Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

19. It is possible that the crucial interaction between 5-ASA and COVID-19 determining outcome does not occur in the intestine, but in the lungs. Mesalazine-induced respiratory disease is unusual, but well-recognised, and may be severe.[4] It is interesting to consider the hypothesis that SARS-CoV-2 infection might decrease the threshold for 5-ASA–associated respiratory disease. In susceptible patients, salicylates could augment the production of cysteinyl leukotrienes, thus leading to a stronger inflammatory response. If this hypothesis is valid, then leukotriene antagonists might prove beneficial in patients on 5-ASA with severe COVID-19, or in COVID-19 overall. Hopefully, the trial of montelukast in COVID-19 will provide much-needed answers to this question (NCT04389411).

Although ACE2 and TMPRSS2 are known to be main molecules of SARS-CoV-2 entry, other molecular modifiers also are involved; more recently neuropilin-1 (NRP1) was implicated.[5] Our preliminary re-analysis highlights increased *NRP1* expression both in active Crohn's disease of the ileum and in the mucosa of active ulcerative colitis in data from Vancamelbeke et al.[6] A greater expression of *NRP1* in Crohn's disease of the ileum compared with ulcerative colitis or controls can be found in data from Haberman et al.[7] In ileal biopsies of anti–TNFα-refractory Crohn's disease patients gathered by Peters et al,[8] inflamed ileal mucosa had a greater expression of *NRP1* relative to uninflamed tissue ($P = .002$).[8] Of interest, oncostatin M receptor, which allows oncostatin M to exhibit TNFα-like effects in the presence of anti-TNFα, consistently and strongly correlated with *NRP1* in the ileal and colonic mucosa in these 3 datasets (Pearson's $r > 0.7$ and $P < 10^{-22}$).

Overall, the evidence for the increased susceptibility to SARS-CoV-2 entry in the inflamed intestine is growing, and our understanding is further strengthened by additional details, such as involvement of specific cell types described by Bangma et al. Defining the relevance of these observations to clinical observation and practice represents an important area for immediate translational research in IBD, and more generally in patients with multisystem COVID-19 illness.

JAN KRZYSZTOF NOWAK
Translational Gastroenterology Unit
Nuffield Department of Medicine
Experimental Medicine Division
University of Oxford
John Radcliffe Hospital
Oxford, UK *and*
Department of Pediatric Gastroenterology and Metabolic Diseases
Poznan University of Medical Sciences
Poznan, Poland

RAHUL KALLA
MRC Centre for Inflammation Research
Queens Medical Research Institute
University of Edinburgh
Edinburgh, UK

JACK SATSANGI
Translational Gastroenterology Unit
Nuffield Department of Medicine
Experimental Medicine Division
University of Oxford
John Radcliffe Hospital
Oxford, UK *and*
Institute of Genetics and Molecular Medicine
University of Edinburgh
Edinburgh, UK

References

1. Singh AK, et al. United European Gastroenterol J 2021; 9:159–176.
2. Ungaro RC, et al. Gut 2021;70:725–732.
3. Brenner EJ, et al. Gastroenterology 2020;159:481–491.e3.
4. Magro F, et al. Gastroenterology 2020;160:1884–1885.
5. Daly JL, et al. Science 2020;370:861–865.
6. Vancamelbeke M, et al. Inflamm Bowel Dis 2017; 23:1718–1729.
7. Haberman Y, et al. J Clin Invest 2014;124:3617–3633.
8. Peters LA, et al. Nat Genet 2017;49:1437–1449.

Acknowledgments
The authors thank Dr Jonas Halfvarson and Dr Petr Ricanek for their comments.

Conflicts of interest
The authors have made the following disclosures: Jan Krzysztof Nowak reports personal fees from Norsa Pharma and nonfinancial support from Nutricia outside the submitted work. Rahul Kalla has served as a speaker for Ferring and has received support for research from IBD-Character (EU FP7 2858546). Jack Satsangi has served as a speaker, a consultant, and an advisory board member for MSD, Ferring, AbbVie, and Shire, consultant with Takeda, received speaking fees from MSD, travel support from Shire, and has received research funding from AbbVie, Wellcome, CSO, MRC, and the EC grant IBD-BIOM.

Funding
Supported by EU FP7 grant IBD-Character (2858546).

https://doi.org/10.1053/j.gastro.2021.02.011

The Usefulness of Fecal Calprotectin in the era of the COVID-19 Pandemic

Dear Editors:

The coronavirus disease 2019 (COVID-19) pandemic has caused significant modifications in patient management, especially for chronically immunocompromised individuals. With approximately 3 million patients in the United States with inflammatory bowel disease (IBD) and the absence of substantial data in the era of coronavirus,

this has become a complicated matter for gastroenterologists.[1,2] We have encountered concerns among patients with IBD, given the nature of IBD therapies, requiring comprehensive discussions regarding the pros and cons of different management.

To protect patients and providers, American Gastroenterological Association published guidelines for endoscopic procedures and endorsed delaying elective procedures along with using a N95 and full personal protective equipment when performing essential procedures.[3] Shortly thereafter, the American Gastroenterological Association published a practice update regarding the management of IBD.[2] This update is congruent with previous endoscopic guidelines, and it also has great recommendations about how to care for patients who are suspected or confirmed to be infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with different clinical scenarios related to the severity of the underlying IBD and COVID-19 infection and a detailed discussion about the safety concerns regarding IBD therapies and how to modify them.[2,3]

The practice update has also addressed options for disease assessment in these patients, given the need to avoid nonurgent procedures. Fecal calprotectin (FC) is a calcium-binding, primarily neutrophilic-specific protein and its concentration is proportional to the concentration of neutrophils in the colorectal mucosa. FC is useful for evaluation of gut inflammation in patients with gastrointestinal symptoms and can help us not only differentiate between irritable bowel syndrome and IBD, but also in assessment of disease activity of IBD.[4] Currently, FC testing is underused, with most testing being done alongside endoscopic procedures; however, during this pandemic it may be a great diagnostic tool for the assessment of possible flares in patients with IBD.[5]

FC has been studied extensively in the setting of IBD and has demonstrated usefulness as a noninvasive marker for diagnosis and assessment of disease activity, given its correlation with intestinal inflammation.[6] FC has a great sensitivity and specificity for the detection of histologic remission in patients with IBD with colitis, depending on the cut-off value being used. A sensitivity of 100%, specificity of 77%, negative predictive value of 100%, and positive predictive value of 81.2% has been reported with a cut off value of <100 μg/g.[6] It may also help predict future flare. In patients who are in clinical remission, a FC of >150 μg/g has shown a 2-fold and 14-fold increased risk of relapse among patients with Crohn's disease and ulcerative colitis, respectively.[7]

For the patient with irritable bowel syndrome symptoms, FC is more reliable than C-reactive protein and the erythrocyte sedimentation rate to screen for IBD. The 2018 guidelines endorsed incorporating the use of FC in the management of patients with IBD and, given the limitations that COVID-19 has caused on performing endoscopic procedures, it seems even more crucial to take advantage of this underused diagnostic tool.[5]

However, one should use caution in interpreting FC results in patients with COVID-19, because a positive FC may occur with both bacterial and viral colonic infections. Thus, the FC data elicited from COVID-19–positive patients should be analyzed judiciously; SARS-CoV-2 viral RNA has been noted in fecal samples with an unclear effect on intestinal inflammation, with 1 reported case of a patient with COVID-19 whose initial symptom was bloody diarrhea and was found to have hemorrhagic colitis.[8]

Inflammatory markers being used for the evaluation of symptomatic patients with IBD to confirm the presence of active flares may be elevated in those with COVID-19.[2] This issue may affect their usefulness for evaluation of IBD flare among those infected with SARS-CoV-2, because intestinal inflammation from any etiology may increase inflammatory markers. It is important to know that, although a high level of FC in an patient with IBD and COVID-19 with diarrhea may not be very helpful in distinguishing an active IBD flare from the effect of SARS-CoV-2 on the gastrointestinal tract, a FC level of <100 μg/g should be used to rule out the presence of active inflammation in patients with history of colitis based on its high sensitivity and negative predictive value for the detection of inflammation. This approach will minimize the unnecessary use of essential personal protective equipment and decrease disease transmission. Although FC testing cannot completely obviate the need for the endoscopic evaluation of patients with new symptoms, it may help many patients with IBD to postpone endoscopic evaluation until the end of this crisis and possibly even beyond this time.

SHEENA MAGO
Department of Medicine
University of Connecticut Health Center
Farmington, Connecticut

HALEH VAZIRI
Department of Medicine
Division of Gastroenterology-Hepatology
University of Connecticut Health Center
Farmington, Connecticut

MICHEAL TADROS
Department of Medicine
Division of Gastroenterology-Hepatology
Albany Medical College
Albany, New York

References

1. Dahlhamer JM, et al. MMWR Morb Mortal Wkly Rep 2016;65:1166–1169.
2. Rubin DT, et al. Gastroenterology 2020;159:3350–3357.
3. Sultan S, et al. Gastroenterology 2020;159:1935–1948.
4. Lichtenstein GR, et al. Am J Gastroenterol 2018; 113:481–517.
5. Schoepfer AM, et al. J Crohns Colitis 2012;6:412–418.
6. Zittan E, et al. Inflamm Bowel Dis 2016;22:623–630.
7. Costa F, et al. Gut 2005;54:364–368.
8. Carvalho A, et al. Am J Gastroenterol 2020;115:942–946.

Conflicts of Interest
The author(s) discloses no conflicts.

Most current article

https://doi.org/10.1053/j.gastro.2020.05.045

Severe Inflammatory Bowel Disease Flares and COVID-19: Expand the Gastroenterology–Surgery Team to Include an Infectious Disease Specialist

Dear Editors:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new virus that was first identified in Wuhan, China, and has now spread worldwide. It causes a potentially fatal infectious respiratory syndrome called coronavirus disease 2019 (COVID-19), which has rapidly evolved into a pandemic.[1] COVID-19 is a major health emergency that has had a substantial impact on everyday clinical practice. It has raised several new questions and concerns about its potential impact on patients with chronic illnesses, especially those treated with immunomodulating drugs.

In the field of inflammatory bowel disease (IBD), the British Society of Gastroenterology[2] and American Gastroenterological Association[3] have recently provided guidance on the management of patients with Crohn's disease and ulcerative colitis during this complicated period. For example, the American Gastroenterological Association recommends following standard therapeutic algorithms for patients hospitalized for IBD who also have mild or incidentally identified COVID-19.[3] It also recommends scheduling the usual surgical consultation, but acknowledges that it is reasonable to medically attempt to postpone surgery during the pandemic. Perhaps because of the lack of empirical evidence, these guidelines did not specifically address the challenging case of IBD patients hospitalized owing to a severe flare of disease with subsequent or concomitant pneumonia owing to SARS-CoV-2.

Especially in ulcerative colitis, a severe flare of disease is a life-threatening emergency that requires prompt recognition, hospitalization, early initiation of treatment, and close monitoring.[4] The outcome of severe flares is measured in terms of surgery and mortality rates. Therefore, a multidisciplinary approach involving a gastroenterologist and a colorectal surgeon is essential. This professional pair shares the responsibility in correctly identifying the most effective type and timing of rescue therapy or surgery. However, in the COVID-19 pandemic, this professional pair may not be enough to effectively manage the infection in an IBD patient with a severe disease flare.

We recently published a prospective, observational study of 79 IBD patients with COVID-19.[5] The study found that active disease, age >65 years and comorbidities associated with worse outcomes, both pneumonia and death, whereas the use of immunosuppressant and biological therapies did not. Four of the patients had been diagnosed with the infection during hospitalization for a severe flare of IBD, and 2 of them died. To further illustrate the therapeutic challenge these patients present, here we examine the emblematic new case of a 40-year-old man who was admitted to our hospital for severe clinical and endoscopic recurrence of ulcerative pancolitis not responding to systemic oral steroids. At admission, he reported bloody diarrhea, with >15 bowel movements per day, and mild abdominal pain. Laboratory tests showed mild normocytic anemia and markedly increased C-reactive protein. Chest and abdominal radiographs were normal, and a nasopharyngeal swab for SARS-CoV-2 was negative. After 6 days of intravenous steroids with an unsatisfactory clinical response, excluded colonic superinfection with cytomegalovirus, we began to consider the need for salvage therapy with infliximab. However, the same day, the patient developed fever (38.5°C) and cough, and repeat chest radiography demonstrated interstitial pneumonia. A new nasopharyngeal swab was positive for SARS-CoV-2. Therefore, intravenous steroids were tapered, and azithromycin and hydroxychloroquine were started according to local protocols.

At this point, the gastroenterologist and surgeon involved an infectious disease specialist in determining the best therapeutic strategy among several options: (1) surgery, (2) a drastic decrease in of steroids and starting with cyclosporine, and (3) a drastic decrease in steroids and starting with infliximab. Option 1 offered the possibility of fully solving the gastrointestinal problem, but poses a risk of fatal complications in patients with COVID-19.[6] Options 2 and 3 offered a likely clinical response of the gastrointestinal disease[4] and a potential therapeutic effect on the infection,[7,8] but could also worsen the course of infection and complicate a later surgical intervention. Finally, assessing the risk–benefit ratio we decided to start with infliximab at 5 mg/kg.

We do not yet know what will be the final effect of this treatment and the outcome for the patient. Nonetheless, we think that the issues raised by this case are of great interest to physicians managing IBD patients during the COVID-19 pandemic. In particular, we suggest that an infectious disease specialist join the gastroenterologist and surgeon on the team managing IBD patients hospitalized for a severe flare of disease. In this way, they will become "three of a perfect pair"

CRISTINA BEZZIO
SIMONE SAIBENI
Gastroenterology Unit
Rho Hospital
ASST Rhodense
Rho (MI), Italy

References

1. Zhou P, et al. Nature 2020;579:270–273.
2. Kennedy NA, et al. Gut 2020;69:984–990.