CLINICAL PERSPECTIVES

Practical management of inflammatory bowel disease patients during the COVID-19 pandemic: expert commentary from the Gastroenterological Society of Australia Inflammatory Bowel Disease faculty

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Abstract

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has emerged as a public health emergency and challenged healthcare systems globally. In a minority of patients, SARS-CoV-2 manifests with a severe acute respiratory illness and currently there are insufficient data regarding the virulence of COVID-19 in inflammatory bowel disease patients taking immunosuppressive therapy. This review aims to summarise the current literature and provide guidance on the management of inflammatory bowel disease (IBD) patients in the context of the COVID-19 pandemic in the Australasian setting.

Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has emerged as a public health emergency and challenged healthcare systems globally. It has rapidly spread across the world without regard for borders, manifesting as an acute respiratory illness that ranges broadly in severity from asymptomatic carriage to mild, non-specific symptoms to severe pneumonia, sepsis and death.[1] Mortality is estimated to be between 1% and 2% with disease severity associated with advanced age, chronic respiratory illness, hypertension, diabetes and other comorbidities.[1] There is limited information on the impact of COVID-19 on immunosuppressed patients, in particular, those with inflammatory bowel disease (IBD).

IBD is a relapsing and remitting inflammatory condition of the bowel.

A significant proportion of IBD patients are treated with long-term immunomodulator/immunosuppressive therapy which potentially places them at increased risk of infections and associated complications. Practitioners and patients alike are therefore concerned about the risk and implications of COVID-19 infection in the IBD patient, despite a paucity of evidence supporting an altered predisposition to disease or more severe disease course. As higher quality evidence gradually accumulates, this article aims to provide an interim practical guide for IBD management during this uncertain time.

COVID-19: the virus, the disease and the gut

SARS-CoV-2 is an RNA coronavirus that causes the disease COVID-19. SARS-CoV-2 was first reported in

Wuhan, China, in December 2019 and is transmitted via direct contact and exhaled droplets from an infected individual.[2] Human-to-human transmission is enabled by the interaction of the SARS-CoV-2 spike (S)-protein with human angiotensin-converting enzyme 2 (ACE2) receptor.[3] ACE2 is expressed on multiple cell types throughout the body including alveolar type 2 (AT2) cells in the lungs and enterocytes of the small intestine and colon. Once the virus is attached to ACE2 it uses the host serine protease TMPRSS2 for S priming allowing fusion of viral and cellular membranes and viral entry into the cell.[3]

The median incubation period of COVID-19 is 4–5 days, with the majority of patients developing symptoms within 2 weeks.[2] The most commonly reported symptoms include fever, dry cough and shortness of breath.[1] Gastrointestinal symptoms include diarrhoea in 2–49.5% of patients and vomiting in 3.6–15.9% of patients.[4] Gastrointestinal symptoms in COVID-19 are important to note, as there is a subgroup of patients with mild disease who initially present with diarrhoea rather than respiratory symptoms, and this can lead to a delay in diagnosis.[5] The pathophysiology of diarrhoea in COVID-19 has not been elucidated; however, virus RNA has been detected in up to 50% of stool specimens and stool can remain persistently positive after clearance of respiratory tract samples in approximately 20% of patients.[6] In fact, the Australian government is currently looking at methods of testing sewerage for SARS-CoV-2 RNA as part of the Australian wide monitoring programme to predict future spread and act as an early warning signal for imminent COVID-19 outbreaks.[7] Therefore, it is possible that enteric symptoms are caused by invasion of SARS-CoV-2 into ACE2 expressing enterocytes of the gastrointestinal tract. The implications of gastrointestinal shedding are unknown, as a polymerase chain reaction (PCR) positive stool sample does not equate to viable virus, and whether the disease is transmissible via the faecal-oral route remains unclear. Furthermore, whether gastrointestinal symptoms are more prevalent in patients with IBD is ill-defined, but if an IBD patient presents with worsening diarrhoea, especially in the context of respiratory symptoms and/or fevers, excluding SARS-CoV-2 infection is prudent.

In suspected cases, diagnosis of COVID-19 is via nucleic acid amplification testing (NAAT) of nasopharyngeal and oropharyngeal swabs.[2] Serology testing and stool testing for SARS-CoV-2 are not currently widely available in Australia. A suspected case of COVID-19 can only be cleared following two consecutive negative COVID-19 PCR swabs due to the potential of false-negatives.

IBD, COVID-19 risk factors and non-pharmacological measures to mitigate these risks

Despite concerns regarding immunosuppression and consequent predisposition to infection, there is no evidence to suggest increased infection rates of COVID-19 in IBD patients to date. Reports from China and Italy suggest very low infection rates in IBD patients and, at the time of writing, an international COVID-IBD registry reported only 798 (466 Crohn disease (CD); 329 ulcerative colitis (UC)/unspecified) cases worldwide, despite almost 3 million confirmed COVID-19 cases.[8,9] Hence, expert consensus currently is that patients with IBD do not appear to be at increased risk of SARS-CoV-2 infection compared with the general population.[10] Importantly, this should not negate attempts to minimise infection in IBD patients, particularly those with comorbidities including cardiovascular disease, hypertension, chronic pulmonary disease, diabetes and cancer which place them at increased risk of significant morbidity and mortality with COVID-19 infection.[1] More specific risk factors for severe infection in immunocompromised patients include age >50 years, receipt of corticosteroids, lymphopenia and neutropenia.[2] Mechanisms to protect these particularly vulnerable patients are crucial and include:

- Proactively reducing transmission – patients should practice good hand hygiene by washing hands with soap and water for at least 20 s or use an alcohol based hand sanitiser, apply social distancing including working from and staying at home where possible and standing at least 1.5 m apart from people, as well as avoiding non-essential travel.
- Managing hospital and healthcare facility exposure – evidence from China and Italy suggest attendance at hospitals and healthcare facilities for non-COVID-19 reasons may increase the risk of COVID-19 exposure.[11] To reduce this risk, outpatient appointments should be moved to telehealth where possible and non-urgent pathology requests limited. Elective surgery and endoscopy should be postponed, but when an urgent endoscopic procedure needs to occur, pre-screening for symptoms and exposure to COVID-19 prior to endoscopy should occur. Endoscopy should still be undertaken for acute severe ulcerative colitis, confirmation of a new diagnosis of IBD, cholangitis in primary sclerosing cholangitis and in an unresolved partial bowel obstruction. To limit pharmacy visits, prescriptions can be delivered via post; in Australia there is currently a free delivery service available for vulnerable members of the community.

• Infusion access – patients should continue to have access to infusions. To reduce the risk of transmission within infusion centres, patients should be screened for symptoms or risks of COVID-19 prior to presenting and on attendance to the centre, with a temperature check on arrival. Where possible the infusion centre should be moved to an 'off-site location' or 'clean' COVID-19 free area of the hospital with a separate entrance. In addition, there should be 2 m between patient chairs and if feasible a single nurse per patient arranged to prevent infection spread. Finally, infliximab infusions should be converted to a 30–60 min protocol where safe to do so to limit the duration patients are in the infusion centre.

• Optimising nutrition – malnutrition significantly increases the risk of infection in patients with IBD.[12] Therefore nutritional status should be optimised and preferential use of exclusive enteral nutrition (EEN) for treatment of CD flares where appropriate and acceptable to patients should be considered. Low vitamin D levels may increase susceptibility to COVID-19 hence supplementation if levels are low is reasonable.[2]

• Reducing disease activity – there is evidence that moderate to severe disease activity increases the risk of infection in IBD patients.[12] Active disease may also lead to corticosteroid use which can increase susceptibility and severity of COVID-19 and/or hospitalisation which may inadvertently lead to COVID-19 exposure. Therefore, optimisation of medical therapy to maintain tight disease control is optimal.

• Smoking cessation – smoking may increase the chance of developing severe COVID-19 symptoms, therefore smoking cessation encouragement and support should be a priority.[8]

• Vaccination – to reduce co-infection with influenza and other respiratory infections, influenza (quadrivalent inactivated vaccine) and pneumococcus (PCV13 and PPSV 23) vaccination should be provided and maintained in accordance with schedule recommendations.

Medication management of non-COVID-19 IBD patients

Recommendations for the management of IBD medications during the pandemic are summarised in Table 1 and a more detailed analysis can be found in a recently published review on the prevention, diagnosis and management of COVID-19 in the IBD patient.[2] Overall, medications should not be ceased without careful consideration of risk of disease flare, and corticosteroids should be avoided or exposure minimised.

Table 1 Management of inflammatory bowel disease (IBD) medications during the COVID-19 pandemic

Medication	Management during COVID-19 pandemic
5-Aminosalicylates	Safe to start
	Continue in all patients
Corticosteroids	Avoid where possible
	Wean rapidly but instruct patient not to abruptly cease
	Instruct patients not to self-administer
	If corticosteroid or induction agent required consider switch to budesonide or exclusive enteral nutrition in CD or budesonide MMX system in UC
Budesonide	Safe to start
	Continue if required
	Use in preference to systemic corticosteroids where possible
Immunomodulatory	Avoid commencing or altering dose unless required, to prevent side-effects and reduce pathology monitoring
Thiopurines (azathioprine, mercaptopurine)	Continue in most patients
Methotrexate	If on combination with biologic therapy, in deep remission, with good anti-TNF levels on TDM and particularly if >65 years: consider drug holiday for immunomodulator
Anti-TNF (infliximab, adalimumab, golimumab)	Continue
	Subcutaneous route preferential if commencing new agent to avoid healthcare contact
	Avoid elective switching to subcutaneous infusions due to risk of flare
	If on combination with biologic therapy, in deep remission, with good anti-TNF levels on TDM and particularly if >65 years: consider drug holiday for immunomodulator
Anti-Integrin (vedolizumab)	Safe to start
	Continue therapy
Ustekinumab	Safe to start
	Continue therapy
JAK inhibitors	Avoid commencing due to side-effects and need for frequent pathology monitoring
	Continue if currently on tofacitinib with lower maintenance dose of 5 mg BD where possible

CD, Crohn disease; JAK, Janus kinase; MMX, multi-matrix; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; UC, ulcerative colitis.

1 5-Aminosalicylates (5-ASA) and sulfasalazine
  • There are no reports of increased risk of infection including serious or opportunistic infections with 5-ASA medications.[13]
  • Considered safe to start and continue.

2 Corticosteroids
- Prednisolone and other systemic corticosteroids are associated with substantial increased risk of respiratory tract infections and other infections in IBD patients.[14]
- They have also been associated with worse outcomes when used to treat Middle Eastern respiratory syndrome (MERS), severe acute respiratory syndrome (SARS) and influenza.[15]
- Avoid commencing prednisolone where possible. If induction agent required, alternatives include budesonide or EEN for CD and budesonide multimatrix (MMX) system for UC as well as topical steroids for distal disease.
- If systemic steroids are required, we recommend rapid tapering where possible but balance this against risk of flare and advise against sudden cessation.
- Council patients to avoid self-commencing corticosteroids to control IBD symptoms, alternatively supporting ready to access medical advice.

3 Immunomodulators – thiopurines and methotrexate
- Thiopurines (azathioprine and mercaptopurine) are associated with an increased risk of serious and opportunistic infections and reduce immune response to viruses.[2] However, there is limited evidence to suggest an increased risk of either upper respiratory tract infections or pulmonary infections, and mercaptopurine has actually been shown to inhibit one of the proteases essential to viral maturation of MERS-CoV *in vitro*.[16] Although no further animal based models exist and the studies have not been replicated for COVID-19, it does raise the possibility that thiopurine use may not necessarily pose an increased risk from COVID-19.
- Of note, thiopurines can cause lymphopenia. Patients with lymphopenia caused by SARS-CoV-2 have a worse prognosis and have an increased risk of death associated with the virus.[1] Hence, blood counts should be carefully monitored and thiopurine doses altered accordingly, where necessary.
- A recent systematic review found that in the non-rheumatoid arthritis inflammatory disease population, methotrexate does not increase the risk of infection including respiratory infections.[17]
- Overall there is limited evidence of increased risk of infection with the use of immunomodulators. They appear to be relatively safe at the doses typically used for immune-mediated disease, and most patients will not require dose modification.

4 Anti-tumour necrosis factor (TNF) therapies (infliximab, adalimumab, golimumab)

- Anti-TNF have been shown in multiple studies to increase the risk of upper and lower respiratory tract infections, as well as serious and opportunistic pulmonary infections.[2,18]
- Serious infection risk is most evident in patients using combination therapy with an immunomodulator and steroids.[18]
- Overall, anti-TNF are considered safe to continue during the pandemic.
- In older patients in deep remission with good biologic levels, consider drug-holiday from immunomodulator if on combination therapy.
- When initiating therapy, consider monotherapy with therapeutic drug monitoring and utilising subcutaneous formulations where possible to reduce hospital exposure.
- It is not recommended to switch from intravenous to subcutaneous formulations due to risk of loss of response and consequent flare.[2]

5 Anti-interleukin-23 therapies (ustekinumab)
- The risk of severe respiratory tract infections, severe infections or opportunistic infections does not appear to be increased in long term follow-up studies of ustekinumab in both IBD and psoriasis.[2]
- Ustekinumab is considered safe to start and continue during the pandemic.

6 Anti-integrin (vedolizumab)
- Vedolizumab is a monoclonal antibody to the $\alpha_4\beta_7$ integrin that modulates gut lymphocyte trafficking. Hence, there is a theoretical risk of increased susceptibility to gastrointestinal infections. However, respiratory tract infections, severe infections or opportunistic infections do not appear to be increased in long term follow-up studies of vedolizumab in IBD.[19]
- Vedolizumab is considered safe to start and continue during the pandemic.

7 JAK-kinase inhibitor (tofacitinib)
- Tofacitinib impairs immunity to viral infections in long-term extension trials.
- Doses of 10 mg twice daily are associated with increased serious infection risk when compared to 5 mg twice daily.[20]
- Continue tofacitinib but ideally at the lower dose of 5 mg twice daily.
- Avoid commencing tofacitinib unless no other alternatives are available, to avoid potential side effects and frequent pathology monitoring.

Patient management if they are exposed to or develop COVID-19

There are currently no evidence-based guidelines on medical management of IBD in a patient who becomes

Table 2 Management of mediations if exposed to or develops COVID-19[2]

Medication	Elimination half-life	Recommendations if exposed to COVID-19 or test positive for SARS-CoV-2 but asymptomatic	Recommendations if develops COVID-19
5-ASA	NA	No evidence of increased risk of viral infections Likely safe to continue	No evidence of increased risk of viral infections Likely safe to continue
Budesonide	2–3.6 h	Continue if required	Continue if required
Corticosteroids	Prednisolone: 3–4 h	Taper dose where possible, particularly if ≥20 mg Consider switch to budesonide if required	Taper dose where possible, particularly if ≥20 mg Consider switch to budesonide if required
Immunomodulators Thiopurines (azathioprine, mercaptopurine) Methotrexate	3–10 h but effect continues through active metabolites for longer than drug elimination	Temporarily withhold for 2 weeks of symptom-free observation	Temporarily withhold for at least 14 days with at least 3 days of no fever and clinical improvement
Anti-TNF (infliximab, adalimumab, golimumab)	Infliximab: 7–12 days Adalimumab: 17.8–23.9 days Golimumab: 14 days	Temporarily withhold for 2 weeks of symptom-free observation	Temporarily withhold for a minimum of 14 days with at least 3 days of no fever and clinical improvement
Anti-Integrin (vedolizumab)	25 days	Temporarily withhold for 2 weeks of symptom-free observation	Temporarily withhold for a minimum of 14 days with at least 3 days of no fever and clinical improvement
Ustekinumab	19 days	Temporarily withhold for 2 weeks of symptom-free observation	Temporarily withhold for a minimum of 14 days with at least 3 days of no fever and clinical improvement
JAK Inhibitors	3 h	Temporarily withhold for 2 weeks of symptom-free observation	Temporarily withhold for a minimum of 14 days with at least 3 days of no fever and clinical improvement

JAK, Janus kinase; TNF, tumor necrosis factor.

COVID-19 positive. Table 2 summarises our recommendations. Based on the lack of data, in most patients we recommend temporary withholding of immune-suppressing therapies until the resolution of active infection as would be typical in the setting of any serious infection. In those exposed but with no symptoms, this should be weighed up against the risk of IBD flare. It is also important to note that many IBD medications may take months to be eliminated from the body so the utility of cessation in the short-term is likely to be limited. (Table 2).

There is currently no evidence to guide the recommencement of medication following exposure to or infection with SARS-CoV-2. Most patients will develop symptoms within 14 days of exposure or testing positive for disease. Of note, prodromal asymptomatic infection is increasingly being recognised in outbreak settings with a recent study of nursing home patients demonstrating that 24 of 27 (89%) asymptomatic patients who tested positive for SARS-CoV-2 developed symptoms within the subsequent 7 days.[21] Therefore

we recommend that IBD medications can be restarted after 14 days in exposed or asymptomatic infected patients provided they have not developed symptomatic illness.

In those who develop COVID-19, testing for clearance of virus before recommencing medications or accessing infusion centres may have limited utility as some patients shed virus for extended periods of time despite not being actively infected or infectious. Relying on testing to clear these patients may result in unnecessary delays to IBD treatment.[6] In Australia, COVID-19 patients are cleared from isolation and considered no longer infectious 10 days from symptoms onset if they have clinical improvement and no fever for at least 3 days. European guidelines, however, suggest waiting 14 days in those who have been on immunosuppressive therapies due to the potential for prolonged shedding of virus.[22] Therefore, in patients with mild to moderate COVID-19, recommencing therapy after at least 14 days in those who are currently asymptomatic or have clinical improvement with no fever for at least 3 days is likely

safe. In more severe cases, clinical judgement should be used, and a greater window between COVID-19 improvement and medication recommencement may be prudent.

Serology testing is currently not widely available to help guide these decisions and the impact of immuno-suppressive medications on seroconversion is as yet unknown. However, these tests may be utilised in the future.

Nutritional support

Supporting the nutritional requirements of COVID-19 affected patients is critical. This is of increased importance in the IBD patient secondary to the increased probability of premorbid malnutrition. Early dietician review is therefore warranted. Nutritional interventions are particularly important in those unable to maintain adequate oral nutritional intake due to a need for prolonged intubation or non-invasive respiratory support, and in those with increased gastrointestinal losses. The latter may occur in the setting of active IBD, or as a consequence of the virus itself.[4] Enteral feeding via nasogastric tube (NGT) remains the preferred first line option, and should be considering within 24 h of admission for those requiring intensive care support.[23] Delayed gastric emptying with elevated residual gastric volumes can occur in critically unwell COVID-19 patients, increasing the risk of aspiration and therefore continuous rather than bolus feeding is preferable.[23,24] In addition, prone positioning is often required for respiratory care and treatment in severe COVID-19 and may hinder NGT feeding.[25] Where necessary, nasojejunal tubes and parenteral nutrition are valid routes for nutritional support, although the former carries the risks of endoscopic placement and the latter requires intensive dietician input with risk of hyperglycaemia, refeeding syndrome and central line infections.[23,24] Of note, NGT insertion is considered an aerosol generation procedure[26] and thus appropriate personal protective equipment with full airborne precautions is recommended.[23]

Maintaining quality of care during the COVID-19 pandemic

The unintended immediate and longer term consequences of the COVID-19 pandemic may be a loss of IBD control and an increased rate of flare. Inappropriate cessation of medications poses risks to patients with IBD, further compounded by a potential lack of access to healthcare. Maintaining quality IBD care is imperative. Engagement with IBD Services can be facilitated through IBD Helplines, telemedicine clinics, as well as dissemination of accurate information via a regular IBD newsletter. While access to endoscopy for disease activity assessment is limited, objective monitoring may be undertaken using non-invasive tools such as faecal calprotectin and gastrointestinal ultrasound. Utilisation of IBD-specific smart-phone applications as well as decision-aid tools may also be helpful where available and the COVIDSafe app, accessible in Australia, may be useful to notify IBD patients of close contact with a COVID-19 case.

Conclusion

Many patients with IBD are treated with long-term immunomodulating therapy and there is concern amongst patients and clinicians alike that this may predispose to an increased risk of COVID-19. However, available data are reassuring and despite understandable anxiety, patients with IBD do not appear to be at increased risk of COVID-19. In order to prevent COVID-19 infection and its complications, optimisation of disease activity, nutrition, co-morbidities, smoking and vaccination status is important and where possible, corticosteroids should be avoided. If a patient with IBD does develop COVID-19, IBD medications can be temporarily withheld and recommenced with timing of recommencement dependent on severity of COVID-19 and baseline IBD disease.

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