REVIEW

COVID-19 and the gastrointestinal tract: recent data

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The COVID-19 pandemic continues to have a tremendous impact on health and care provision internationally. There is a sustained increase in cases worldwide, accompanied by high morbidity and mortality. The gastrointestinal impact of the virus remains of great interest, both through direct manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the gastrointestinal system, and through the impact on patients with chronic gastrointestinal disorders, and how we care for them. Data to support public health and clinical guidance are evolving rapidly with the need to revise and update the guidance as evidence accumulates and larger data sets emerge.

We have previously reviewed the early publications.[1] This article includes additional data published over the subsequent months which we feel has impacted on the evolving guidance. It raises issues that must be considered as we move forward and battle with this challenging virus, to reduce the longer-term impact both on our patients and also on ourselves and the wider population.

GASTROINTESTINAL SYMPTOMS AND COVID-19: CASE–CONTROL STUDY FROM THE USA

Gastrointestinal symptoms are common in COVID-19 and can be present prior to the onset or in the absence of respiratory symptoms. There are some data to suggest that their presence reflects more severe disease.[2] In a case–control study, Nobel *et al* compared the prevalence of gut symptoms in patients referred for COVID-19 testing (standard criteria respiratory symptoms with the intent to hospitalise/respiratory symptoms in essential personnel) who tested positive (n=278) with those who tested negative (n=238).[3] Patients who had gastrointestinal symptoms (diarrhoea or nausea/vomiting) were more likely to test positive (61% vs 39%, p=0.04). Patients without gastrointestinal symptoms were equally likely to test positive or negative. Following regression analysis, the OR of testing positive with gastrointestinal symptoms was 1.7 (95% CI 1.1–2.5). Patients with gastrointestinal symptoms had a longer illness duration (>1 week: 33% vs 22%, p=0.048). There was a non-significant trend towards lower rate of intensive care unit (ICU) admission and a significantly lower rate of death (0.0% with gastrointestinal symptoms vs 5.0% without gastrointestinal symptoms, p=0.03) during short-term follow-up. This article discusses the limitations in the data and particularly the potential impact of the short follow-up on the data set and the possibility of recall bias in a small retrospective case–control study (https://www.gastrojournal.org/article/S0016-5085(20)30490X/pdf).

FEATURES OF 20 133 UK PATIENTS IN HOSPITAL WITH COVID-19 USING THE ISARIC WHO CLINICAL CHARACTERISATION PROTOCOL: PROSPECTIVE OBSERVATIONAL COHORT STUDY

This data set was collected prospectively during the growth phase of the first wave of the pandemic to explore risk factors associated with mortality in patients admitted to hospital (6 February 2020 to 19 April 2020; minimum 2 weeks follow-up; 20, 133 patients; 208 acute care hospitals).[4] Of note, 41% of patients were discharged alive, 26% died and 34% continued to receive care at the reporting date. Increasing age, male sex and comorbidities were associated with a significantly higher mortality. The most common risk factors were chronic cardiac disease, non-asthmatic chronic

pulmonary disease, chronic kidney disease and liver disease. Obesity was a major additional risk factor. Of note, 23% reported no major comorbidity. Diarrhoea was recorded in approximately 20%, nausea/vomiting in 20% and abdominal pain in less than 10%. The limitations of this large study included significant missing data and lack of data on patients in community settings (https://www.bmj.com/content/369/bmj.m1985).

CORTICOSTEROIDS, BUT NOT TNF ANTAGONISTS, ARE ASSOCIATED WITH ADVERSE COVID-19 OUTCOMES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASES: RESULTS FROM AN INTERNATIONAL REGISTRY

This study reports data from the Service Epidemiology of Coronavirus Under Research Exclusion (SECURE) for Inflammatory Bowel Disease which is a large, international registry created to monitor the outcomes of inflammatory bowel disease (IBD) patients with confirmed COVID-19.[5] Five hundred and twenty-five cases from 33 countries are reported: 31% were hospitalised, 37 (6%) had severe COVID-19 (ICU, ventilated and death) and 16 patients (3%) died. Of note, 50% of deaths were in patients over age 70 years and 50% of deaths were in patients with cardiovascular comorbidities. Risk factors for severe COVID-19: age, two or more comorbidities (2.9, 95% CI 1.1–7.8), steroid use (6.9, 95% CI 2.3–20.5), 5-aminosalycylate use (3.1, 95% CI 1.3–7.7), but not anti-tumour necrosis factor (TNF) therapy (0.9, 95% CI 0.4–2.2). Standardised mortality rate (from COVID-19) is similar to general population at 1.8 (95% CI 0.9–2.6). The authors openly discuss potential confounders in this physician-reported cohort. The data do however support the well-established premise to use steroid sparing treatments where possible and that IBD *per se*, and specifically monoclonal antibody therapy, is not a risk factor or predictor of a poor outcome of COVID-19 infection (https://www.gastrojournal.org/article/S0016-5085(20)30655-7/pdf).

OUTCOMES OF COVID-19 IN 79 PATIENTS WITH IBD IN ITALY: AN IG-IBD STUDY

This paper reports the characteristics of COVID-19 in patients with IBD in Italy (March 2020).[6] Seventy-nine patients with IBD and COVID-19 from 24 IBD referral units were included: 36 patients had COVID-19-related pneumonia (46%); 22 (28%) were hospitalised; 7 (9%) required non-mechanical ventilation; 9 (11%) required continuous positive airway pressure therapy and 2 (3%) had endotracheal intubation; 6 (8%) died. Age over 65 years (p=0.03), UC diagnosis (p=0.03), IBD activity (p=0.003) and a Charlson comorbidity index (CCI) score >1 (p=0.04) were significantly associated with COVID-19 pneumonia, but not concomitant IBD treatments. Age over 65 years (p=0.002), active IBD (p=0.02) and higher CCI score were significantly associated with COVID-19-related death. Active IBD, old age and comorbidities were associated with a negative COVID-19 outcome, but not IBD treatments (https://gut.bmj.com/content/69/7/1213).

2019 NOVEL CORONAVIRUS DISEASE (COVID-19) IN PATIENTS WITH IBD

This paper reports data on patients with IBD who have had COVID-19 from the Madrid region in Spain.[7] Reporting is until early April 2020. From a population of 1918 with IBD, 12 were reported: average age 52 years, 75% female, 8/12 required hospitalisation and two patients died. Diarrhoea was the presenting symptom in 5/12.

Only 12/1918 IBD patients were diagnosed of COVID-19. IBD patients had a lower adjusted incidence ratio of COVID-19 (OR 0.74, 95% CI 0.70–0.77; p<0.001), and a similar associated mortality ratio (OR 0.95, 95% CI 0.84–1.06; p=0.36), compared with the general population. This may be related to patients shielding from exposure.

In this population, IBD patients did not have an increased risk of COVID-19, and associated mortality, compared with the general population, although data were only collected until 8 April 2020 while case numbers remained high. These are important data to help us reassure our patients and inform decisions about issues including clinical management and the potential need for 'shielding' according to clinical risk (https://onlinelibrary.wiley.com/doi/full/10.1111/apt.15804?af=R).

FAECAL CALPROTECTIN INDICATES INTESTINAL INFLAMMATION IN COVID-19

Faecal calprotectin (FcP) represents a widespread and sensitive marker for intestinal inflammation and is frequently used in screening patients for IBD. This manuscript presents data on 40 patients with COVID-19 from Innsbruck, Austria.[8] Their analyses determined that none of the nine patients presenting with COVID-19-related diarrhoea were positive for faecal SARS-CoV-2. However, FcP in this group was observed to be a mean of 123.2 µg/g, compared with 17.3 µg/g and 37.2 µg/g in those with no diarrhoea and those who had previously had diarrhoea, respectively.

These data point to active gut inflammation in SARS-CoV-2 infection, but only in those with gastrointestinal symptoms. Interestingly, the maximal FcP observed in this study was <250 µg/g, a value that is relatively low compared with levels typically seen in both IBD and bacterial gastrointestinal infection, potentially reflecting only mild gut inflammation. The FcP level did however correlate with serum IL-6 levels, consistent with a systemic inflammatory response (https://gut.bmj.com/content/early/2020/05/05/gutjnl-2020-321388).

EVIDENCE FOR GASTROINTESTINAL INFECTION OF SARS-COV-2

In this article, Xiao and colleagues describe multiple site sampling from COVID-19 patients, including oesophageal, gastric, duodenal and rectal tissue from a single patient.[9] In the single patient with multiple specimens, histological examination did not demonstrate any significant differences in the epithelium, but numerous plasma cells and lymphocytes were seen in the lamina propria. ACE2 receptors, one of the molecules through which the SARS-CoV-2 virus enters cells, were seen throughout the intestinal ciliated epithelium, but was rare in squamous oesphageal cells. Staining of the viral nucleocapsid protein was positive in all biopsies other than the oesophagus. These data point to the vulnerability of glandular epithelial cells, expressing ACE2 receptors, as an entry point for SARS-CoV-2, with the squamous epithelium of the oesophagus largely free of viral infiltration. Of the 73 additional patients reported, 39 (53.4%) tested positive for SARS-CoV-2 RNA in the stool, including a patient as young as 10 months of age (https://www.gastrojournal.org/article/S0016-5085(20)30282-1/fulltext).

EXPRESSION OF SARS-COV-2 ENTRY MOLECULES ACE2 AND TMPRSS2 IN THE GUT OF PATIENTS WITH IBD

In this study, researchers from Florida sought to determine whether the receptors which SARS-CoV-2 uses to enter cells, namely the viral entry receptors ACE2 and TMPRSS2, are expressed in the gastrointestinal tissue of patients with IBD or controls.[10] Using publicly available duodenal, ileal and colonic mucosal biopsies, generated organoids and animal models of IBD, they assessed the expression of these receptors in inflamed and non-inflamed tissues. Overall, both ACE2 and TMPRSS2 were widely expressed in the duodenum, ileum and colon of IBD patients, and similar levels of expression were highly comparable with control patients. Considering patients with active disease, ACE2 expression was downregulated in inflammation and also in commonly used IBD therapy, including anti-tumour necrosis factor drugs, vedolizumab, ustekinumab and steroids. While these data provide some reassurance that these receptors are not expressed at greater levels in patients with underlying gut pathology, they must also be interpreted with some caution. All samples were retrospectively analysed and none of the organoids or patients were infected with SARS-CoV-2. Further data detailing the effect of viral infection of either animal models of IBD or in biopsies from affected patients are needed (https://academic.oup.com/ibdjournal/article/26/6/797/5825063).

SARS-COV-2 PRODUCTIVELY INFECTS HUMAN GUT ENTEROCYTES

Data from the Netherlands, published in *Science*, appear to confirm the susceptibility of intestinal tissues to infection with SARS-CoV-2.[11] Using small intestinal organoids, containing enterocytes, goblet cells and enteroendocrine cells, the researchers were able to confirm infection of cells within the organoids by SARS-CoV-2. The virus appeared to infect proliferating cells and enterocytes, spreading throughout the whole organoid within around 60 hours. Following confirmation of infection, Lamers *et al* performed RNA sequencing of organoid cells, demonstrating an induction of gene expression highly enriched for 'defence response to virus' and 'type 1 interferon response' (typical of cells infected by viruses). These data provide an excellent model to study the effect of SARS-CoV-2 on the gastrointestinal tract, with the ability to translate to intestinal organoids reflecting specific conditions, such as IBD, and assess the impact of infection in these diseases (https://science.sciencemag.org/content/early/2020/04/30/science.abc1669).

INFECTIOUS SARS-COV-2 IN FAECES OF PATIENT WITH SEVERE COVID-19

The potential for faecal–oral transmission of SARS-CoV-2 has shaped guidelines and strategy surrounding gastroenterology practice during the pandemic. There have been multiple studies describing the presence of viral RNA in the stool, however PCR testing targets only selective areas of the viral RNA sequence.[12] While quantitative PCR (qPCR, or real-time PCR) can quantify the relative viral RNA load, whether live virus exists in the stool is of great interest. This study, published in the US Centers for Disease Control and Prevention journal *Emerging Infectious Diseases*, describes for the first time viable virus cultured from the stool of a patient with COVID-19.[13] In this manuscript, the authors describe a single patient with severe SARS-CoV-2 infection for whom faecal samples were retrieved 5 days after intubation and ventilation. The authors initially confirmed the presence of SARS-CoV-2 RNA in the stool from four separate days while the patient was ventilated. Following this, the Vero E6 cell line was inoculated with processed samples derived from the second stool specimen. The cell line demonstrated infection 2 days after second-round passage, with confirmation by full-length viral genome sequencing. Culture supernatant was examined by electron microscopy, revealing viral particles. Of specific interest, of the three patients which Xiao and colleagues attempted to isolate live virus from (including the patient for whom viral culture was achieved), they were able to observe live virus in two cases.

This study requires corroboration and assessment in patients with less severe disease. Despite this, it confirms the possibility of faecal–oral transmission, and it must be noted in future guidance (https://

wwwnc.cdc.gov/eid/article/26/8/20-0681_article?deliveryName=USCDC_333-DM28664).

MORTALITY AND PULMONARY COMPLICATIONS IN PATIENTS UNDERGOING SURGERY WITH PERIOPERATIVE SARS-COV-2 INFECTION: AN INTERNATIONAL COHORT STUDY

There are rightly concerns about the impact of COVID-19 on postoperative recovery, particularly as patients could potentially be operated on during the asymptomatic phase of infection. This has driven the implementation of preoperative strategies including isolation and clinical or laboratory screening. In this multicentre cohort study including 235 hospitals, 24 countries and 1128 procedures, data collected from January to March 2020 reported all patients who were COVID-19-positive 7 days before surgery to 30 days after they were enrolled.[14] The primary outcome was 30-day mortality. Of note, 74% of surgical operations were emergency procedures. Mortality for the whole cohort was 23.8%, higher in the patients with pulmonary complications (82.6% of all deaths). Independent risk factors for mortality included male sex 1.75 (95% CI 1.28–2.4), age >70 years 2.3 (95% CI 1.65–3.22), American Society of Anaesthesiologists grades 3–5, surgery for malignant disease, emergency versus elective surgery and major (compared with minor) surgery. The authors advocate that consideration should be given to postponing surgery, if possible, with use of strategies when surgery is required to reduce in-hospital transmission and mitigate the risk of postoperative complications (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31182X/fulltext).

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