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Correspondence

Asymptomatic screening for SARS CoV-2 prior to commencement of biologic therapies in patients with inflammatory bowel disease - a potentially harmful practice.

Dear Editor,

We read with interest the recent publication by Zingone et al "Screening for active COVID-19 infection and immunization status prior to biologic therapy in IBD patients at the time of the pandemic outbreak" [1]. They advocate for screening all patients with inflammatory bowel disease (IBD) for SARS CoV-2 prior to commencement of biologic agents with the use of both IgM and IgG antibodies and nasopharyngeal PCR testing, intending to identify both current infection with, and previous exposure to, the virus [1]. We argue that universal adoption of such a protocol warrants careful consideration and presently lacks adequate evidence.

For universal screening to be of benefit, we would expect the positive predictive value (PPV) of the test to be sufficient to differentiate infectious patients amongst an asymptomatic cohort, and for subsequent actions to improve individual or public health outcomes. It is difficult to justify how the aforementioned screening protocol prior to biologics would meet these requirements. Firstly, it is unclear whether IBD patients are more or less likely to develop asymptomatic COVID-19 when infected by SARS CoV-2. In addition, apart from those on high dose corticosteroids, IBD patients do not appear more likely to develop severe complications overall in comparison to patients without IBD [2,3]. Secondly, preliminary data cautiously suggests that patients with immune mediated inflammatory diseases (IMIDs) on biologics may be less likely to become infected with SARS CoV-2, with lower rates of seropositivity when comparing similarly socially exposed IMID patients and controls [4,5]. Whether this indeed reflects a lower rate of infection with SARS CoV-2, or alternatively lower rates of detectable antibody response, is unclear. Thirdly, there is no evidence to support Zingone et al's [1] concerns regarding the development of a more aggressive COVID-19 course in those who are asymptomatic at the time of biologic administration- the use of biologics may actually be beneficial in the setting of COVID-19, dampening the aberrant systemic immune response that contributes to acute respiratory distress syndrome and adverse outcomes [6]. Hence, universal COVID-19 screening prior to biologic initiation is not warranted on the basis of IBD patients being more frequently infected with COVID-19, nor because biologics worsen outcomes when infected. Furthermore, delaying biologic treatment on the basis of routine SARS-CoV-2 testing in asymptomatic patients may actually perpetuate IBD disease activity and necessitate systemic corticosteroid use, both of which are factors known to increase complications of COVID-19 [3].

Depending on population and hence health care worker (HCW) prevalence, SARS CoV-2 acquisition may occur more commonly in hospitalized inpatients, including those with IBD, where biologic therapies are frequently required. In this circumstance, asymptomatic screening is prudent. Anecdotally, our unit has managed a case of a patient who acquired COVID-19 during an inpatient stay, as a consequence of asymptomatic health care related exposure. Asymptomatic infection of HCW presents a nosocomial infection risk, particularly when personal protective equipment (PPE) availability is suboptimal or where re-use of PPE is necessary [7]. Rates of seropositivity in HCW exceed that of the general population-most markedly in front line workers and in those caring for patients known to have COVID-19, but additionally in HCW more broadly [7] . HCW have an adjusted hazard ratio (HR) for returning a positive COVID-19 test of 11·61 (95% CI 10.93 – 12.33) compared to the general community [7]. Of note, the strength of this association varies between countries and may in part be contributed to by an increased frequency of testing in HCW. However, rates of infection remain higher in HCW when adjusted for testing eligibility, with an adjusted HR of 3·40, (95% CI 3·37–3·43) [7]. Thus, considering acquisition of SARS CoV-2 from HCW in all inpatients, including those with IBD, is important from the perspective of infection control precautions. This is particularly necessary when operating in a health care system with mobile HCW's, working in settings with a variable exposure to SARS-CoV-2, and variable availability of PPE. However, whether identifying asymptomatic SARS-CoV-2 infection alters individual management in IBD beyond avoidance of unnecessary aerosol generating procedures and corticosteroids is not defined.

Test characteristics are an important consideration when evaluating the role of universal screening. Real time PCR (RT-PCR) is a highly sensitive and specific test to detect SARS-CoV-2, is generally clearly interpretable as positive or negative, and thus has the performance characteristics needed for a screening test. In contrast, the sensitivity of serological testing varies markedly depending on the assay used and the timing of the test relative to symptom onset, as well as having a very limited role in the acute diagnosis of COVID-195. From an infection control perspective, the Centers for Disease Control and Prevention (CDC) does not currently recommend altering public health recommendations for PPE or social distancing on the basis of SARS CoV-2 serological results [8]. Although neutralising antibodies may correlate with antibody titres reported from commercial serological assays, there is insufficient evidence to define an individual as 'immune' [5,8]. Some individuals infected with SARS CoV-2 may not develop a detectable antibody response, and for those that do, the durability of positive antibodies is poorly defined [8]. Zingone et al [1] do not describe how results of serological assays would be utilised in a screening

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algorithm, but these limitations preclude the use of serological assays in this context at the present time.

Critical to the PPV of a test is the prevalence of the condition in question: in low prevalence settings, the proportion of false positive results increases, as does the relative cost of the intervention. Zingone et al do not define which populations may benefit from screening. This would ideally be defined as a population prevalence threshold for which asymptomatic infection detection shows favourable risk/benefit. In such circumstances, screening implementation should be considered.

The overall lack of resounding evidence based recommendations from major international gastroenterological societies in regards to pre-endoscopy SARS CoV-2 screening highlights the dearth of existing knowledge. Present recommendations from the American College of Gastroenterology [9] do not advocate for routine pre-endoscopy SARS CoV-2 testing- rather, a screening questionnaire based approach is advocated for, with nasopharygeal PCR testing performed in accordance with local prevalence, questionnaire identified risks and institutional recommendations. Contrastingly, Hayee et al advocate for symptom based questionnaire screening in all undergoing elective procedures, with deferral of procedures for those with identifiable risk factors for COVID-19 positivity. In asymptomatic low risk individuals with a negative screening questionnaire, a nasopharyngeal PCR is recommended 48 hours prior to procedure performance [10]. The negative predictive value of such tests are sufficiently high to provide adequate reassurance prior to endoscopy at present levels of community prevalence [10]. Although recommendations made by Zingone et al regarding pre-biologic screening do not appear to relate specifically to infection control precautions and HCW safety, the apparent widespread reliance on institution based infection control screening protocols prior to comparatively high risk, aerosol generating endoscopic procedures further reinforces the need for caution in making broad screening recommendations without supporting high level evidence.

In conclusion, the balance of accumulating evidence favours the use of biological therapies in those patients with IBD who otherwise require them on the basis of IBD severity, as opposed to deliberate avoidance for fear of adverse outcomes. We agree with Zingone that there is much to learn about COVID-19 infection in this patient population, and that the testing of asymptomatic individuals is likely to contribute to our understanding. However, we suggest screening should be considered as part of a well-designed research study, rather than proactively instituting widespread screening that currently lacks an established evidenced based management plan for implementation on returning a positive result. Evidence to support or refute the need for screening is urgently needed.

Authorship

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Declaration of Competing Interest

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