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## Inflammatory Bowel Diseases and COVID-19: The Invisible Enemy



An P, Ji M, Ren H, et al. Protection of 318 inflammatory bowel disease patients from the outbreak and rapid spread of COVID-19 infection in Wuhan, China. *Lancet* 2020 Feb 27 [Epub ahead of print]

A new beta-coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was recently identified in Wuhan, China (*N Engl J Med* 2020;382:727–733). The virus proved to be transmitted from person to person and to be highly contagious, causing the onset of a pandemic in a short time (WHO Director-General's opening remarks at the media briefing on COVID-19, March 11, 2020. Available at: [www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020](http://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020)). SARS-CoV-2 infection can be asymptomatic or cause coronavirus disease 2019 (COVID-19), which mainly includes respiratory and gastrointestinal symptoms and in severe cases it can be fatal (*JAMA* 2020;323:1061–1069). Several measures have been taken to prevent the further spread of the virus, including the use of masks, gloves, and disinfectants, and restrictions to avoid traveling to risk areas and having close contact with other people (Q&A on coronaviruses (COVID-19). Available at: [www.who.int/news-room/q-a-detail/q-a-coronaviruses](http://www.who.int/news-room/q-a-detail/q-a-coronaviruses)). Moreover, many countries have imposed quarantine and lockdown of schools and all nonessential activities (*J Travel Med* 2020 Mar 17 [Epub ahead of print]). In this context, particular attention should be paid to patients treated with immunosuppressive drugs or biologics, because they have a higher risk of infection (*Clin Gastroenterol Hepatol* 2020;18:69–81.e3). Other risk factors identified for the development of COVID-19 are advanced age, the presence of chronic diseases such as hypertension and diabetes, some professional categories (eg, health care personnel, policemen, and supermarket clerks) and exposure to infected people (Q&A on coronaviruses (COVID-19). Available at: [www.who.int/news-room/](http://www.who.int/news-room/)

[q-a-detail/q-a-coronaviruses](#)). In a recent work published in the *Lancet* (*Lancet* 2020 Feb 27 [Epub ahead of print]), precautions taken by a Wuhan center for inflammatory bowel diseases (IBD) were reported. All biological and immunosuppressive treatments were discontinued, visits in person were replaced by online consultations, and 318 patients were daily recommended to wash their hands frequently, to decrease the time spent outside the home, and to use masks outside the home (*Lancet* 2020 Feb 27 [Epub ahead of print]). It is important to underline that a relevant percentage of evaluated patients had risk factors of infection: chronic diseases (15.4%), immunosuppressive agent therapy (11.0%), elderly (10.4%), high-risk professional categories (7.5%), and biological therapy (6.3%) (*Lancet* 2020 Feb 27 [Epub ahead of print]). Recommendations were followed by 90% of patients and no cases of COVID-19 infection were detected after a period of approximately 2 months (*Lancet* 2020 Feb 27 [Epub ahead of print]). Finally, the authors stressed the importance of daily warnings and recommendations, which favored a wide adherence of patients and contributed to avoid viral contagion (*Lancet* 2020 Feb 27 [Epub ahead of print]).

**Comment.** The COVID-19 health emergency has forced physicians to deal with problems never before encountered and to take quick decisions in consideration of the urgent needs. In addition, the limited knowledge regarding transmission modalities, clinical symptoms, and natural history of the virus infection has made the management of patients with IBD and the adoption of preventive measures even more complex and difficult. Currently, the main source of transmission seems to be mediated by air droplets (*Lancet* 2020 Feb 27 [Epub ahead of print]), although ever-increasing evidence supports the possibility of a fecal–oral infection route (*Gastroenterology* 2020;158:1518–1519). As of March 29, 2020, the World Health Organization has reported 634,835 confirmed cases of infection worldwide and 29,957 deaths (Novel coronavirus (2019-nCoV) situation reports. Available at: [www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports](http://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports)). So far,

epidemiologic data of COVID-19 in patients with IBD have not been published and it is unclear whether patients with IBD have an increased risk of infection. Interestingly, patients with active ulcerative colitis and Crohn's disease have a greater tissue concentration of angiotensin-converting enzyme 2, the molecule that allows SARS-CoV-2 spike protein to bind the host cell and infect humans (Gut 2020;69:841–851). Similarly, the level of serine protease, an essential primer to activate the spike protein, is about 10 times higher in patients with IBD than in healthy subjects, suggesting an increased risk of infection in these patients (Front Cell Infect Microbiol 2020;10:21). These data justify concerns for patients with IBD and highlight the need to clarify whether there is an association between immunosuppressive/biological therapies and coronavirus infection. Importantly, a 3 times higher risk of serious viral infections (cytomegalovirus, Epstein-Barr virus, varicella zoster virus, and herpes simplex virus) was detected in patients with IBD compared with the general population (United European Gastroenterology Journal 2019;2050640619889763). Although the absolute risk of developing a viral infection was acceptable, the presence of an active disease and treatment with thiopurines were reported as the factors most influencing the infectious risk (United European Gastroenterology Journal 2019;2050640619889763). Recently, the International Organization of IBD stated that vedolizumab and ustekinumab are safe drugs and do not increase the risk of infection, although the risks of infection related to treatments with thiopurine, anti-tumor necrosis factor agents, and tofacitinib are uncertain (IOIBD update on COVID19 for patients with Crohn's disease and ulcerative colitis | IOIBD. Available at: [www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-and-ulcerative-colitis/](http://www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-and-ulcerative-colitis/)).

In the work from An et al (Lancet 2020 Feb 27 [Epub ahead of print]) all patients discontinued therapy and no patient contracted the infection. This patient management should be discussed. First, some drugs such as thiopurines have a very high clearance time and therefore it would take a long time before decreasing the risk of infection (Nat Rev Gastroenterol Hepatol 2020;17:253–255). Second, therapy discontinuation is associated with an increased risk of disease recurrence/worsening and may lead to an increase of negative outcomes such as hospitalizations and surgeries (Cochrane Database Syst Rev 2018;5:CD012540; Am J Gastroenterol 2017;112:120–131; J Crohns Colitis 2018;12:17–31). Third, in this period many countries are lockdown and hospitals are overloaded with work and have changed their organization, minimizing nonessential outpatient activities and focusing on COVID-19 patients (N Engl J Med 2020 Mar 18 [Epub ahead of print]; N Engl J Med 2020 Mar 23 [Epub ahead of print]). All these factors result in greater difficulty in managing IBD recurrences and do not allow to guarantee the best management of patients with active diseases. **For these reasons, IBD drug discontinuation should not be recommended in all patients not suspected of COVID-19** (IOIBD update on COVID19 for patients with Crohn's disease and ulcerative colitis | IOIBD. Available at: [www.ioibd.org/](http://www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-)

[and-ulcerative-colitis/](http://www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-and-ulcerative-colitis/); N Engl J Med 2020 Mar 18 [Epub ahead of print]). The therapeutic approach should be personalized and should be based on the balance between the risk of viral infection and the risk of disease recurrence. The ongoing therapies should be stopped only in clearly COVID-19 patients, while in positive SARS-CoV-2 cases (without disease) the decision should be based on the type of drug and the risk of COVID-19 occurrence (IOIBD update on COVID19 for patients with Crohn's disease and ulcerative colitis | IOIBD. Available at: [www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-and-ulcerative-colitis/](http://www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-and-ulcerative-colitis/); N Engl J Med 2020 Mar 18 [Epub ahead of print]). Large national and international studies are needed to identify the best way to prevent COVID-19 in patients with IBD, to understand whether patients with IBD are at increased risk of being infected, and to clarify whether they should be considered as a high-risk population as well as the impact of IBD-related drugs on COVID-19.

Another aspect suggested by An et al (Lancet 2020 Feb 27 [Epub ahead of print]) is the relevance of the continuous assistance to patients with IBD also at home. Home patient management has been called telemedicine and it is a well-accepted approach by patients, as evidenced by the high adherence to home therapies or recommendations from physicians (Dig Dis Sci 2007;52:357–364; BMJ Evid Based Med 2019;24:37–38). Telemedicine has also been associated with a reduction in gastroenterological consultations and hospitalizations and could be a valid alternative to improve the quality of IBD patient care during the COVID-19 outbreak (BMJ Evid Based Med 2019;24:37–38). Chinese experience showed that telemedicine is possible and effective, although long-term follow-up of this cohort is essential to confirm the real impact of the preventive strategies. Furthermore, the biggest challenge for Western countries will be to extrapolate Chinese success and overcome cultural differences that could hinder adhesion rates. In conclusion, the coronavirus pandemic is straining the existing health systems and will leave an indelible mark on both patients and physicians, but it is providing new insights and could be a starting point for investing in new approaches and increasingly personalizing patient care.

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#### Conflicts of interest

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## You Are What You Eat, But Can Diet Prevent Inflammatory Bowel Diseases?



Khalili H, Håkansson N, Chan SS, et al. Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from 2 large prospective cohort studies. *Gut* 2020 Jan 3 [Epub ahead of print].

The increasing incidence of inflammatory bowel disease (IBD) across the world, especially in areas undergoing fast modernization, suggest that environmental factors may play a determinant role in disease pathogenesis. One of the most important environmental factors that we are exposed on a daily basis is diet. This is also one of the main modulators of the gut microbiome, thought to play a major and causative role in IBD. Therefore, it comes as no surprise that there are an increasing number of studies trying to explore the role of dietary interventions to manage adult IBD. The study by Khalili et al takes a step back and addresses whether a dietary intervention could impact disease risk.

Investigators linked the data from two prospective cohorts, the "Swedish Mammography Cohort" and the "Cohort of Swedish Men," to the Swedish Patient Register. A total of 66,651 women aged 40–74 years, and 45,906 men aged 45–79 years were recruited and completed the questionnaires that were administered at given timepoints during follow-up. Questionnaires detailed lifestyle factors (smoking, physical activity, alcohol consumption, etc), medications, medical illnesses, and diet. Overall, 83,147 provided dietary data at baseline using a 96-item semiquantitative food frequency questionnaire that had been previously validated in the same population and reflects food intake over a 1-year period. Investigators calculated a modified Mediterranean diet (MD) score (mMED score), based on the relative adherence to a traditional MD adapted from a diet scale previously reported. Using this score, cumulative points were given for beneficial food intake (eg, legumes, fruits and vegetables, nuts, fermented dairy products) above the median, or for non-beneficial food intake below the median (eg,

red and processed meat), with higher scores meaning higher adherence to a MD.

During the mean follow-up time of 17 years, 164 incident cases of CD and 395 incident cases of UC were diagnosed. Age at diagnosis ranged from 47 to 83 years, reflecting the cohorts demographics. Results showed that, after adjusting for age, body mass index, education level, smoking, total caloric intake, and physical activity, a higher mMED score was associated with a lower risk of developing Crohn's disease (CD). For those with higher mMED scores, there was a 58% reduction in the risk of developing CD (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.22–0.80), as compared with those with the lowest mMED scores, where the HR was 0.69 (95% CI, 0.48–0.99). Overall, low adherence with a MD was associated with an adjusted population risk of 12% (95% CI, 3%–26%) for late-onset CD. Interestingly, no protective effect of diet was observed for ulcerative colitis.

**Comment.** For a long time, the topic of diet in causing or treating IBD was not a major focus of the research community, even if this is one of the most frequently posed questions by patients. The truth is that, even today, except for avoiding fiber in the setting of strictures, and for the use of exclusive enteral nutrition in pediatric patients, there is no single widely accepted recommended dietary intervention for managing patients with IBD. This finding comes in contrast with the well-known role of diet in altering the gut's metabolome, in modulating the composition of the microbiome, in promoting the growth of bacteria producing immunomodulatory metabolites, and in impacting the mucus layer—all factors known to be involved in the pathogenesis of IBD. Perhaps the most compelling evidence comes from the epidemiologic transition in IBD, with a increase rise in disease incidence in developing societies adopting a westernized diet. A Western diet, characterized by a high consumption of saturated fat, refined carbohydrates, salt, and processed foods and by low consumption of fiber, fruit, and vegetables, has been shown to have pro-inflammatory effects and has been associated with a vast array of diseases, including IBD (*Nutrients* 2019;11(5)).

Prior cohort studies (the Nurses Health Study and the EPIC cohort) had shown that higher intake of fiber could protect from CD development, partly supporting the findings presented by Khalili et al. A prior small non-randomized study applying a 6-week MD in patients with CD, observed a reduction in serum inflammatory biomarkers, changes in blood gene expression and in gut microbiome (*Hum Genomics* 2013;7:24). The study presented by Khalili et al shows evidence that being adherent to a MD may lower the risk for developing CD, even after adjusting for potential confounders. The findings, which are merely associative, bear nevertheless epidemiologic credibility, given the known role of the MD in preventing other metabolic and inflammatory diseases such cardiovascular diseases, coronary heart disease, myocardial infarction, overall cancer incidence, neurodegenerative diseases, and diabetes (*Am J Clin Nutr* 2010;92:1189–1196). Adherence to a MD pattern has been shown to be associated with lower