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5. Streszczenie w języku angielskim:

"Impact of gastrointestinal symptoms on the clinical course of SARS-CoV-2 infection"

Aim:

The main aim of the study was to determine the frequency of gastrointestinal (GI) symptoms (defined as abdominal pain, diarrhea, nausea, vomiting and loss of appetite) among 441 patients hospitalized for COVID-19. The influence of GI symptoms on the course of COVID-19 was examined, taking into consideration the time of their occurrence and their possible relationship with drugs used in the treatment of SARS-CoV-2.

Patients and methods:

It is a single-center, retrospective study, which included 441 patients, 18 years of age and older with confirmed SARS-CoV-2 infection, hospitalized from March 15th to June 15th, 2020 at the Central Clinical Hospital of the Ministry of the Interior and Administration. The diagnosis was made on the basis of the applicable standard, i.e. a positive result of the reverse transcriptase test – polymerase chain reaction (target genes: RdRp, E and N) for SARS-CoV-2 in nasopharyngeal swabs.

Results:

Among 441 hospitalized COVID-19 patients, 255 (57,8%) had GI symptoms. The most common symptom was lack of appetite, which was reported in 124 (48,6%) cases. Other GI symptoms such as diarrhea were observed in 109 (42,7%), abdominal pain in 95 (37,3%), vomiting in 37 (14,5%) and nausea in 32 (12,5%) patients. The gender distribution was similar in both groups, 49,4% of women in the group with GI symptoms (research group) vs. 48,4% in the group without GI symptoms (control group); p=0,083. Patients with GI symptoms were significantly older, i.e. 68,44 years vs. 64,45 years in the control group; p=0.02 and had significantly more comorbidities 91,0% vs 82,3%; p=0,007.

The cohort was divided into two groups: 142 (32,2%) patients who experienced GI symptoms before admission to hospital and 113 (25,62%) patients who experienced GI symptoms during hospitalization.

In the group of 142 patients (32,2%) who experienced GI symptoms before admission to the hospital versus patients without GI symptoms, a statistically significant reduction in the length of stay (LOS) was observed, i.e. 15 days vs. 17 days; p=0,04, reduction in the frequency of stays in the Intensive Care Unit, i.e. 16,9% vs 26,8%; p=0.02 and lower demand for mechanical ventilation 14,1% vs 23,4%; p=0,02. No statistical significance was found for mortality among patients with GI symptoms before admission to hospital, i.e. 53 (37,3%) vs in asymptomatic patients, i.e. 95 (31,8%); p=0,24. Sex distribution, age, comorbidities, used proton pump inhibitors (PPI), CDI incidence were not a risk factor for GI symptoms before hospitalization. In the group of patients with GI symptoms before admission to the hospital, the most common symptom was lack of appetite in 84 (19,9%), followed by abdominal pain in 70 (15,9%), diarrhea in 60 (13,6%), vomiting in 11 (2,5%) and nausea in 10 (2,2%) cases.

113 (25,62%) patients who experienced GI symptoms during their stay in hospital (compared to patients without symptoms) had a statistically significantly longer duration of hospital stay (LOS), i.e. 21 days vs 15 days; p=0,0001, more frequent visits to the Intensive Care Unit, i.e. 38,1% vs 18,6%; p=0,0003, greater need for mechanical ventilation, i.e. 32,7% vs 16,2%; p<0,001 and more frequent occurrence of CDI, i.e. 22,1% vs 7,0%; p=0,0001. Mortality was not statistically significant among patients with gastrointestinal symptoms during the stay vs. the asymptomatic group, i.e. 46 (40,1%) vs 102 (31,1%), respectively; p=0,06. Age, CDI frequency, some specific drugs used in the treatment of COVID-19 (antibiotics, azithromycin, antibiotics other than azithromycin and lopinavir + ritonavir) were risk factors for gastrointestinal symptoms during hospitalization. Gender, comorbidities, PPI, and chloroquine use were not risk factors for GI symptoms during hospitalization. In the group of patients with gastrointestinal symptoms during hospitalization, the most common was diarrhea - present in 49 (11,1%) cases, followed by lack of appetite in 40 (9,1%), vomiting in 26 (5,9%), abdominal pain in 25 (5,7%) and nausea in 22 (5,0%).

Of 441 patients hospitalized for COVID-19, 48 patients (10,9%) developed *Clostridioides difficile* infection. Age, hospitalization time, treatment with antibiotics other than azithromycin, certain comorbidities (cardiovascular disease, chronic kidney

disease, and nervous system disease), and the appearance of abdominal symptoms during hospitalization were all risk factors for CDI. All variables had a significant but weak effect (Cramer V=0,1–0,3). Antibiotics were used to treat 354 patients (80,3%) with COVID-19, including 42 (87,5%) with CDI and 312 (79,4%) without CDI (V=0,06, p=0,18). Surprisingly, no statistical significance was observed for the use of azithromycin - it was used in a total of 214 patients (48,5%), including 28 (58,3%) with CDI and 186 (47,3%) without CDI (V=0,07, p=0,15). In 300 patients (68%), antibiotics other than azithromycin were administered - more often in patients with CDI (39 [81,3%]) than without CDI (261 [66,4%]), (V=0,1; p=0,037). There was an increase in antibiotic use, defined as daily antibiotic consumption per 100 person per days of hospitalization, from 57,2 before the pandemic to 105 during the pandemic. Due to the lack of data on the effects of drugs used in COVID-19, the effects of chloroquine and lopinavir + ritonavir were also tested, which in the initial period of the pandemic were recommended by the Polish Society of Epidemiologists and Doctors of Infectious Diseases, and I have proved that they did not affect the development of CDI.

Parameters that differed between COVID-19 patients with CDI and patients without CDI were included as predictors in the multivariate logistic regression model with CDI as the outcome variable. Significant variables in the model were hospitalization time (p=0,01), stay in the intensive care unit (ICU) (p=0,006), and occurrence of abdominal symptoms during hospitalization (p=0,001). One day prolongation of hospitalization increased the risk of CDI by 3% (OR 1,03; 95% CI 1,01–1,05). Surprisingly, in ICU patients the CDI risk was 76% lower (OR 0,24; 95% CI 0,08–0,61), and 3,4 times higher in patients with abdominal symptoms during hospitalization (OR 3, 38; 95% CI 1,71– 6,72). The other variables were irrelevant in the model. The evaluation of the model using the chi2 test confirmed that all variables were significant together (p=0,001). Nagelkerke's R2 ratio was low (22%), indicating the presence of other unassessed variables that influenced the incidence of CDI in patients with SARS-CoV-2 infection. Additional evaluation with the Hosmer-Lemeshow fit test (p=0,13) confirmed the good fit of the model to the data.

During the COVID-19 pandemic, compared to the pre-pandemic period, the incidence of CDI increased significantly: 10,9% (48 CDI cases out of 441 patients) versus 2,6% (77 CDI cases out of 2,961 patients); p<0,0001. Comparison of the incidence of CDI before and during the COVID-19 pandemic showed a significant relationship between the incidence of SARS-CoV-2 infection and gender, the use of

antibiotics, the incidence of chronic kidney disease, and the incidence of nervous system disease in patients with CDI. Men with SARS-CoV-2 infection were more likely to suffer from CDI than before the pandemic (45,8% vs 28,6%; V=0,18; p=0,049). Antibiotics were taken by 87,5% of CDI patients infected with SARS-CoV-2 compared with 67,5% of CDI patients before the pandemic (V=0,22; p=0,012). There were no significant differences in age, hospitalization time, and frequency of proton pump inhibitor (PPI) use between SARS-CoV-2 infected patients with CDI and those treated before the pandemic. Chronic kidney and nervous system disease was more common in CDI patients infected with SARS-CoV-2 than in CDI patients before the pandemic, with a stronger impact on nervous system disease (31,3% vs 15,6%) V=0,19; p=0,038 for chronic kidney disease and 11,7% vs 39,6%; V=0,33; p<0,001 for diseases of the nervous system). A significant association between CDI in patients with SARS-CoV-2 infection and patients with CDI prior to the pandemic of other comorbidities has not been established.

Summary and Conclusions:

Symptoms of GI during COVID-19 that appeared before admission to the hospital correlate with a reduced severity of the disease. Conversely, GI symptoms that appear during hospitalization correlate with a more severe course of COVID-19. Certain drugs, such as antibiotics and lopinavir-ritonavir, significantly correlated with symptoms during hospitalization and with disease worsening. Given that this correlation is not a causal relationship, this requires further research and may be useful in stratifying the severity of COVID-19 patients. However, the inclusion of gastrointestinal symptoms (before and during hospitalization) in disease severity prediction models appears to be promising. However, in the group of patients who develop gastrointestinal symptoms during their stay, attention should be paid to concomitant treatment.

The study found a significant increase in the incidence of CDI among hospitalized patients during the pandemic compared to the pre-pandemic period. The widespread use of antibiotics was a significant risk factor for CDI, although its effect was weak. Treatment-related or SARS-CoV-2 infection related disturbances of the gut microbiota may explain the increased incidence of CDI. As the incidence of CDI is rising significantly, stringent antibiotic management programs and further research into changes in the gut microbiome to COVID-19 are needed. The appearance of GI

symptoms during hospitalization may be a significant signal of the development of CDI. Clinicians should be aware of the risks of co-infection and be vigilant - adherence to CDI screening protocols during a pandemic is of utmost importance.

The main conclusions of the study:

1. Abdominal symptoms are a frequent manifestation of COVID-19, they occurred in 57,8% of patients with SARS-CoV-2 infection.

2. Patients with COVID-19 who developed abdominal symptoms before admission to the hospital had a milder course of the disease compared to patients who developed these symptoms during hospitalization. The use of certain medications, in particular antibiotics, seems to be of key importance, and should be limited as they are associated with worsening of COVID-19; one of the reasons may be changes in the gut microbiome.

Clostridioides difficile infection was diagnosed in 10,9% of patients, for which the use of antibiotics was the main risk factor. Other drugs used in COVID-19 have not been found to influence the development of the disease. Disturbances in the gut microbiota caused by the extensive use of antibiotics may have contributed to the increased incidence of CDI.