WARUNEK, Aleksandra, GRONOWICZ, Gabriela, WANAT, Joanna, DZIKOWSKA, Izabela, HOMA, Wojciech, SIEJKA, Agata, STEFANIAK, Daria, ZIELIŃSKA, Weronika and CHRÓL, Michał. Irritable bowel syndrome: An Underestimated Consequence of Post-Acute COVID-19. A Literature Review. Journal of Education, Health and Sport. 2025;79:59072. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.79.59072
https://apcz.umk.pl/JEHS/article/view/59072

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 27.02.2025. Revised: 12.03.2025. Accepted: 15.03.2025. Published: 17.03.2025.

Irritable bowel syndrome: An Underestimated Consequence of Post-Acute COVID-19. A Literature Review

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Abstract:

Irritable bowel syndrome (IBS) is a significant health issue affecting many individuals globally. The precise mechanisms underlying its development are still being researched, as various factors contribute to its onset, including stress, dysfunction of the gut-brain axis, intestinal hypersensitivity, prior infections, and medications that disrupt gut homeostasis. The COVID-19 pandemic has led to a notable increase in IBS cases, prompting investigations into the link between coronavirus infection and the risk of developing post-infectious IBS. Research suggests that stressors such as isolation, fear of mortality, bereavement, financial insecurity, uncertainty about the future, changes in routine, and remote work stress significantly influence this condition's development. Additionally, the virus can disrupt gut microbiota and trigger the release of pro-inflammatory mediators, potentially resulting in the death of intestinal cells. Medications used during the pandemic, including antibiotics, steroids, and antiviral agents, may also impair gut function, leading to long-term consequences. This complexity presents challenges for modern medicine, highlighting the need for further research to aid those affected by this condition. This paper reviews current insights into the development of post-inflammatory IBS in COVID-19 patients, integrating established knowledge with novel findings from the pandemic.

Aim:

This article aims to review the current researches on the discussed relationship between irritable bowel syndrome and a previous infection with the SARS-CoV-2 virus, the changes that occur in the gastrointestinal microbiome during the infection and the pathophysiological reason for that.

Materials and Methods:

A comprehensive literature review was conducted using PubMed, focusing on articles and research papers published between 2007 and 2024. Search terms included "SARS-CoV-2", "COVID-19", "Irritable bowel syndrome", "Microbiota", "Dysbiosis", "Gut-brain axis", "nutrition".

Keywords: SARS-CoV-2, COVID-19, Irritable bowel syndrome, Microbiota, Dysbiosis, Gut-brain axis, nutrition

Introduction of SARS-CoV-2 infection

In December 2019 a series of acute atypical respiratory infections ravaged the Wuhan city of Chinese Hubei province and started to spread rapidly, becoming a worldwide pandemic. The responsible pathogen was soon identified to be a coronavirus, Coronaviridae family new member, that shares 80% identity with SARS coronavirus (SARS-CoV). Due to the similarity with SARS-CoV, which was responsible for the pneumonia pandemic during the years 2002 and 2003, starting from China Guangdong Province, it was named as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). [1–3] In a short amount of time the human-to-human virus transmission caused the outbreak to approximately 200 countries beyond China and killed hundreds of thousands of people all over the world. On Jan 30, 2020, coronavirus disease 2019 (COVID-19) came to be declared by the World Health Organization (WHO) a public health emergency of international concern. Subsequently on March 11, 2020, it was changed by WHO to a pandemic state.[1,4]

Clinically Covid-19 was classified into 3 groups:
-mild to moderate disease (non-pneumonia and pneumonia)
-severe disease (dyspnoea, oxygen saturation <93%, respiratory frequency >30/min, PaO_2/FiO_2 ratio<300 and/or lung infiltrates>50% of the lung field within 24–48 hours)
-critical (respiratory failure, septic shock and/or multi-organ dysfunction/failure).[5]

Even though 80% of COVID-19 cases are mild to moderate, from all patients who got admitted in the hospital, 26–32% needed admission in the ICU.[6]
The illness process can be symptomatic or asymptomatic with the same incidence.[7]

In 98% of cases the time from exposure to the onset of the symptoms was a maximum of 12 days and the statistic median age of patients with verified positive covid tests was 56 years (range 55-65 years).[5]

Most characteristic and often presented signs of Covid-19 were fever, changes in smell and/or taste, myalgias, and respiratory tract symptoms, especially cough and dyspnea.[8]

However, SARS-CoV-2 not only impacts the lungs of those infected but also harms other body organs. The organs most affected—such as the heart, blood vessels, kidneys, intestines, nervous system, and brain—contain a higher number of angiotensin-converting enzyme 2 (ACE-2) receptors on their surface, which facilitate the virus's entry into the infected cells. SARS-CoV-2 spreads more easily than other recognized coronaviruses due to its greater attraction to ACE-2 receptors. [9] Also men because of a genetically higher than women concentration of ACE2 were more frequently affected by the virus.[5]

Like in other infectious diseases, patients who recover often experience various long-term effects. These can include neuropsychiatric issues like fatigue, anxiety, depression, post-traumatic stress disorder and insomnia. It still remains unclear whether these symptoms arise. From the infection itself, the general treatment (primarily medical therapies), or from mechanisms that we still didn't discover.[10]

On this review we focused on long-distance gastrointestinal tract (GI tract) complications conected with Covid-19 disease. Almost 15% of infected by SARS-Cov-2 develop symptoms related to GI tract in the future. There is an increasing amount of evidence regarding complications related to SARS-CoV-2, including those affecting the gastrointestinal system. One such complication is post-infection irritable bowel syndrome (PI-IBS), which can occur in up to 10.1% of patients following a gastrointestinal infection.[11]

What is an IBS?

Irritable bowel syndrome (IBS) is a common chronic (>6 months) intestinal disorder that causes abdominal pain, bloating ,diarrhoea and/or constipation. Changes that it causes in bowel function have a significant impact on patients' quality of life.[12,13]

We still don't fully understand the pathophysiology of IBS even though the condition affects between 5 to 10% of the general human population. What we know is that vital importance in IBS course is gut-brain interaction. Several studies have shown that IBS patients have lower

pain thresholds in their colon compared to healthy individuals. These studies have shown that IBS patients have reduced sensory thresholds during rectal balloon distension.[13,14] Additionally, a meta-analysis indicated that IBS patients exhibit heightened activation of brain areas linked to emotional response and endogenous pain modulation when exposed to rectal balloon stimulation, compared to healthy controls. Moreover, multiple studies have revealed a significant occurrence of comorbid anxiety and depression disorders in individuals with IBS. Other minor mechanisms might include:

-genetic associations

-disturbance in gastrointestinal microbiota

-mucosal and immune dissfunction. [13–15]

Statistically patients with IBS are currently the largest subgroup seen in gastroenterology clinics. Almost 12% of patients in primary care practice who seek for help with bowel disorder are later diagnosed with irritable bowel syndrome. [16] Most commonly diagnosis can be made by gathering the basic medical history without broader medical evaluations, unless alarm symptoms are present. ”Red flags” that should draw our attention to organic diseases are weight loss, rectal bleeding, family history of colorectal cancer, inflammatory bowel disease or coeliac disease.[14] The diagnosis of IBS is based on the revised Rome IV criteria. A key feature is the presence of recurrent abdominal pain occurring at least once a week over the past three months, which is associated with at least two of the following factors:

-related to bowel movements,

-linked to a change in stool frequency,

-connected to a change in stool consistency.

These criteria must have been met in the last three months, with symptoms having started at least six months prior to the diagnosis.[17]

While a significant number of patients may see spontaneous improvement over time, there is no existing treatment that can cure IBS; managing symptoms is the best outcome that can be hoped for.[18]

Changes in Gastrointestinal microbiota

Post-infectious IBS (PI-IBS) is considered one of the potential causes of IBS. Consequently, changes in fecal microbiota have been suggested as a possible factor contributing to IBS. In a systematic review, Pittayanon et al. found that IBS patients exhibited higher levels of the Enterobacteriaceae family (phylum Proteobacteria), Lactobacillaceae family, and genus

Bacteroides, while showing lower levels of uncultured Clostridiales I, genus Faecalibacterium (including Faecalibacterium prausnitzii), and genus Bifidobacterium.[15]

The findings indicate that long-term advantages in reducing PI-IBS may be achieved through the primary prevention of infectious gastroenteritis (IGE). [19]

How is Human Microbiota Affected by COVID-19

Fecal samples from SARS-CoV-2 positive patients tested using RT-PCR have confirmed the presence of the virus in the intestines (RNA-based genome), highlighting an additional factor that necessitates attention and specialized management. Additionally, Park et al. reported in clinical trials that the virus can be detected in fecal samples up to 50 days.[20] SARS-CoV-2 can persist not only in symptomatic patients but also it was found in the intestines of asymptomatic individuals. For instance, the viral RNA signature of SARS-CoV-2 was detected in the stool samples of an asymptomatic child, even though its parents tested negative for the virus two weeks apart.[21]

As noted earlier, SARS-CoV-2 binds to ACE2 in order to enter human cells and infect the host. In particular, this receptor is found in the muscularis mucosa and mucosa of the intestine, encompassing epithelial cells, cholangiocytes, hepatocytes, pancreatic ductal, acinar, and islet cells, as well as in the gastrointestinal blood vessels. ACE2 appears to be crucial for maintaining intestinal homeostasis and its functions.[10] Curren research indicates that ACE2 is involved in inflammation and immune modulation, as well as in the pathophysiology of irritable bowel syndrome (IBS), contributing to the exacerbation of low-grade inflammation in the enteric nerve plexuses. [22] The theory of intestinal inflammation is backed by the observation of notably higher levels of fecal cytokines, such as IL-8, IL-23 and a lower IL-10 concentration in COVID-19 patients compared to uninfected controls. Ultimately, the detection of virus-specific immunoglobulin A (IgA) in stool samples indicates that the gastrointestinal tract could be immunologically engaged during SARS-CoV-2 infection.[23]

In an intestinal infection caused by SARS-like viruses, the gastrointestinal mucosa can suffer a significant harm, resulting in cytopathic changes that propagate through the cell layers and lead to cell detachment within 24 to 48 hours. The functions of mature enterocytes are derailed. Several enzymes are highly overexpressed in atypical areas, which may lead to malfunctions or irreversible damage in enterocytes, ultimately inducing an apoptosis.[20,24]

Gastrointestinal dysbiosis may arise following a COVID-19 infection, even in the absence of gastrointestinal symptoms. [25] However, research indicates that individuals who experience acute gastrointestinal symptoms during COVID-19 are four times more likely to develop persistent gastrointestinal issues compared to those who do not exhibit such acute symptoms. The opinions regarding this issue are polarized. Some researchers support the notion that gastrointestinal symptoms occurring during the acute phase of infection serve as a predictive factor for the subsequent development of IBS. In contrast, others contest this viewpoint. [26] Additionally, several factors can contribute to dysbiosis, including antibiotic treatments, secondary bacterial infections, and enteral nutrition. The consequences of an altered microbiota may include inflammatory changes in the gastrointestinal tract, malnutrition, and increased susceptibility to viral and bacterial infections. [25] It is also possible that patients with COVID-19 had an altered gut microbiota prior to the onset of the illness. In such cases, COVID-19 may exacerbate dysbiosis, potentially leading to chronic conditions like obesity and metabolic disorders. [27] Recognizing the importance of proper nutrition is essential for restoring microbiota following a COVID-19 outbreak, with prebiotics and probiotics playing a key role. By modulating the microbiota, we can expect a restoration of microbiome function and an enhancement of the immune response. [28]

Role of probiotics

In February 2020, the National Health Commission and the National Administration of Traditional Chinese Medicine recommended the administration of probiotics to patients diagnosed with COVID-19. This recommendation was primarily based on findings indicating that up to 70% of these patients had been treated with antibiotics, thereby significantly heightening their risk of subsequent intestinal infections. [20] Thanks to their multifaceted effects, probiotics can impact the progression of COVID-19 through several mechanisms.
These mechanisms include:
-enhancing antiviral responses,
- providing protection against secondary infections
-generating antimicrobial peptides,
-exhibiting anti-inflammatory properties.

The direct action of probiotics against the SARS-CoV-2 virus encompasses the production of various antiviral substances, including hydrogen peroxide, nitric oxide, bacteriocins, and subtilisin. These substances contribute to neutralizing virulence factors, obstructing viral receptors, binding to viral particles, and directly and indirectly inhibiting the renin-angiotensin system.[25] Additionally, probiotics suppress the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway and inhibit histone deacetylase activity. The immunomodulatory effects of probiotics primarily target the enhancement of interleukin-12 (IL-12) production, which serves to activate natural killer (NK) cells, T helper 1 (Th1), and T helper 2 (Th2) immune cells. Furthermore, probiotics promote increased production of interleukin-10 (IL-10), thereby facilitating an elevation in regulatory T (Treg) cells that play a critical role in the regulation of inflammation.[25]

A clinical study has demonstrated that the administration of probiotics resulted in a reduction of systemic pro-inflammatory biomarkers in patients with colitis, encompassing both gastrointestinal and non-gastrointestinal conditions, after a treatment period of 6 to 8 weeks.[29]

Recent studies have examined the effects of probiotics on respiratory illnesses. Two randomized controlled trials demonstrated that critically ill patients undergoing mechanical ventilation who received probiotics, specifically Lactobacillus rhamnosus GG, live Bacillus subtilis, and Enterococcus faecalis, exhibited significantly lower rates of ventilator-associated pneumonia in comparison to those receiving a placebo. Consequently, it may be postulated that pneumonia associated with COVID-19 could be similarly alleviated through the administration of probiotics.[30,31]

Currently, numerous researchers around the world are examining the relationship between the microbiome and susceptibility to COVID-19. In parallel, they are assessing the efficacy of various probiotic strains in mitigating viral load through a range of mechanisms.[29,32]

It is compelling to consider that probiotics may serve as a viable complementary strategy for the treatment and prevention of viral infections, including COVID-19. Nonetheless, in the absence of comprehensive evidence regarding the pathogenesis of the novel coronavirus and its effects on the gut microbiome, the broad recommendation of conventional probiotics for addressing COVID-19 is premature. Extensive research involving well-structured randomized controlled trials is required to ascertain both their efficacy and safety.[29]

What are some additional potential triggers for IBS?

As mentioned before viral enteritis is recognized as a significant risk factor for the development of PI-IBS. [10] Research conducted by Porter et al. indicates that individuals who suffer from acute gastroenteritis during a confirmed norovirus outbreak exhibit an increased likelihood of experiencing dyspepsia, constipation, and gastroesophageal reflux disease. This finding implies that disorders related to gastrointestinal motility may emerge as a consequence of viral infections.[33]

Also medications prescribed during a coronavirus infection can significantly affect intestinal health. This includes not only antibiotics but also other treatment options used in Covid-19 pandemic such as corticosteroids and antiviral drugs, all of which have been linked to dysbiosis. Animal studies indicate that subcutaneous administration of prednisolone, a systemic glucocorticoid, alters the gut microbiota in mice. Specifically, this treatment results in decreased levels of Verrucomicrobiales and Bacteroidales, while increasing levels of Clostridiales in mice intestine microbiome compared to control groups.[10]

The impact of antiretroviral drugs, specifically the adenosine nucleotide analogue prodrug remdesivir and the protease inhibitor lopinavir combined with ritonavir, on the microbiome is not well understood. [34] Current research mainly focuses on HIV treatment but has shown that these medications can cause changes in the microbiome beyond those effects associated with HIV itself.[10]

The final point, which is one of the most important, is the co-morbidity of IBS and psychological distress. This study highlights that 4 out of 5 patients with IBS also have associated psychiatric disorders.[35,36]

Psychosocial issues are prevalent in IBS patients, with anxiety symptoms affecting 39.1% and depressive symptoms impacting 28.8%. These rates are approximately three times higher than those found in healthy individuals.[37]

Furthermore, it is noteworthy that early adverse life events and major traumatic experiences are frequently reported in relation to the onset of IBS. Such experiences may include disruptions in close relationships, marital separations, or a family member departing from the household.[38]

The findings suggest that individuals in home isolation report a more significant improvement in their overall health status compared to those in centralized isolation. Patients in centralized isolation often experience heightened feelings of loneliness, helplessness, and isolation. This specific environment may lead them to concentrate more on their persistent COVID-19

symptoms. Such psychological reactions are likely to adversely impact patients' self-assessments of their health levels. [39] Also patients IBS have reported experiencing lower levels of social support compared to those without such symptoms. Notably, for many patients with functional gastrointestinal disorders, the stress associated with social activities and professional interactions can be more distressing than remaining isolated at home.[40] Overall, psychological disturbances associated with COVID-19 are considerable and may significantly contribute to the incidence of IBS. [10]

Conclusion:

The COVID-19 pandemic has highlighted complex interactions between SARS-CoV-2 infection and the subsequent development of irritable bowel syndrome (IBS). Key factors contributing to post-infection IBS include the disruption of gut-brain communication, alterations in the gut microbiome due to the virus and associated treatments, and inflammatory responses that impact intestinal health. Additionally, the psychological stress and anxiety linked to the pandemic have exacerbated gastrointestinal symptoms. Together, these elements create an environment that may predispose individuals to IBS after recovering from COVID-19. Understanding these connections is crucial for developing effective management strategies for those affected. Further research is needed to explore the underlying mechanisms and improve care for patients experiencing these long-term complications.

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All authors have read and agreed with the published version of the manuscript.

Founding Statement: The study did not receive funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: The authors declare no conflicts of interest. Acknowledgments: Not applicable.

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