# Gastrointestinal Perspective of Coronavirus Disease 2019 in Children—An Updated Review

*†Amit Assa, ‡Marc A. Benninga, §Osvaldo Borrelli, ||Ilse Broekaert, ¶Javier Martin de Carpi, #Marco Deganello Saccomani, **Jernej Dolinsek, ††Emmanuel Mas, ‡‡Erasmo Miele, §§Mike Thomson, and ||||Christos Tzivinikos, The Gastrointestinal Committee of ESPGHAN

**ABSTRACT**

Gastrointestinal symptoms are common findings in children with severe acute respiratory syndrome coronavirus 2 infection, including vomiting, diarrhoea, abdominal pain, and difficulty in feeding, although these symptoms tend to be mild. The hepato-biliary system and the pancreas may also be involved, usually with a mild elevation of transaminases and, rarely, pancreatitis. In contrast, a late hyper-inflammatory phenomenon, termed multisystem inflammatory syndrome (MIS-C), is characterized by more frequent gastrointestinal manifestations with greater severity, sometimes presenting as peritonitis. Gastrointestinal and hepato-biliary manifestations are probably related to a loss in enterocyte absorption capability and microscopic mucosal damage caused by a viral infection of intestinal epithelial cells, hepatocytes and other cells through the angiotensin conversion enzyme 2 receptor resulting in immune cells activation with subsequent release of inflammatory cytokines. Specific conditions such as inflammatory bowel disease (IBD) and liver transplantation may pose a risk for the more severe presentation of coronavirus disease 2019 (COVID-19) but as adult data accumulate, paediatric data is still limited. The aim of this review is to summarize the current evidence about the effect of COVID-19 on the gastrointestinal system in children, with emphasis on the emerging MIS-C and specific considerations such as patients with IBD and liver transplant recipients.

**Key Words:** coronavirus, gastrointestinal manifestations, multisystem inflammatory disease, paediatric

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**What Is Known**

- Gastrointestinal symptoms are common findings in children with severe acute respiratory syndrome coronavirus 2 infection.
- A late hyper-inflammatory phenomenon, termed multisystem inflammatory syndrome, is characterized by more frequent gastrointestinal manifestations with greater severity.

**What Is New**

- Gastrointestinal symptoms are associated with more severe disease and younger age.
- Attention should be given to rare complications such as intussusception, necrotizing enterocolitis-like disease and pancreatitis.
- Non-alcoholic fatty liver disease increases the risk for severe coronavirus disease 2019 (COVID-19).
- In children with inflammatory bowel disease multiple comorbidities, moderate/severe disease activity, sulfasalazine/mesalamine use and corticosteroid use increase the likelihood of severe COVID-19.

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From the *Department of Paediatrics, Assuta Ashdod University Hospital, Ashdod, the †Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel, the ‡Department of Paediatrics, Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, The Netherlands, the §Division of Neurogastroenterology & Motility, Department of Paediatric Gastroenterology, Great Ormond Street Hospital, London, UK, the ||Department of Paediatrics, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, the ¶Hospital Sant Joan de Déu, Barcelona, Spain, the #Department of Paediatrics, Woman's & Child's University Hospital of Verona, Italy, the **Department of Pediatrics, University Medical Center Maribor, Maribor, Slovenia, the ††Unité de Gastroentérologie, Hépatologie, Nutrition et Maladies Héréditaires du Métabolisme, Hôpital des Enfants, and IRSD, Université de Toulouse, INSERM, INRAE, ENVT, UPS, Toulouse, France, the ‡‡Department of Translational Medical Science, Section of Pediatrics, University of Naples ''Federico II'', Naples, Italy, the §§Cen-Centre for Paediatric Gastroenterology, Sheffield Children's Hospital NHS Foundation Trust, Weston Bank, Sheffield, UK, and the ||||Paediatric Gastroenterology Department, Al Jalila Children's Specialty Hospital, Dubai, UAE.

Address correspondence and reprint requests to Amit Assa, MD, MHA, Department of Pediatrics, Assuta, Ashdod University Hospital, 7 Harefua St., Ashdod 7747629, Israel (e-mail: dr.amit.assa@gmail.com).

All authors contributed equally to the manuscript.

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The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing global challenge, currently lasting more than a year, resulting in significant morbidity and mortality with a detrimental effect on the world economy. Children represent approximately 2% of all confirmed cases (1), although the incidence of paediatric disease may be underscored by asymptomatic underdiagnosed cases. Although COVID-19 is generally milder in children than in adults, approximately 1% of children develop severe disease requiring admission to intensive care units (1). Moreover, since the emergence of COVID-19, a unique presentation characterized by severe systemic hyperinflammation, has been increasingly reported and ultimately termed multisystem inflammatory syndrome in children (MIS-C).

Several systematic reviews and meta-analyses (2–4) summarized that the most frequently reported symptoms in children are cough, fever, pharyngitis, rhinorrhoea and to a lesser extent headache, myalgia, rash and conjunctivitis. Gastrointestinal manifestations were reported to range from 5% to 20% (5) with uncommon liver involvement and a few reported cases of pancreatitis. In contrast, fever and gastrointestinal manifestations prevail in the presentation of MIS-C with greater severity sometimes mimicking appendicitis and peritonitis (6,7). Hereby, we review and discuss the updated literature regarding gastrointestinal involvement in children with SARS-CoV-2 infection.

## METHODS

PubMed, Embase, and the Cochrane library were searched from 1 December 2019 to 23 March 2021 using the following search terms: Coronavirus [OR] COVID-19 [OR] SARS-CoV-2 [OR] multisystem inflammatory syndrome [OR] Paediatric/Pediatric Multisystem Inflammatory Syndrome [AND] Children [OR] Paediatric/Pediatric [AND] Gastrointestinal [OR] Intestinal [OR] Liver [OR] Hepatic [OR] Transaminases [OR] Biliary [OR] Bile duct [OR] Gallbladder [OR] Pancreas [OR] Pancreatic [OR] Inflammatory Bowel Disease [OR] Crohn's/Crohn [OR] Ulcerative Colitis [OR] Liver Transplant/Transplantation.

## Pathogenesis of Severe Acute Respiratory Syndrome Coronavirus 2 in the Gastrointestinal Tract

Similar to its entrance to lung epithelial cells, SARS-CoV-2 mainly enters intestinal epithelial cells through the angiotensin conversion enzyme 2 (ACE2) receptor following binding of the spike protein S to the receptor, a process regulated by the cell surface–associated transmembrane protease serine protease 2 (TMPRSS2) (8). Once the cell is infected, SARS-CoV-2 causes immune cells activation with subsequent release of inflammatory cytokines such as interleukin (IL)-2, IL-6, IL-17 and tumour necrosis factor alpha (TNFα), which mediate local and systemic inflammation (9). Gastrointestinal symptoms are thus presumed to be related to a loss in enterocyte absorption capability and microscopic mucosal damage (10) as was demonstrated by the absence of macroscopic endoscopic findings and the presence of microscopic inflammatory activity (11). ACE2 and TMPRSS2 are more abundantly expressed in the ileum and colon, a finding that may explain the more common involvement of these segments (12). ACE2 is also expressed on hepatocytes and cholangiocytes and may facilitate the elevation in aminotransferases reported in patients with COVID-19 although any viral disease may facilitate liver inflammation (13).

The mechanism of MIS-C is still not clearly understood. The syndrome may be related to a delayed inflammatory response attributed to both the adaptive immune system through complement activation by virus–antibody complexes and the innate immune system through direct infection of T cells by SARS-CoV-2 resulting in an impaired antiviral response (14).

Viral RNA is detected in faecal samples of up to 50% of patients with COVID-19 while SARS-CoV-2 RNA shedding in stool persists between 1 and 12 days (11). Nevertheless, the significance of this finding for establishing faecal-oral transmission is debated as RNA presence may not represent infectious SARS-CoV-2 (15). In children, a meta-analysis (16) reported a pooled detection rate of faecal RNA of 43.7% with a higher detection rate in those who presented with gastrointestinal symptoms (77.1% vs 57.7%), and patients with more severe disease (68.3% vs 34.6%). In another systematic review (17), the duration of gastrointestinal shedding ranged from 10 days to 5 weeks following symptom onset. In a subset of patients who were sampled repeatedly, the mean duration of viral shedding was $23.6 \pm 8.8$ days from symptom onset, with a range of 10–33 days.

## Gastrointestinal Manifestations of Coronavirus Disease 2019 in Children

COVID-19 is associated with gastrointestinal symptoms such as diarrhoea, nausea and vomiting, abdominal pain, and feeding difficulties in up to one-fifth of patients (18,19). In addition, several case reports have described ileus and mesenteric adenopathy with terminal ileitis, presenting as atypical appendicitis (18–21).

The first observation from China reported nausea or vomiting and diarrhoea in 5% and 3.7% of patients, respectively (22). However, the frequency of gastrointestinal manifestations differs between adults and children and also among different paediatric cohorts. Pooled data from 2023 patients demonstrated that anorexia was the most frequent gastrointestinal manifestation in adults, diarrhoea the most common symptom in both adults and children, while vomiting was found to be more common in children (23). Gastrointestinal symptoms have been reported alone or as initial symptoms of SARS-CoV-2 infection in 14.2–24.8% (24–26) and in 14% of children, respectively (26). Table 1 shows the prevalence of gastrointestinal manifestations in children with COVID-19 as reported in cohort studies and in large case series (5,25–38). The pooled prevalence of the gastrointestinal symptoms from these studies was 36.8% (range: 13.9–62%).

Only recently, the clinical characteristics of 244 COVID-19 positive children from Wuhan, China, were reported, of whom 13.9% presented with gastrointestinal symptoms (36). Young age (<2 years) and fever were associated with gastrointestinal symptoms.

A systematic review on laboratory-confirmed SARS-CoV-2 infection in infants younger than 3 months of age revealed a similar incidence of diarrhoea (14%), vomiting (14%) to that reported in the data pooled in Table 1 (33). In this review, feeding difficulties were reported in 24% of the infants. In Brazilian children, gastrointestinal symptoms such as inappetence, nausea/vomiting, and diarrhoea, were more frequently reported in children younger than 2 years of age whereas abdominal pain was more frequently found in children older than 3 years (34).

Gastrointestinal symptoms were shown to be associated with more severe disease (25,26,37). Indeed, children with COVID-19 and gastrointestinal manifestations have an increased risk of admission to intensive care units (odds ratio [OR] 5.90, 95% confidence interval [CI]: 1.67–20.83, $P = 0.006$) (26). Children with gastrointestinal symptoms show significantly increased levels of C-reactive protein and procalcitonin, suggesting more severe disease (26).

TABLE 1. Gastrointestinal symptoms of children affected by COVID-19

| Author (reference) | Country | No. of children | Median age (y) | Diarrhea, no. (%) | Nausea/vomiting, no. (%) | Abdominal pain, no. (%) | Feeding difficulties, no. (%) |
|---|---|---|---|---|---|---|---|
| Ashktorab et al (5) | USA | 6639 | 14.8 | 730 (11) | 876 (13.2) | 671 (10.1) | NA |
| CDC (26) | USA | 291 | NA | 38 (13) | 32 (11) | 17 (5.8) | NA |
| Esmaeili Dooki et al (27) | Iran | 18 | 6.9 | 6 (33.3) | 7 (38.9) | 6 (33.3) | 15 (83.3) |
| Gaborieau et al (28) | France | 192 | 1 | 32 (16.7) | 19 (9.9) | NA | 17 (8.9) |
| Giacomet et al (24) | Italy | 127 | 4.8 | 28 (22) | 12 (9.4) | 8 (6.3) | NA |
| Gonzalez Jimenez et al (25) | Spain | 101 | 9.4 | 33 (32.7) | 35 (34.7) | 35 (34.7) | NA |
| Kainth et al (29) | USA | 65 | 10.3 | 7 (11) | 22 (34) | 40 (62) | 40 |
| Liu et al (31) | China | 46 | 0.42 | 1 (2.2) | 5 (10.9) | NA | NA |
| Lu et al (30) | China | 171 | 6.7 | 15 (8.8) | 109 (64) | NA | NA |
| Rabha et al (33) | Brazil | 115 | 2 | 15 (13) | 20 (17.4) | 9 (8.7) | 25 (21.7) |
| Xia,et al. (34) | China | 20 | 2.1 | 15 (3) | 2 (10) | NA | NA |
| Xiong et al (35) | China | 244 | 6.3 | 15 (6.1) | 23 (9.4) | 4 (1.6) | 3.3 |
| Zachariah et al (36) | USA | 50 | 9.9 | 2 (4) | 3 (6) | 5 (10) | NA |
| Zheng et al (37) | China | 25 | 3 | 3 (12) | 2 (8) | 2 (8) | NA |
| Total | | 8104 | | 1015 (12.5) | 1167 (14.4) | 797 (10.4) | |

NA = not applicable.

## Gastrointestinal Manifestations of Coronavirus Disease 2019 Multisystem Inflammatory Syndrome

Rare severe presentations of COVID-19, similar to Kawasaki disease, were reported in a few children during the early phase of the pandemic (39). Since then, many reports of similarly affected children were published worldwide and the condition has been termed MIS-C.

Case definitions vary slightly between different healthcare authorities but generally require fever, elevated inflammatory markers, signs of multisystem involvement, evidence of SARS-CoV-2 infection or exposure and exclusion of other potential causes (40).

While the incidence of MIS-C in different regions is uncertain, it appears to be a rare complication of COVID-19 in children. In one report, the estimated incidence of laboratory-confirmed SARS-CoV-2 infection in individuals <21 years old was 322 per 100,000 and the incidence of MIS-C was 2 per 100,000 (40).

In most studies, there was a lag of several weeks between the peak of COVID-19 cases within communities and the rise of MIS-C cases. This three- to four-week lag coincides with the timing of acquired immunity and might suggest that MIS-C represents a post-infectious complication (41).

Despite initial reports mostly including severely affected children with MIS-C, it is now obvious that the spectrum of disease severity ranges from mild to severe. The initial case series largely reported the most severe end of the spectrum, resulting in a high reported incidence of shock, myocardial involvement, and respiratory failure. It remains unclear how common each presentation is, how frequently children progress from mild to more severe manifestations, and what are the underlying factors predisposing such progression (42). Patients with MIS-C usually present with persistent fever, abdominal pain, vomiting, diarrhoea, skin rash, mucocutaneous lesions and, in severe cases, with hypotension and shock (Table 2). Not all children will have the same signs and symptoms, and some children may have symptoms not listed above.

Gastrointestinal symptoms (abdominal pain, vomiting, diarrhoea) are particularly common and prominent in MIS-C, involving up to 90% of patients. In some children, presentation can mimic acute appendicitis (18,43). Some children have been noted to have terminal ileitis on abdominal imaging and/or colitis on colonoscopy mimicking acute onset of inflammatory bowel disease (7,44). In general, although any segment of the gastrointestinal tract may be affected, inflammation in the ileum and colon predominates. Progressive bowel wall thickening can lead to luminal narrowing and obstruction. In one small study of 16 patients, abdominal imaging findings included ascites (6/16, 38%), hepatomegaly (6/16, 38%), bowel wall thickening (3/16, 19%), gallbladder wall thickening (3/16, 19%), mesenteric lymphadenopathy (2/16, 13%), and splenomegaly (1/16, 6%) (45). Most will have a resolution of intestinal inflammation with medical therapies; however, rarely, surgical resection may be required (44). Other organs may be involved including pancreatitis, hepatitis, gallbladder hydrops or oedema (46).

## Coronavirus Disease 2019 and Hepato-Biliary-Pancreatic Manifestations

In adult patients, SARS-CoV-2 infection is frequently associated with abnormal liver tests, mainly transaminases. The incidence of increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, in fact, ranged from 2.5% to 61.1% (47). Elevated bilirubin is reported in 0–35% of cases, whereas raised alkaline phosphatase and γ-glutamyl transferase are rarely described. Whether these laboratory findings are associated with a worse prognosis remains controversial.

TABLE 2. Presenting symptoms* of multisystem inflammatory syndrome in children (MIS-C)

| |
|---|
| Persistent fevers (median duration 4–6 days) |
| Gastrointestinal symptoms (abdominal pain, vomiting, diarrhoea) |
| Rash |
| Mucous membrane involvement |
| Conjunctivitis |
| Respiratory symptoms |
| Neurocognitive symptoms (headache, lethargy, confusion) |
| Myalgia |
| Swollen hands/feet |
| Lymphadenopathy |

*Symptoms are presented in decreasing frequency.

In contrast, in children with COVID-19 disease, liver enzymes are usually normal or only slightly increased. Bourkhissi et al (48) analysed 68 children with confirmed COVID-19 in Morocco and observed no cases of abnormal liver tests. Nevertheless, an Italian study (49) reported mild elevations of ALT and AST in 13% and 20% of patients, respectively. Furthermore, Zhou et al (50) described liver involvement as more prevalent in children under 3 years of age compared to older patients (91.7% vs 26.1%). Due to the mild nature of hepatic involvement in children, the American Association for the Study of Liver Diseases recommends to evaluate all children with elevated transaminases for underlying liver diseases and not to focus per se on SARS-CoV2 infection (51).

Liver damage in SARS-CoV2 infection may be caused by a direct effect of the virus on hepatocytes, by systemic inflammation, by the toxicity of drugs used in these patients or as a result of a combination of these mechanisms (47). As mentioned before, ACE2 receptor is expressed by hepatocytes and bile duct cells that may be then directly infected by the virus (13). Hepatic involvement may also be the consequence of the severe inflammatory response induced by the virus with massive immune activation and an increase in cytokines levels (52). In fact, several studies in adult patients with SARS-CoV-2 infection demonstrated higher values of inflammatory cytokines in patients with hepatic injury compared to those with normal liver tests (53). Furthermore, liver involvement was observed more often in subjects with severe disease compared to those with mild infection (54). Conversely, no differences in cytokine levels were observed in patients with or without increased hepatic enzymes (48). Liver injury may be due to the toxic effect of drugs used during SARS-CoV-2 infection such as antipyretics (eg, paracetamol), antibiotics, antivirals or herbal medicines (47).

The impact of SARS-CoV-2 in subjects with chronic liver disease is still unclear. Patients with chronic liver disease do not seem to have a greater risk of contracting COVID-19 (55). However, children with autoimmune hepatitis may potentially have a more severe course of the infection (55). Recent evidence in children with underlying chronic liver disease have shown that patients with non-alcoholic fatty liver disease (NAFLD) had higher odds of severe disease (56,57). In a recently published meta-analysis (58) (March 21), the adjusted odds ratio (aOR) for severe COVID-19 in adult patients with NAFLD versus those without NAFLD was 2.60 (95% CI 2.24–3.02). All eight studies performed multivariable analyses adjusting for multiple covariates, which included body mass index, implying that NAFLD is an independent risk factor for severe disease, regardless of obesity. Obesity, by itself, was shown to increase the risk of severe COVID-19 in patients with NAFLD (aOR 6.32, 95% CI 1.16–34.54) (59).

Recently, reports from adults have shown that COVID-19 can also present as acute pancreatitis (60). Alloway et al (61) described for the first time acute pancreatitis in a 7-year-old girl with SARS-CoV-2 infection. Two cases of acute pancreatitis as the initial presentation of MIS-C have also been reported (62). Suchman et al (63) observed a point prevalence of pancreatitis of 1.8% in children with SARS-CoV-2 infection compared to 0.14% in COVID-19 negative patients. Based on their results, authors speculate that pancreatitis may be more common in children with COVID-19 disease.

A suggested mechanism is a direct cytopathic effect of the virus on pancreatic cells, as ACE2 receptors are also expressed in the pancreas (62) though pancreatic damage may be a consequence of a systemic inflammatory response (62).

## Rare gastrointestinal Complications of Coronavirus Disease 2019 in Children

Acute appendicitis in children infected with SARS-CoV-2 is increasingly reported (though still rare) regardless of the disease phase (typical COVID-19 or MIS-C) (18,20,21,43,64). Other causes of acute onset lower right abdominal pain associated with COVID-19 are reported, including one case of COVID-19-related acute onset pneumatosis intestinalis diagnosed by abdominal CT scan (65), and another of diffuse mesenteric lymphadenopathy, again, diagnosed on abdominal CT with no other potential aetiology in an adolescent (66).

Intussusception is another reported association of COVID-19, with a classic presentation in five infants of vomiting, diarrhoea, acute onset abdominal pain and mucousy bloody stools (67–70). COVID-19 should probably be looked for during the present pandemic in infants presenting with intussusception. An older child has been described presenting with COVID-19-related acute functional intestinal obstruction with epigastric pain and abdominal distension with diffuse jejunal dilation on CT contrast with no mechanical obstruction (71). Two adolescents have been reported presenting with acute severe enteritis with abdominal pain and GI bleeding resolving with conservative management as the sole presenting features of COVID-19 (72).

## Specific Considerations

### *Inflammatory Bowel Disease*

The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) consortium, which collects worldwide available data on patients with IBD who were infected with COVID-19, has released several pivotal reports on the effect of IBD and related medications on COVID-19 disease outcomes. Ungaro et al (73) described 1439 cases of whom 112 patients (7.8%) had severe COVID-19. Compared with tumour necrosis factor (TNF) antagonist monotherapy, thiopurine monotherapy (aOR 4.08, 95% CI 1.73–9.61) and combination therapy with TNF antagonist and thiopurines (aOR 4.01, 95% CI 1.65–9.78) were associated with an increased risk of severe COVID-19. Any mesalamine/sulfasalazine compared with no mesalamine/sulfasalazine use was associated with an increased risk (aOR 1.70, 95% CI 1.26–2.29). Interleukin-12/23 and integrin antagonists were not associated with increased risk. For reference, it was reported that the adjusted pooled weighted OR for the severe disease was 1.2 (95% CI 0.96–1.38) for any immune suppression (74). It is not clear why mesalamine is associated with increased incidence of severe COVID-19. It is possible that the comparison to other drugs such as anti-TNFα, which may reduce the risk for severe disease, results in a false positive aOR. Alternatively, unadjusted confounders such as differences in socioeconomic status or access to care in mesalamine treated patients may be involved (73).

Brenner et al (75) reported a standardized mortality ratio for patients with IBD between 1.5 and 1.8 (depending on the region reporting). Risk factors for severe COVID-19 included increasing age (aOR 1.04, 95% CI 1.01–1.02), >2 comorbidities (aOR 2.9, 95% CI 1.1–7.8), systemic corticosteroids (aOR 6.9, 95% CI 2.3–20.5), and sulfasalazine or 5-aminosalicylate use (aOR 3.1, 95% CI 1.3–7.7). The observed increased risk for severe disease in patients treated with systemic corticosteroids was confirmed in a report by Singh et al (76), which included 232 patients with IBD and 19,776 without IBD. A higher proportion of patients in the IBD group presented with nausea, vomiting, diarrhoea and abdominal pain.

The same consortium reported 209 cases of COVID-19 in paediatric patients with IBD (75). There were no deaths in the study population, and 14 children (7%) were hospitalized, of whom only two (1%) required mechanical ventilation. The two children requiring mechanical ventilation were on either sulfasalazine/mesalamine and developed MIS-C. Hospitalization was associated with non-IBD comorbidities, moderate/severe IBD disease activity, gastrointestinal symptoms, sulfasalazine/mesalamine use, and corticosteroid use.

Anti-TNF monotherapy was associated with a decreased likelihood of hospitalization (7% vs 51%).

There is one report of a 14 years old patient with recently diagnosed Crohn disease who presented with severe COVID-19 infection compatible with MIS-C who rapidly responded to one infusion of infliximab (77). Another case (16 years old, Crohn disease) with MIS-C slowly recovered following combined treatment of corticosteroids, intravenous immunoglobulin and infliximab (78).

Immunosuppressive drugs may cause an attenuated response to anti-SARS-CoV-2 vaccines. A preliminary report found that infliximab, especially in combination with an immunomodulator, was associated with attenuated immunogenicity to a single dose of two different anti-SARS-CoV-2 vaccines when compared to vedolizumab. Further studies should address the effect of IBD related medications on the efficacy of approved anti-SARS-CoV-2 vaccines (79).

## Liver Transplant Recipients

Most data on the outcome of COVID-19 in liver transplant recipients come from adult multi-centre cohorts with predominantly elderly patients with significant comorbidities. The four most prominent cohorts (80–83) included between 57 and 243 patients and all of those reported a very high rate of hospitalization (72–87%), ICU admissions (11–19%) and death (12–22%), but these outcomes were not significantly different from a matched general population (82). Variables associated with severe outcome included older age, comorbidities (particularly diabetes mellitus and chronic kidney disease) while tacrolimus seems to have a protective effect. Liver injury during COVID-19 was significantly associated with mortality and ICU admission.

In children, the evidence is limited to small cohorts or case reports. In a mixed cohort of paediatric solid organ recipients whereof 10 with a liver transplant, the hospitalization rate was 31%, but all patients recovered rapidly (84). One death was reported in a 3-year-old liver transplant recipient due to multi-organ failure (85). In the most recent study, which included 47 patients <21 years post liver transplant, recipients had lower odds of severe SARS-CoV-2 infection when compared to patients with the chronic liver disease despite immunosuppression burden (84).

## SUMMARY AND CONCLUSIONS

Gastrointestinal symptoms are common findings in children with SARS-CoV-2 infection, but they are usually mild. Gastrointestinal symptoms are associated with more severe disease and younger age. MIS-C is an uncommon life-threatening late complication of COVID-19 in which gastrointestinal involvement predominates. Hepato-biliary involvement is common in children but is usually mild. Similar to adults, multiple comorbidities, moderate/severe disease activity, sulfasalazine/mesalamine use, and corticosteroid use increase the likelihood of severe COVID-19 in paediatric IBD patients, however, the disease is mild in most cases. Paediatric data on liver transplant recipients is very limited, but so far increased risk for severe COVID-19 has not been demonstrated. In contrast, NAFLD increases the risk for severe COVID-19. With the accumulation of data, questions such as the efficacy of vaccinations in patients treated with immune-suppressing agents or the potential adverse effects of anti-SARS-CoV-2 vaccines on paediatric patients with immune-mediated conditions, should be addressed.

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