID-19 patients**

In addition to gastrointestinal symptoms, patients with COVID-19 may suffer from liver damage, as attested by increased levels of enzymes in blood tests. Although the mechanism of liver damage is not yet fully investigated, it can be assumed that it is caused both by direct liver damage with damage to hepatocytes, SARS-CoV-2, and development of pathological immune mechanisms or drug hepatotoxicity [20]. It is also assumed that the virus is able to bind to cholangiocytes through the ACE-2 receptor, impairing the regulation of liver function [21]. No viruses are detected in the liver. It is still unclear whether SARS itself (COVID-19) is capable of adversely affecting the liver and what other mechanisms are involved in its damage.

According to available literature sources, almost 50% of COVID-19 patients had abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) with a slight increase in serum bilirubin during the disease [12-14, 17, 22]. In a commentary describing 56 patients with COVID-19, elevated gamma-glutamyl transpeptidase levels were observed in 54% of 28 patients. In most cases, liver damage is mild and transient, but serious complications are not excluded. The proportion of liver damage is higher in patients with severe COVID-19 [12, 14].

In a group of 99 patients in Wuhan, 43 patients had elevated ALT or AST levels. One of them with critical COVID-19 had severe hepatitis C virus with an increase in serum ALT levels to 7590 U/l [13]. According to our own data, an increase in the level of transaminases of no more than 2-3 times was recorded in 4.6% of COVID-19 patients who received treatment for moderate and severe pneumonia in our hospital. The bilirubin level remained normal in all cases.

In particular, we observed a successful treatment outcome in a patient with symptoms of liver
damage associated with COVID-19.

**Clinical case 3**

Patient B., 43 y/o In mid-March 2020, catarrhal changes in the pharynx, low-grade fever appeared, the patient was treated on an outpatient basis. Deterioration of the condition was noted on 21 April 2020 - the patient experienced shortness of breath, extreme fatigue, dry coughing episodes, loose stools, and stomach rumble. On 24 April 2020, the patient’s husband had a positive PCR test for COVID-19. On the same day, the patient underwent CXR: a pattern of viral bilateral lower lobe pneumonia, CT-2. The patient was admitted to the Department of infectious disease of the Ministry of Health of Russia for the treatment of the novel coronavirus infection COVID-19. The therapy was carried out, sonogram showed no liver damage. As a result of the treatment, according to CXR, pneumonia was resolved, the repeated throat swab was twice negative. Dynamic laboratory observation demonstrated normalization of the level of transaminases on day 6 of treatment. The stool returned to normal on day 7 of treatment.

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**Clinical case 4**

Patient S., 41 y/o On admission, the patient complained of unproductive cough, fever in the evening hours 38°C and higher, with chills, lost or changed sense of smell, taste, headache. The patient fell ill 4 days before admission. Outpatient treatment had no effect.

<table>
<thead>
<tr>
<th>Index</th>
<th>Norm</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (WBC) x 10^9/l</td>
<td>4.00-11.00</td>
<td>7.87    5.76</td>
</tr>
<tr>
<td>Red blood cells (RBC) x 10^12/l</td>
<td>4.2-6.1</td>
<td>4.28    4.92</td>
</tr>
<tr>
<td>Hemoglobin (HGB), g/l</td>
<td>120-180</td>
<td>118     143</td>
</tr>
<tr>
<td>Platelets (PLT), x10^9/l</td>
<td>130-400</td>
<td>212     430</td>
</tr>
<tr>
<td>Lymphocytes (LYMPH), x10^9/l</td>
<td>0.90-5.20</td>
<td>0.82    1.1</td>
</tr>
</tbody>
</table>

Table 1. Blood count of patient S. in dynamics

<table>
<thead>
<tr>
<th>Index</th>
<th>Norm</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer, ng/ml</td>
<td>0.550</td>
<td>960     618</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>11.5-14.5</td>
<td>14.3    14.0</td>
</tr>
<tr>
<td>Prothrombin index, %</td>
<td>&gt; 0.00</td>
<td>72.4    75.3</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>24.0-35.0</td>
<td>34.6    33.4</td>
</tr>
<tr>
<td>Activated partial thromboplastin time, s</td>
<td>2.00-4.00</td>
<td>6       6</td>
</tr>
</tbody>
</table>

Table 2. Coagulogram of patient S. in dynamics

<table>
<thead>
<tr>
<th>Index</th>
<th>Norm</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin, μmol/l</td>
<td>3.40-20.50</td>
<td>6       9.3</td>
</tr>
<tr>
<td>Creatinine, μmol/l</td>
<td>50.40-110.50</td>
<td>77.9    80.9</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/l</td>
<td>0.00-55.00</td>
<td>276.5   190</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/l</td>
<td>5.00-34.00</td>
<td>172     70</td>
</tr>
<tr>
<td>Gamma-glutamyl transpeptidase, U/l</td>
<td>12.00-64.00</td>
<td>215     135</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/l</td>
<td>40.00-150.00</td>
<td>358     326</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/l</td>
<td>125.00-220.00</td>
<td>670     390</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>35.00-52.00</td>
<td>39      40</td>
</tr>
<tr>
<td>Ferritin, μg/l</td>
<td>20-300</td>
<td>487     363</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>up to 6</td>
<td>44      24</td>
</tr>
</tbody>
</table>

Table 3. Biochemical blood assay of patient S. in dynamics

In 2017, the patient was diagnosed with chronic hepatitis C virus - HCV RNA positive (genotype 3a), in 2018 the patient received 12-week interferon-free antiviral therapy (Sofosbuvir 400 mg + Daclatasvir 60 mg), and a stable virological response was achieved. The patient was admitted to hospital. CXR - pattern of bilateral polysegmental viral pneumonia. Lesion volume - CT-2. Blood

**Clinical case 4**

Patient S., 41 y/o On admission, the patient complained of unproductive cough, fever in the evening hours 38°C and higher, with chills, lost or changed sense of smell, taste, headache. The patient fell ill 4 days before admission. Outpatient treatment had no effect.

Plaquenil, Azithromycin, as well as pathogenetic therapy (Fluimucil, Enterogel, Enterol, Paracetamol in case of fever).

The therapy was carried out, sonogram showed no liver damage. As a result of the treatment, according to CXR, pneumonia was resolved, the repeated throat swab was twice negative. Dynamic laboratory observation demonstrated normalization of the level of transaminases on day 6 of treatment. The stool returned to normal on day 7 of treatment. **Clinical case 4**

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moderate hepatitis with cholestasis syndrome, without liver dysfunction. On day 2 of admission, discomfort in the right hypochondrium, nausea, loose stools up to 3-4 times a day appeared. Ultrasound of abdominal cavity showed echographic signs of diffuse changes in the parenchyma of the liver and pancreas. Liver density (shear wave elastography): 7.8 kPa (F2). 23 May 2020 CXR in dynamics after 6 days: in both lungs - polysegmental, along the periphery, mainly in the lower lobes, the confluent areas of compaction of the lung tissue like ground glass in combination with the reticular component and consolidation. Lung tissue damage - up to 50%. Conclusion. CT imaging of bilateral polysegmental viral pneumonia (including COVID-19), CT-2. Negative dynamics. That is, the patient with pathological changes in liver enzymes had a protracted course of viral pneumonia. Blood count showed resolution of lymphopenia, a downward trend in D-dimer.

Approaches to the treatment of gastroenterological symptoms of COVID-19

According to the Interim Guidelines of the Ministry of Health of Russia, today there is no evidence of the effectiveness of the use of any drugs of etiotropic action in COVID-19 [23]. In addition, the prescribed antimicrobial and antiviral agents have hepatotoxic and enterotoxic effects, which require management. Pathogenetic therapy involves the use of a sufficient amount of fluid (2.5-3.5 l per day or more, if there are no contraindications for somatic pathology). In cases of severe intoxication, as well as abdominal pain, nausea and/or vomiting, edema that prevent fluid intake, oral intestinal adsorbents (enterosorbents) are indicated (colloidal silicon dioxide, polymethylsiloxane polyhydrate, etc.). Among the known pathogenetic therapy drugs, modern intestinal sorbents have an advantage, since they act simultaneously on various mechanisms of coronavirus infection. In particular, this concerns the restoration of the intestinal mucosal barrier due to the regeneration of the mucous membrane, a decrease in the elevated level of endotoxin in the blood, and the normalization of intestinal dysbiosis. Intestinal adsorbents are agents of non-systemic action, they are not absorbed from the intestine into the blood, therefore, unlike antimicrobial agents, they do not have hepatotoxic and nephrotoxic effects. Moreover, they adsorb excess endotoxin and demonstrate effectiveness in arresting the manifestations of drug hepatitis amid the use of antimicrobial agents.

The advantages of the modern intestinal adsorbent polymethylsiloxane polyhydrate (Enterosgel) in comparison with the classical ones, based on coal and clay, include hydrophobicity, which is manifested in a significantly lower degree of dehydration (exsiccosis) during the treatment [24]. In addition, in contrast to finely dispersed silicon dioxide, polymethylsiloxane, polyhydrate, at least in in vitro studies, did not cause lysis of the normoflora, for example, Escherichia coli [25], and at the same time contributed to the suppression of Staphylococcus aureus growth and production of enterotoxin [26].

The advantages of using contemporary intestinal adsorbents is confirmed by the results of numerous clinical studies carried out in Russia and abroad, which were presented in our reviews [27, 28]. For example, the therapy with polymethylsiloxane polyhydrate promoted significantly timelier stool normalization (cessation of diarrhoea) in 46 HIV patients receiving antiretroviral therapy [29]. The use of Enterosgel allowed for a more rapid resolution of symptoms of intoxication and normalization of dysbiosis in 61 patients with acute hepatitis B virus and concomitant intestinal dysbiosis [30].

In addition, in the UK, a study was completed that demonstrated the efficacy and safety of polymethylsiloxane polyhydrate in the outpatient treatment of acute diarrhoea in adults. Enterosgel

Fig. 2. Tomographic image of patient’s lungs in dynamics: A - 23 May 2020: pattern of bilateral polysegmental viral pneumonia, including COVID-19; A - 29 May 2020: positive dynamics of the treatment of viral pneumonia. CT - stage of stabilization/resolution.
promoted faster normalization of stool [31]. Interim results of a study have been published, which also showed the effectiveness of this therapy. Therapy supplemented with polymethylsiloxane polyhydrate for managing diarrhoea-predominant irritable bowel syndrome promoted relief from pain symptoms and normalization of stool [32].

**Conclusion**

In the comprehensive therapy of the novel coronavirus infection COVID-19, in case of gastrointestinal symptoms and an increase in the level of hepatic transaminases, it is advisable to use modern intestinal adsorbents, for example, polymethylsiloxane polyhydrate, in a standard dose of 22.5 g (1 sachet, or 1.5 tablespoon) 3 times per day. Taking into account the mechanism of action of the intestinal adsorbent, its use can promote faster relief from diarrhoea, reduction of intoxication syndrome and normalization of the level of transaminases.

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