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.

reported an increase in alanine aminotransferase (up to 34.6% of patients), aspartate aminotransferase (up to 40.4% of patients), bilirubin (up to 25.1% of patients), and creatinine (up to 8.0% of patients) in those with confirmed COVID-19.[2] Hence, as Leventhal et al[3] noted, considering that patients with ALI usually have undetectable levels of acetaminophen, ALI/ALF should be considered in COVID-19 patients when acetaminophen ingestion is reported and very high (>2000 IU/L) aminotransferase levels are observed.[4]

We agree, as proposed by others,[3] that clinicians are advised not to dismiss the possibility of acetaminophen toxicity when faced with an undetectable serum acetaminophen level; there is still a need to use N-acetylcysteine in all patients with either a history of suspected acetaminophen poisoning or the biochemical profile that is associated with it, regardless of the presence or absence of the parent compound. This is even more important now with a potential significant increase in the use of acetaminophen owing to the COVID-19 pandemic.[5]

Finally, as Ungaro et al[1] mentioned, patients may complain of gastrointestinal symptoms such as nausea or diarrhea. We found that diarrhea was observed in 6.1% of patients (95% CI, 2.4%–9.7%) in 6 studies, including 457 patients with confirmed COVID-19.[2]

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Managing Inflammatory Bowel Disease During COVID-19: Summary of Recommendations from Gastrointestinal Societies

Dear Editor:

We read the recent article by Ungaro et al[1] with great interest. As the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to spread, gastroenterologists managing patients with inflammatory bowel disease (IBD) face uncertainty amid growing patient concerns regarding risks associated with immunosuppressive medications. Descriptions of initial patient cohorts from China did not include details about concomitant immunosuppressive therapy because immune-mediated diseases did not feature prominently among the reported comorbidities.[2] On the basis of these cohorts, the most important factors associated with poorer outcomes were older age, diabetes, hypertension, and other cardiovascular disease.

An international registry of IBD patients with COVID-19 (Surveillance Epidemiology of Coronavirus [COVID-19] under Research Exclusion) was established.[3] As of April 8, 2020, 382 cases were reported to the registry, of whom 106 had required hospitalization, and 13 had died. In the absence of data to inform decision making, several societies have proposed empiric guidelines for management of IBD patients. These recommendations should be considered in parallel with national/regional guidance from public health authorities, which include instructions for self-isolation that may substantially impact patient livelihoods and thus extend beyond the typical remit of guidelines for disease management. In the context of the rapidly evolving data, we summarize available recommendations from different gastroenterological societies.

Table 1. Summarized Recommendations for the Management of Inflammatory Bowel Disease During the Coronavirus Disease 2019 Pandemic

	British Society of Gastroenterology	European Crohn's and Colitis Organization	International Organization for the Study of Inflammatory Bowel Disease
Mesalamine	• Continue treatment • Optimize treatment in ulcerative colitis patients with uncontrolled symptoms	• Continue treatment	• Continue treatment; also in case of COVID-19
Corticosteroids	• Consider rapid tapering • Consider exclusive enteral nutrition in Crohn's disease or topical corticosteroids	• Consider tapering • Continued use during infection should be weighed carefully	• Consider tapering • Stop (taper as appropriate) in case of COVID-19 • Do not discontinue topical steroids
Immunomodulators (thiopurines, methotrexate)	• Initiation discouraged • Combination therapy with biologics on a case-by-case basis • Consider stopping in patients ≥65 years and/or comorbidities in stable remission	• Initiation discouraged • Combination therapy with biologics on a case-by-case basis • Reasonable to withhold until resolution if COVID-19 develops	• Continue treatment • Withhold until resolution in case of COVID-19
Biologics (TNF antagonists, anti-integrins, anti-interleukin 12/23)	• Continue treatment • No evidence of increased risk of COVID-19	• Continue treatment with unchanged dosing schedule • Withhold until resolution if COVID-19 develops	• Continue treatment with unchanged dosing schedule • Withhold treatment with TNF antagonists, anti-interleukin 12/23 until resolution in case of COVID-19 • Uncertain if vedolizumab should be stopped in case of COVID-19
TNF antagonists	• Initiation in monotherapy • Elective switching from intravenous to subcutaneous not recommended	• Initiation in monotherapy, consider subcutaneous formulation • Unchanged maintenance dosing schedule • Elective switching from intravenous to subcutaneous not recommended	• Uncertain if patients receiving combination therapy should reduce dose of immunomodulator to prevent COVID-19
JAK inhibitors	• No evidence of increased risk of COVID-19 • Continue treatment	• Continue treatment • Avoid initiation if alternative available • Withhold until resolution if COVID-19 develops	• Continue treatment • Withhold until resolution in case of COVID-19
Endoscopy	• Defer surveillance • Consider alternative methods of disease assessment	• Defer surveillance and regular endoscopic follow-up	• Defer surveillance and regular endoscopic follow-up
Clinical trials	• Continuation of screening and recruiting should be discussed locally • Benefit of avoiding corticosteroids and surgery should be balanced against risk of face-to-face visits • Conduct virtual trial visits if possible • Consider unblinding participants if the information changes treatment or assessment and management of suspected COVID-19	• Only include patients without therapeutic alternatives • Minimize corticosteroid exposure for patients between screening and baseline • Discuss with sponsor: postponing nonessential follow-up visits or replacing them with virtual clinics, performing routine testing in local laboratory, organizing home delivery of study drugs	• Continue treatment • Withhold until resolution in case of COVID-19

COVID-19, coronavirus disease 2019; TNF, tumor necrosis factor.

To date, public guidance on the management of IBD patients during the COVID-19 pandemic has been issued by the British Society of Gastroenterology (BSG),[4] Crohn's and Colitis Canada (CCC),[5] European Crohn's and Colitis Organization (ECCO),[6,7] and the International Organization for the Study of Inflammatory Bowel Disease (IOIBD)[8] (Table 1).

All aforementioned societies recommend continuing IBD-specific treatment because risk of active disease was perceived to be higher than the uncertain risks of immunosuppression predisposing to higher risk of infection with SARS-CoV-2. Minimizing corticosteroid exposure by rapid tapering whenever possible is universally recommended, with the BSG also suggesting topical corticosteroids or exclusive enteral nutrition as

alternatives for patients experiencing a flare. Thiopurine initiation is discouraged by both the BSG and ECCO because of increased perceived risk of viral infection and need for concomitant induction corticosteroid. Both BSG and ECCO advise caution with initiating combination therapy; the former also suggests considering stopping thiopurine treatment in patients $\geq$65 years and those with significant comorbidities in stable remission. For patients commencing biological therapy, subcutaneously administered drug may be preferred on the basis of local circumstances to maximize social distancing efforts. Forced switching to subcutaneous biologics should only be used in centers unable to provide infusions. There are no data to favor one class of biologics over another in the context of COVID-19. There is some indication that lower T-helper lymphocyte counts are associated with delayed clearance of viral RNA, which led ECCO to recommend against initiation of tofacitinib if therapeutic alternatives are available, in contrast to BSG and IOIBD.

In case an infection develops, ECCO suggests postponing biologic treatment until resolution and considering stopping thiopurines and tofacitinib for the duration of the infection. On the basis of experience with other coronaviruses and early experience with SARS-CoV-2, the benefits and harms of continuing corticosteroid treatment during infection should be weighed carefully. IOIBD suggests withholding all IBD-related medication, except for mesalamine, topical steroids, and possibly vedolizumab until resolution of symptoms in case COVID-19 develops. Alternatively, medication can be restarted after 2 negative nasopharyngeal polymerase chain reaction tests. For general measures to prevent viral transmission, ECCO and IOIBD emphasize hand hygiene and avoiding contact with infected people; CCC also advocates workplace modifications to enable physical distancing for patients using immunosuppressants. Guidance from the BSG is more stringent in suggesting that patients with a comorbidity or $>$70 years being treated with drugs other than mesalamine/topical corticosteroids should undergo "shielding," a strict form of social distancing mandating the avoidance of face-to-face contact for at least 12 weeks. This recommendation extends to patients taking daily prednisolone equivalent of $\geq$20 mg, those during combination therapy induction, those with moderately-to-severely active disease despite treatment, and those with short bowel syndrome or requiring parenteral nutrition. This stricter guidance from the BSG is an outlier with major implications for individual patients and should be taken in the context of the individual case. Patients treated with biologics or immunomodulators, including stable patients on combination therapy, should practice stringent social distancing, whereas patients treated with mesalamine or topical corticosteroids should adhere to standard social distancing. Surveillance endoscopies should be deferred, and disease assessment endoscopies should be carefully assessed for priority, considering the possibility of alternative methods (biomarkers, radiology, and capsule endoscopy).

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Undesirable Long-Term Outcome of Entecavir Therapy in Chronic Hepatitis B With Cirrhosis

Dear Editor:

The large study of Hou et al[1] is interesting and has provided important information on nucleos(t)ide analogue (Nuc) therapy up to 10 years in chronic hepatitis B virus (HBV) infection. The authors are to be commended for conducting such a well-designed study, with stringent definitions of clinical outcome events (COE), to confirm the long-term efficacy and safety of entecavir (ETV) therapy in chronic HBV infection. However, some important data of this study were not utilized for additional or further analyses and discussion.

First, the number of patients with cirrhosis with Nuc therapy up to 10 years in this study is probably so far the largest ever reported in the literature. Calculations of the Event Adjudication Committee–reviewed data of ETV-treated patients with cirrhosis in their Supplementary Tables 9 and 11 are summarized in Table 1. If the calculations are correct, the much higher rate of non-hepatocellular carcinoma liver disease progression (mostly hepatic decompensation [COE definition]) in the China cohort (17.7% vs 3.0%; $P < .001$) than in the non-China cohort is unexpected and surprising. It will be interesting and informative to know the reason(s) or speculations for these differences.

Table 1. EAC-Reviewed and EAC-Adjudicated Clinical Outcome Events in Entecavir-Treated Patients With Cirrhosis

		Clinical Outcome Event		
Cohort	LC No.	HCC	Non-HCC Disease Progression	Liver Death
China	317	40 (12.6)	56 (17.7)	39 (12.3)
Non-China	943	132 (14.0)	27 (2.9)	124 (13.1)
Total	1260	172 (13.7)	83 (6.6)	163 (12.9)

Values are n (%). Data were calculated from data in Supplementary Tables 9 and 11 in Hou et al.[1]
EAC, Event Adjudication Committee; LC, liver cirrhosis; HCC, hepatocellular carcinoma.

Second, in our recent Taiwan study in 308 patients with cirrhosis (19.5% genotype C HBV–infected) who had stopped a ~3-year course of ETV or tenoforvir therapy after demonstration of undetectable HBV DNA >1 year, only 7 (0.23%) encountered hepatic decompensation at a median of 41 (range, 7–183) weeks after end of therapy.[2] This rate seems lower, at least not higher, than a rate of 17.7% during ~10 years of continuing ETV therapy in their China cohort. It will be most informative if the reason(s) for this high rate in China cohort can be elucidated. A high rate of non-hepatocellular carcinoma cirrhotic complications was also reported in a Korean study of 5-year ETV therapy in 440 patients with cirrhosis (mostly genotype C HBV–infected), namely 15.5% in 297 patients with medication adherence >90% and 41.6% in 143 patients with adherence <90%.[3] Perhaps reanalysis of China cohort may answer whether HBV genotype or "adherence" issues are responsible for the high rate. The risk of hepatic decompensation after stopping Nuc therapy is one of the main reasons against cessation of Nuc therapy in patients with cirrhosis.[4] The results of this study further support the collective data that the incidence is not higher than that in patients with cirrhosis who continue long-term Nuc therapy, hence it is not a convincing reason against finite Nuc therapy in patients with cirrhosis.[5]

Third, up to 10% of the 6216 ETV-treated patients in Hou et al had been lost to follow-up and not completed