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 in children (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

Received March 23, 2021; accepted June 6, 2021.
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 Hériditaires 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 §§Centre for Paediatric Gastroenterology, Sheffield Children’s Hospital NHS Foundation Trust, Weston Bank, Sheffield, UK, and the §§§Paediatric Gastroenterology Department, Al Jilta 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.
A.A. received the last 3 years’ consultation and lectures fees from Abbvie and Takeda and Research grants from Abbvie and Janssen; E.Mi received the last 3 years’ grants/research supports from Nestle Italy and Nutricia Italy and received payment/honorarium for lectures from Discomfarm, Ferring and Shire-Takeda; O.B. received the last 3 years’ consultation and lectures fees from Danone, Nutricia and Mead Johnson; C.T. received the last 3 years’ payment/honorarium for lectures/consultation from Sanofi, Takeda, Nestle, Nutricia, Abbvie; I.B., J.M.C., M.A.B., M.D.S., I.D., E.Ma. M.T. have no conflict of interest to declare.
Disclaimer: Although this paper is produced by the ESPGHAN Gastrointestinal Committee (GIC) working group, it does not necessarily represent ESPGHAN policy and is not endorsed by ESPGHAN.
Copyright © 2021 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.
DOI: 10.1097/MPG.0000000000003204
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] Transamminases [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 ± 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).
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, diarrhea, 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, diarrhea) 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% (46). 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, diarrhea) | 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. Bourkhis 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 cytokine 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. The 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 pneumonitis intestinals 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 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-aminosalicylic acid 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. Gastrointes- tinal 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 immunemediated conditions, should be addressed.

REFERENCES

1. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr 2020;174:882–9.

2. Christophers B, Gallo Marin B, Oliva R, et al. Trends in clinical presentation of children with COVID-19: a systematic review of individual participant data. Pediatr Res 2020. Sep 17. doi: 10.1038/s41390-020-01161-3. Online ahead of print.

3. Li B, Zhang S, Zhang R, et al. Epidemiological and clinical characteristics of COVID-19 in children: a systematic Review and Meta-Ana- lyis. Front Pediatr 2020;8:591132.

4. Viner RM, Ward JL, Hudson LD, et al. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. Arch Dis Child 2020. Dec 17. doi: 10.1136/archdischild-2020-320972. Online ahead of print.

5. Ashktorah Y, Brim A, Pizziorno A, et al. COVID-19 pediatric patients: gastrointestinal symptoms, presentation, and disparities by race/ethni- city in a large. Multicenter US Study. Gastroenterology 2021;160: 1842–4.

6. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094. doi: 10.1136/bmj.m2094.

7. Chen TH, Kao WT, Tseng YH. Gastrointestinal involvements in children with COVID-related multisystem inflammatory syndrome. Gastro- enterology 2021;160:1887–8.

8. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.

9. Li L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect 2020;9:727–32.

10. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology 2020;158:1518–9.

11. Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020;158:1831–3.

12. Burguëño JF, Reich A, Hazime H, et al. Expression of SARS-CoV-2 entry molecules ACE2 and TMPRSS2 in the gut of patients with IBD. Inflamm Bowel Dis 2020;26:797–808.

13. Jothismini D, Venugopall R, Abedin MF, et al. COVID-19 and the liver. J Hepatol 2020;73:1231–40.

14. Zou H, Lu J, Liu J, et al. Characteristics of pediatric multi-system inflammatory syndrome (PMIS) associated with COVID-19: a meta- analysis and insights into pathogenesis. Int J Infect Dis 2021;102:319– 36.

15. Woffel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465–9.

16. Wong MC, Huang J, Lai C, et al. Detection of SARS-CoV-2 RNA in fecal specimens of patients with confirmed COVID-19: a meta-analysis. J Infect 2020;81:e31–8.

17. Xu CLH, Raval M, Schnall JA, et al. Duration of respiratory and gastrointestinal viral shedding in children with SARS-CoV-2: a sys- tematic review and synthesis of data. Pediatr Infect Dis J 2020;39: e249–56.

18. Tullie L, Ford K, Bisharat M, et al. Gastrointestinal features in children with COVID-19: an observation of varied presentation in eight children. Lancet Child Adolesc Health 2020;4:e19–20.

19. Suresh Kumar VC, Mukherjee S, Harne PS, et al. Novelty in the gut: a systematic review and meta-analysis of the gastrointestinal manifes- tations of COVID-19. BMJ Open Gastroenterol 2020;7:e000417. doi: 10.1136/bmjgast-2020-000417.

20. Abdalhadi A, Alkatib M, Mismar AY, et al. Can COVID 19 present like pseudo-appendicitis in an adolescent? Indo JF, Reich A, Hazime H, et al. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020;158:1831–3.

21. Suwanwongse K, Shabarek N. Pseudo-appendicitis in an adolescent ahead of print.

22. Tian Y, Rong L, Nian W, et al. Review article: gastrointestinal features of COVID-19: a systematic review and meta-analysis. Lancet Child Adolesc Health 2020;4:e249–56.

23. Christophers B, Gallo Marin B, Oliva R, et al. Trends in clinical presentation of children with COVID-19: a systematic review of individual participant data. Pediatr Res 2020. Sep 17. doi: 10.1038/s41390-020-01161-3. Online ahead of print.

24. Li B, Zhang S, Zhang R, et al. Epidemiological and clinical characteristics of COVID-19 in children: a systematic Review and Meta-Ana- lyis. Front Pediatr 2020;8:591132.

25. Viner RM, Ward JL, Hudson LD, et al. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. Arch Dis Child 2020. Dec 17. doi: 10.1136/archdischild-2020-320972. Online ahead of print.
25. Giacomel V, Barcellini L, Stracuzzi M, et al. COVID-19 Pediatric network. Gastrointestinal symptoms in severe COVID-19 children. Pediatr Infect Dis J 2020;39:e317–20.
26. Gonzalez Jimenez D, Velasco Rodriguez-Belvis M, Ferrer Gonzalez P, et al. COVID-19 gastrointestinal manifestations are independent predictors of PICU admission in hospitalized pediatric patients. Pediatr Infect Dis J 2020;39:e459–62.
27. Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422–6.
28. Esmaili Dooki M, Mehrabani S, Sorokhi H, et al. COVID-19 and digestive system in children: a retrospective study. Arch Iran Med 2020;23:782–6.
29. Gaboriciu L, Delestrain C, Bensaid P, et al. Epidemiology and clinical presentation of children hospitalized with SARS-CoV-2 infection in suburbs of Paris. J Clin Med 2020;9:22277. doi: 10.3390/jcm9072277.
30. Kaithi MK, Goenka PK, Williamson KA, et al. Northwell Health COVID-19 Research Consortium. Early experience of COVID-19 in a US children’s hospital. Pediatrics 2020;146:e202000186. doi: 10.1542/peds.2020-00186.
31. Liu X, Tang J, Xie R, et al. Clinical and epidemiological features of 46 children <1 year old with coronavirus disease 2019 in Wuhan, China: a descriptive study. J Infect Dis 2020;222:1293–7.
32. Lu X, Zhang L, Du H, et al. Chinese Pediatric Novel Coronavirus Research Study Team. SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663–5.
33. Mark EG, Golden WC, Gilmore MM, et al. Community-onset severe acute respiratory syndrome coronavirus 2 infection in young infants: a systematic review. J Pediatr 2021;228:94–100.
34. Rabha AC, Oliveira Junior FL, Oliveira TA, et al. Clinical manifestations of children and adolescents with COVID-19: report of the first 115 cases from Sabara Hospital Infantil. Rev Paul Pediatr 2020;39:2020305.
35. Xia W, Shao J, Guo Y, et al. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. Pediatr Pulmonol 2020;55:1169–74.
36. Xiong XL, Wang KK, Chi SQ, et al. Comparative study of the clinical characteristics and epidemiological trend of 244 COVID-19 infected children with or without GI symptoms. Gut 2021;70:436–8.
37. Zachariah P, Johnson CL, Halabi KC, et al. Columbia Pediatric COVID-19 Management Group. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children’s hospital in New York City, New York. JAMA Pediatr 2020;174:e202430.
38. Zheng F, Liao C, Fan QH, et al. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. Curr Med Sci 2020;40:775–80.
39. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607.
40. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children with SARS-CoV-2 infection. N Engl J Med 2020;383:347–58.
41. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. Overcoming COVID-19 investigator, CDC COVID-19 response team. N Engl J Med 2020;383:334–46.
42. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with COVID-19 in New York City. New York. JAMA Pediatr 2020;174:e202430.
43. Meyer JS, Robinson G, Moonah S, et al. Acute appendicitis in four children with COVID-19. JAMA Pediatr 2020;174:e202430.
44. Parri N, Lenge M, Buonenso D. Children with COVID-19 in pediatric emergency departments in Italy. N Engl J Med 2020;383:187–90.
45. Zhou YH, Zheng KJ, Targer G, et al. Abnormal liver enzymes in children and infants with COVID-19: a narrative review of case-series studies. Pediatr Obes 2020;15:e12723. doi: 10.1111/jpo.12723.
46. American Association for the Study of Liver Diseases. Clinical insights for hepatology and liver transplant providers during the COVID-19 pandemic. Available at: https://www.aasld.org/about-aasld/covid-19-resources. Accessed March 1, 2021.
47. Adams H, Hübscher G. Systemic viral infections and collateral damage in the liver. Am J Pathol 2006;168:1057–9.
48. Anirvan P, Bharali P, Gogoi M, et al. Liver injury in COVID-19: the hepatic aspect of the respiratory syndrome—what we know so far. World J Hepatol 2020;12:1182–97.
49. Guan W-J, Ni Z-Y, Hu YU, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
50. Di Giorgio A, Nicastro E, Arnauboli S, et al. Health status of children with chronic liver disease during the SARS-CoV-2 outbreak: results from a multicentre study. Clin Res Hepatol Gastroenterol 2021;45:101610.
51. Kehar M, Ebel NH, Ng VL, et al. SARS-CoV-2 infection in children with liver transplant and native liver disease: an international observational registry study. J Pediatr Gastroenterol Nutr 2021;72:807–14.
52. Zhou YJ, Zheng KJ, Wang XB, et al. Younger patients with NAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. J Hepatol 2020;73:719–21.
53. Singh A, Hussain S, Antony B. Non-alcoholic fatty liver disease and clinical outcomes in patients with COVID-19: a comprehensive systematic review and meta-analysis. Diabetes Metab Syndr 2021;15:813–22.
54. Zheng KJ, Gao F, Wang XB, et al. Letter to the Editor: obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. Metabolism 2020;108:154244. doi: 10.1016/j.metabol.2020.154244.
55. Inamdar S, Benias PC, Liu Y, et al. Prevalence, risk factors, and outcomes of hospitalized patients with COVID-19 presenting as acute pancreatitis. Gastroenterology 2020;159:2226–8.
56. Alloway BC, Yaeger SK, Mazzaconaro RJ, et al. Suspected case of COVID-19 associated pancreatitis in a child. Radiol Case Rep 2020;15:1309–12.
57. Stevens JP, Brownell NF, Freeman AJ, et al. COVID-19-associated multisystem inflammatory syndrome in children presenting as acute pancreatitis. J Pediatr Gastroenterol Nutr 2020;71:669–71.
58. Suchman K, Raphael KL, Liu Y, et al. Acute pancreatitis in children hospitalized with COVID-19. Pancreatology 2021;21:31–3.
59. Malhotra A, Sturgill M, Whitley-Williams P, et al. Pediatric COVID-19 and appendicitis: a gut reaction to SARS-CoV-2? Pediatr Infect Dis J 2021;40:e49–55.
60. Rohni P, Karimi A, Tahatbaha RS, et al. Protein losing enteropathy and pneumatosis intestinalis in a child with COVID19 infection. J Pediatr Surg Case Rep 2020;64:101667.
61. Noda S, Ma J, Romberg EK, et al. Severe COVID-19 initially presenting as mesenteric ademopoe. Pediatr Radiol 2020;51:140–3.
62. Rajalakshmi L, Satish S, Naundhni G, et al. Unusual presentation of COVID-19 as intussusception. Indian J Pract Pediatr 2020;22:236.
63. Moazzam Z, Salim A, Ashraf A, et al. Intussusception in an infant as a manifestation of COVID-19. J Pediatr Surg Case Rep 2020;59:101533. doi: 10.1016/j.bepsc.2020.101533.
64. Martinez-Castaino I, Calabuig-Barbero E, Gonzalez-Piña J, et al. COVID-19 infection is a diagnostic challenge in infants with ileocecal intussusception. Pediatr Emerg Care 2020;36:e368. doi: 10.1097/pec.0000000000003255.
65. Makrinioti H, Mac Donald A, Lu X, et al. Intussusception in two children with SARS-CoV-2 infection in children. J Pediatr Infect Dis Soc 2020;9:504–6.
66. Alsabri M, Sakr M, Qaroomi S, et al. COVID-19 Infection in a child presenting with functional intestinal obstruction. Cureus 2020;12: e11448. doi: 10.7759/cureus.11448.
72. Gupta S, Kaushik A, Kest H, et al. Severe enteritis as the sole manifestation of novel coronavirus disease 2019 (COVID-19) in adolescent patients. *Case Rep Infect Dis* 2020;23:8823622.

73. Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut* 2020;70:725–32.

74. Booth A, Reed AB, Ponzo S, et al. Population risk factors for severe disease and mortality in COVID-19: a global systematic review and meta-analysis. *PLoS One* 2021;16:e0247461. doi: 10.1371/journal.pone.0247461.

75. Brenner EJ, Ungaro RC, gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020;159:481–91.

76. Singh S, Khan A, Chowdhry M, et al. Risk of severe coronavirus disease 2019 in patients with inflammatory bowel disease in the United States: a multicenter research network study. *Gastroenterology* 2020;159:1575–8.

77. Dolinger MT, Person H, Smith R, et al. Pediatric Crohn disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab. *J Pediatr Gastroenterol Nutr* 2020;71:153–5.

78. Sweeny KF, Zhang YJ, Crume B, et al. Inflammatory bowel disease presenting with concurrent COVID-19 multisystem inflammatory syndrome. *Pediatrics* 2021. Jan 7. doi: 10.1542/peds.2020-027763. Online ahead of print.

79. Kennedy NA, Lin S, Goodhand JR, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut* 2021. Apr 26. doi: 10.1136/gutjnl-2021-324789. Online ahead of print.

80. Belli LS, Fondevila C, Cortesi PA, et al. ELITA-ELTR COVID-19 Registry. Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with COVID-19: results from the ELITA/ELTR Multi-center European Study. *Gastroenterology* 2021;160:1151–63.

81. Rabiee A, Sadowski B, Adeniji N, et al., COLD Consortium. Liver injury in liver transplant recipients with coronavirus disease 2019 (COVID-19): U.S. multicenter experience. *Hepatology* 2020;72:1900–11.

82. Colmenaro J, Rodríguez-Perálvarez M, Salcedo M, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2021;74:148–55.

83. Becchetti C, Zambelli MF, Pascolo L, et al., COVID-LT group. COVID-19 in an international European liver transplant recipient cohort. *Gut* 2020;69:1832–40.

84. Goss MB, Galván NT, Ruan W, et al. The pediatric solid organ transplant experience with COVID-19: an initial multi-center, multi-organ case series. *Pediatr Transplant* 2021;25:e13868. doi: 10.1111/petr.13868.

85. Nikoupour H, Kazemi K, Arasteh P, et al. Pediatric liver transplantation and COVID-19: a case report. *BMC Surg* 2020;20:224.