

Paediatric COVID-19 and the GUT

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Abstract

Although children with novel coronavirus infection (COVID-19) typically present with fever and respiratory symptoms, some children have reported gastrointestinal (GI) symptoms including vomiting and diarrhoea during the course of the disease. The continuous positive detection of the viral RNA from faeces in children even after nasopharyngeal swabs turned negative suggests that the GI tract may shed virus and a tentative faecal–oral transmission. The presence of angiotensin-converting enzyme 2 receptor and transmembrane serine protease 2, which are the key proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cell entry process, in the GI tract can explain the digestive symptoms in COVID-19. COVID-19 has implications for the management of children with chronic luminal diseases. There is increasing concern regarding the risk that children with inflammatory bowel disease being infected with SARS-CoV-2.

Keywords: Chronic luminal diseases, COVID-19, intestine

INTRODUCTION

The evidence of gastrointestinal (GI) system involvement in novel coronavirus infection (COVID-19) in children was first reported by a group in China. At present, there are increasing clinical evidence showing that the GI tract might also represent target organ of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and that infected patients could have corresponding organ damage and symptoms. More importantly, the evidence of SARS-CoV-2 detection in patient stool and the tentative faecal–oral route transmission have raised great concern and posed a challenge for control and prevention of COVID-19. In this crucial juncture in the contemporary history of humankind, it is imperative for the paediatric gastroenterologists to be updated with the scientific facts and armed with the expertise and united in the battle against COVID-19.

GASTROINTESTINAL SYMPTOMS OF COVID-19 IN CHILDREN

Although children with COVID-19 patients typically present with a respiratory illness, some children have reported GI symptoms including poor appetite, nausea, vomiting, diarrhoea and abdominal pain during the course of the disease.

COVID-19-related diarrhoea most often occurred 1–8 days after the onset, with a median time of 3.3 days. Some patients had diarrhoea as the first symptom, and the diarrhoea lasted for 1–14 days with diarrhoea appearing watery in one-third.^[1,2] Jin *et al* in an adult study reported that 11.4% COVID 19 patients at presentation had at least one GI symptom (nausea, vomiting or diarrhoea). Moreover rate of increased AST, but not ALT, was significantly higher in patients with COVID-19 with GI symptoms than in those without GI symptoms.^[3]

Lu *et al.* have reported that diarrhoea and vomiting were observed in 15 (8.8%) and 11 (6.4%) in a cohort of 171 children with COVID-19.^[4]

In another study by Yi *et al.* that investigated viral shedding in paediatric COVID-19 patients, diarrhoea was observed in three out of the ten infected children. They have observed positive real-time polymerase chain reaction results in rectal

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swabs in eight out of ten children which remained detectable well after nasopharyngeal swabs turned negative, suggesting that the GI tract may shed virus and faecal–oral transmission may be possible.^[5]

It is evident that patients can present with GI symptoms early in the disease course of COVID-19 as evident from clinical experience in adults. The first COVID-19 patient in the US had nausea and vomiting 2 days before going to the hospital and developed diarrhoea on the 2nd day of admission,^[6] whereas the two young adults in the early familial COVID-19 cluster had diarrhoea upon presentation to the hospital.^[7] Diarrhoea can be one initial symptom and may even occur earlier than pyrexia or respiratory symptoms in some cases.^[8]

Although different clinical features, such as a milder disease course and less respiratory symptoms have been proposed in COVID-19 children, the GI symptoms appear to be similar compared to adults, although more clinical data are needed to arrive at such a conclusion.

GASTROINTESTINAL TRACT INVOLVEMENT IN COVID-19

Evidence regarding the macroscopic changes of the GI tract in children with COVID-19 is yet to be described. There is scanty medical literature on this aspect event in the adult clinical reports on COVID-19. In the only one case who underwent endoscopy because of upper GI bleeding from a cohort of 73 adult patients with COVID-19, no abnormalities were observed in the stomach, duodenum, colon and rectum, with the exception of multiple bleeding ulcers (diameter 4–6 mm) in the oesophagus by endoscopy. Histology showed numerous infiltrating plasma cells and lymphocytes as well as interstitial oedema in the lamina propria of the stomach, duodenum and rectum.^[9]

Autopsy studies are important to help investigating the histopathological change of the GI tract in COVID-19. Currently, there is only one published autopsy report in an octogenarian man with COVID-19, which showed segmental dilatation and stenosis in the small intestine.^[10] Further studies are needed to clarify whether this finding is secondary to COVID-19 or a pre-existing GI comorbidity.

MECHANISMS OF GASTROINTESTINAL TRACT INVOLVEMENT

There are many reasons why SARS-CoV-2 appears to cause digestive symptoms.

1. Angiotensin-converting enzyme 2 (ACE-2) receptor and transmembrane serine protease 2 (TMPRSS2) are key proteins of SARS-CoV-2 cell entry process. Coexpression of these two proteins in the same cell is critical for viral entry. Alveolar type II cells are the main cell type coexpressing ACE-2 and TMPRSS2 in the lung tissue. In

addition, ACE-2 and TMPRSS2 are also coexpressed in both upper epithelial and gland cells from the oesophagus and absorptive enterocytes from the ileum and colon.^[11] After viral entry, virus-specific RNA and proteins are synthesised in the cytoplasm to assemble new virions, which can be released to the GI tract. The continuous positive detection of the viral RNA from faeces suggests that the infectious virions are secreted from the virus-infected GI cells. This GI tropism of SARS-CoV-2 can explain the digestive symptoms including diarrhoea and faecal–oral transmission could be an additional route for viral spread^[9]

2. SARS-CoV-2 indirectly or directly (due to a possible enteropathic effect) damages the digestive system through an inflammatory response and causes digestive symptoms
3. The virus itself may cause disorders of the intestinal flora, which could result in digestive symptoms
4. Changes in the composition and function of the digestive tract flora affect the respiratory tract through the common mucosal immune system, and respiratory tract flora disorders also affect the digestive tract through immune regulation. The effect is called the ‘gut-lung axis,’ which may further explain why patients with COVID-19 pneumonia often have digestive symptoms.^[12]

IMPLICATIONS IN PAEDIATRIC GASTROINTESTINAL PRACTICE

The immediate implication of these data is certainly on the disease infectivity. A recent environmental study suggested that SARS-CoV-2 could remain viable in aerosols for hours and could stay stably on plastic and stainless steel for at least 72 h. While more studies are needed to demonstrate its replication competence, its abundance in stool and stability in the environment would poise SARS-CoV-2 favourably to spread among human hosts. This faecal source can lead to viral transmission, especially when aerosols are generated.

The GI involvement of COVID-19 would necessitate a need to consider several clinical policies, such as incorporation of rectal swab testing before discharging patients and our preparedness for personal protective equipment in the endoscopy setting.^[13]

IMPACT OF PAEDIATRIC COVID-19 IN PATIENTS WITH CHRONIC LUMINAL DISORDERS

COVID-19 has implications for the management of children with chronic luminal diseases. Indeed, the presence and number of comorbidities is associated with poorer clinical outcome in patients with COVID-19 from the adult clinical experience. There is increasing concern regarding the risk that inflammatory bowel disease (IBD) patients being infected with SARS-CoV-2.^[10] After the initial cases have been diagnosed in Wuhan, China, in December 2019, COVID-19 has rapidly spread to countries in the South Asian region

and the Indian subcontinent where paediatric IBD is more prevalent.

ARE CHILDREN WITH INFLAMMATORY BOWEL DISEASE PATIENTS BE AT AN INCREASED RISK FOR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2-INDUCED INFECTIONS?

Coronaviruses bind to their target cells through ACE-2, a monocarboxypeptidase best known for cleaving several peptides within the renin–angiotensin system and other substrates. ACE-2 is constitutively expressed by epithelial cells of the lung, intestine, kidney and blood vessels and is present in the terminal ileum and colon in concentrations that are amongst the highest in the body. The expression of ACE-2 is increased in the inflamed gut of patients with IBD. Moreover, proteomic analysis of tissue samples of IBD patients has revealed a significantly higher expression of ACE-2 in Crohn's disease (CD) than in ulcerative colitis. Along with binding to ACE-2, the fusion of the coronavirus envelope with host cell membranes is critical for establishing a successful infection. This process is mediated by a specific fusion, or 'spike' protein, which is activated through a proteolytic cleavage induced by host cell trypsin-like proteases, the activity of which has been reported to be upregulated in IBD. These observations suggest that the inflamed gut of IBD patients represents an optimal doorway through which the virus enters human tissues.

There are two functional and distinct forms of ACE-2. The full-length ACE-2 contains an extracellular domain, which acts as a receptor for the spike protein of SARS-CoV-2, and a structural transmembrane domain, which anchors the extracellular domain to the plasma membrane. In contrast, the soluble form of ACE-2 lacks the membrane anchor and circulates in small amounts in the blood. *In vitro* studies have shown that the latter form of ACE-2 might act as a competitive interceptor of SARS-CoV-2 by preventing binding of the viral particle to the surface-bound, full-length ACE-2. Notably, the level of the soluble ACE-2 is upregulated in the peripheral blood of IBD patients, raising the possibility that this isoform could contribute to limit SARS-CoV-2 infection.

Although the live SARS-CoV-2 is detectable in faeces, there is no clear-cut evidence that the content of ACE-2 in the ileum and colon influences entry and replication of the virus within the intestinal cells and hence, facilitates its transmission by an extra-respiratory route. SARS-CoV-2 may require additional and yet unidentified cellular attachment-promoting factors to ensure robust infection of host cells. This is in line with the demonstration that SARS-CoV-2 spreads rapidly through the respiratory route despite the modest ACE-2 expression in the upper respiratory tract.

Another aspect relevant for COVID-19 infection in IBD relates to current therapy, as many patients are taking immune suppressors (e.g., azathioprine and methotrexate) for inducing and maintaining remission as well as for

preventing IBD-associated complications. The use of such compounds has been associated with increased risk of infections as they block intracellular signals needed for the host to fight pathogens. On the other hand, it is noteworthy that suppression of the effector cytokine-driven inflammatory response in IBD (e.g., using cytokine blockers) could be beneficial not only for dampening the ongoing mucosal inflammation but also for preventing COVID-19-driven pneumonia. Indeed, the profile of cytokines documented in patients with severe COVID-19 resembles that seen in the inflamed intestine of IBD patients and during the 'cytokine storm' syndrome, a life-threatening condition characterised by hyperactivation of T cells and massive production of interleukin (IL)-1, IL-6, tumour necrosis factor (TNF) and interferon- γ . Consistently, blockers of IL-1 or IL-6 have been used with success in pathologies characterised by cytokine storm syndrome, and preliminary evidence supports the use of IL-6 receptor antagonists in the treatment of COVID-19-driven pneumonia.

The overall available evidence suggests that IBD patients do not have an increased risk of developing COVID-19 and should stay on IBD medications. Patients receiving immune suppressors should be carefully monitored for the occurrence of symptoms and/or signs suggesting COVID-19.^[14]

KEY RECOMMENDATIONS FOR MANAGING PAEDIATRIC INFLAMMATORY BOWEL DISEASE DURING THE COVID-19 EPIDEMIC

General

- IBD *per se* does not currently seem to be a risk factor for acquiring SARS CoV-2, nor for a more severe infection
- For decreasing the risk of contracting SARS-CoV2 in children with IBD, standard pandemic practices should be followed (e.g., good hand hygiene, avoiding contact with anyone with respiratory symptoms and social distancing)
- When possible by local situation and resources, children should continue follow-up visits to ensure appropriate monitoring of the disease. However, remote telemedicine consultations, along with the use of surrogate markers of inflammation (ESR, CRP and patient-reported outcomes) may be an alternative to face-to-face office visits during the epidemic, especially for those in remission. The option of delaying visits should be considered on an individual basis
- Active IBD disease should be treated according to the standard guidance PIBD protocols as before the epidemics, since the risk of IBD complications in active IBD outweighs any risk of COVID-19 complications, especially in children^[10,15]
- There is currently no concrete evidence that any of the IBD treatments increases the risk for acquiring SARS-CoV-2 or for a more severe infection once infected. Therefore, uninfected children should generally continue their medical treatment, including immunomodulators and

biologic therapies, as the risk of a disease flare outweighs any estimated risk of SARS-CoV-2 infection.^[10,15]

Medication for patients with inflammatory bowel disease

- Continue the current treatment if disease is stable and contact your doctor for suitable medicine if disease has flared
- Corticosteroids can be used to treat disease relapses, but as always recommended in children, the drug should be weaned as soon as possible
- In CD, exclusive enteral nutrition should be preferred
- The use of mesalamine should be continued and should not increase the risk of infection
- The use of anti-TNFs should be continued at the regular intervals and doses. Infusion centres should minimise crowding and implement screening procedures for suspected COVID-19
- Switching from infliximab to adalimumab in a stable child should be discouraged unless impossible to provide intravenous infusions, since the risk of disease exacerbation after such a switch has been documented in the clinical trial setting.

Surgery and endoscopy

- Postpone elective surgery and non-urgent endoscopy
- Screening for COVID-19 before emergency surgery.

Patients with inflammatory bowel disease and fever

- Contact your IBD doctor about potential option to visit fever outpatient clinic with personal protection provisions if temperature continues over 38°C
- Suspend immunosuppressive treatment during an acute febrile illness until fever subsides and the child returns to normal health, irrespective of the SARS-CoV-2 testing status
- Mesalamine should never be suspended.

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