

Gastrointestinal involvement in children with SARS-COV-2 infection: an overview for the pediatrician

Elena Chiappini¹, Amelia Licari², Marco Motisi³, Sara Manti⁴, Gian Luigi Marseglia², Luisa Galli³, and Paolo Lionetti³

¹University of Florence, Meyer Children's Hospital

²Fondazione IRCCS Policlinico San Matteo

³University of Florence

⁴UOC Genetics and Immunology Paediatrics

August 25, 2020

Abstract

Gastrointestinal symptoms are common findings in children with SARS-CoV-2 infection. Diarrhea and vomiting have been reported in about 8-9% of cases, reaching more than 20% in some studies. Children with gastrointestinal involvement appear to be younger than those without, but the severity of the disease seems to be similar between the two groups of subjects. Fecal shedding in children has been reported in 20-30% of children and has been observed both in those with and those without overt gastrointestinal involvement. Moreover, prolonged fecal elimination, lasting several days after negativization of real-time polymerase chain reaction assay on respiratory swabs, have been reported with variable frequency in children with SARS-CoV-2 infection. These observations raise the question regarding the possibility of oral-fecal transmission and the possible role of children in spreading the infection, particularly when they appear asymptomatic or with gastrointestinal symptoms but with no respiratory involvement, as well as during their convalescent phase.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), associated with the ongoing coronavirus disease 2019 (COVID-19) pandemic, is spreading at a remarkable high rate, with more than 5 million subjects infected worldwide. Children represented approximately 2% of all cases.¹ The available data suggest that mild forms are more frequent in children than adults, and the percentage of severe cases, requiring admission to intensive care unit and/or mechanical ventilation, accounts for about 1% of overall pediatric cases.¹ Few deaths have also been reported.¹ However, it is under debate whether this low percentage is due to lower susceptibility to infection among children with respect to adults or similar infection rates but higher proportions of asymptomatic cases. Since children with no symptoms or paucisymptomatic forms are less likely to be tested, exact population denominators are absent, and accurate estimates cannot be calculated.

The proportion of various symptoms reported in pediatric case-series varies, and it is also affected by the definition of the case, the number of diagnostic tests performed, and the study setting. A recent systematic review, including 18 studies and 1065 children, showed that the most frequently reported symptoms are cough, fever, pharyngitis, and rhinorrhea, with varying percentages among studies.² Other frequently observed symptoms were headaches, myalgia, rash, conjunctivitis, syncopal episodes, and gastrointestinal manifestations such as vomiting, diarrhea, abdominal pain, and difficulty in feeding. Kawasaki-like syndrome, probably representing a post-infectious inflammatory syndrome, is also reported.³ Hereby, we review and discuss the available literature regarding the gastrointestinal involvement in children with SARS-CoV-2 infection.

Gastrointestinal symptoms in children

The respiratory system appears to be the main target of SARS-CoV-2; however, numerous evidence supports the fact that the gastrointestinal tract and the liver may also be involved both in children as well as in adults.⁴ This involvement can be associated with isolated modifications of some laboratory parameters (for example, liver enzymes) or with overt symptoms. In adults, the reported incidence of diarrhea varies from 2% to 50% of cases, and the overall percentage of diarrhea was estimated to be 10.4%.⁵

In children, the available data are sparse, however gastrointestinal symptoms, including nausea, vomiting, diarrhea, and abdominal pain, seem to occur frequently. Diarrhea and vomiting have been reported in about 8-9% of cases, reaching more than 20% in some studies (Table 1). Therefore, although COVID-19 in children seems to have a milder course than in adults and respiratory symptoms are less frequently reported, the incidence of gastrointestinal symptoms is similar to that observed in adults.

Unfortunately, both in adult and pediatric studies, the characteristics of diarrhea are not usually reported, and information related to the total number of evacuations, consistency of the stools, and duration of symptoms is poor. On one study, diarrhea appeared 1 to 8 days after the onset of the disease, with a median of 3.3 days.⁴ Watery diarrhea appears to be more frequently reported. Bloody diarrhea, probably associated with SARS-CoV-2 colitis, has been described only in one adult patient so far.⁶ Few adult cases of esophagitis are also reported.⁷

Some children presented with diarrhea or vomiting as the first symptom of the disease, even before or in the absence of respiratory manifestations. For example, there are some case reports of infants or older children who developed fever and diarrhea as the only or main manifestation of the disease.⁸ Thus, it is currently discussed whether, in the course of an epidemic, diagnostic tests for SARS-CoV-2 in children presenting with diarrhea alone or associated with fever should be considered.⁹ Furthermore, the fact that, in some cases, gastrointestinal symptoms may precede systemic and respiratory ones support the hypothesis that the gastrointestinal system represents a possible route of viral invasion and transmission.

In adult case-series, gastrointestinal symptoms have been reported to be associated with more severe disease.^{7,10} In a systematic review, diarrhea was found to be more common in patients with severe forms of COVID-19 than those with the non-severe disease (5.8% vs. 3.5%, respectively) and patients with diarrhea, nausea and vomiting were more likely to develop acute respiratory distress or to require mechanical ventilation compared to patients without gastrointestinal symptoms (6.76% vs. 2.08%, $p = 0.034$). However, other studies did not confirm this finding with gastrointestinal symptoms occurring at a similar rate in patients with severe and not-severe forms.¹⁰ The discrepancies among study results may be influenced by several factors, including the variable proportion of patients with diarrhea observed in the various studies and by the fact that some antiviral drugs, likely used in more severe cases, include diarrhea as a possible adverse event (e.g., lopinavir/ritonavir). To date, a possible correlation between the presence of diarrhea and the severity of COVID-19 does not seem to be found in children.⁴ In a recent Chinese study on 244 SARS-CoV-2 infected children, authors compared disease severity between 34 (13.9%) children with at least one gastrointestinal symptom (diarrhea, nausea, vomiting, abdominal pain, decreased feeding) with those without gastrointestinal involvement. Patients with gastrointestinal symptoms were younger (14 vs. 86 months; $p < 0.05$) and were more likely to have a fever on admission (70.6% vs. 35.7%, $p < 0.05$), but no other significant differences were found between the two groups, including respiratory symptoms, the duration of RT-PCR positivity for SARS-CoV-2 and lung radiology findings.¹¹

As regards liver involvement, a modest increase in liver enzymes is well described in the pediatric population, with varying percentages among studies, ranging from 13% to 50%. In two pediatric studies reporting two datasets in Italy and China, overall including over 270 children, increased serum levels of aspartate aminotransferase (> 50 U/L) (20.4-50% of cases) were more frequently observed than increased in alanine aminotransferase serum levels (> 45 U/L) (13-35% of cases).¹² This data, together with the fact that the increase in transaminases is often associated with the increase in creatine kinase and lactic dehydrogenase serum levels, suggests that hypertransaminasemia may be an expression of myositis than liver damage in

many cases.⁴

However, in children, a severe increase in serum liver enzymes is considered a warning sign. This recommendation is mainly based on data obtained from adult studies that report increased serum liver enzymes being more frequent in severe COVID-19 cases (40-60%) than in mild or asymptomatic forms (18-25%).⁴ Abnormal bilirubin levels may also occur, although to a lesser extent than increases in alanine aminotransferase and aspartate aminotransferase.

The pathogenesis of liver damage in adults is complex and related to direct viral invasion, systemic inflammation, hepatic ischemia, and hypoxia. Liver involvement may be part of multiorgan failure in the context of a multisystem inflammatory disorder. Moreover, pre-existing liver disease and drug-related liver toxicity may play a role.¹³

ACE-2 expression may be enriched in cholangiocytes, indicating that SARS-CoV-2 might directly bind to these cells to dysregulate liver function. Gamma-glutamyltransferase, a biomarker for cholangiocyte injury, has been elevated in 30 (54%) of 56 patients with COVID-19 in one adult study.¹³

In pediatrics, however, it should be bared in mind that severe COVID-19 forms are exceptional and in children with SARS-CoV-2 infection and abnormalities in liver function tests, investigation for possible etiologies of liver or muscle damage other than SARS-CoV-2 should be considered.⁴

Pathogenesis of gastrointestinal symptoms

Intestinal involvement has many reasons. The angiotensin-converting-enzyme 2 receptor (ACE-2) and transmembrane protease, serine 2 (TMPRSS2), are key proteins in the cellular entry process of the virus. The co-expression of these two proteins in the same cell is essential for the entry of SARS-CoV-2.¹³ Like the type II alveolar cells in the lung, the glandular cells of the gastric, duodenal and rectal epithelium, and the enterocytes of the ileum and colon can express both proteins at a high level. The esophageal epithelium expresses ACE-2 at a lower level. ACE-2 is also expressed on the surface of hepatocytes, and to a greater extent, on the surface of cholangiocytes.

Although the specific mechanisms involved in diarrhea's pathogenesis are not fully understood, the infection is likely to alter intestinal permeability, with malabsorption by enterocytes. Furthermore, ACE-2 has been proposed to be involved in the absorption of dietary amino acids, regulating the expression of antimicrobial peptides, and promoting homeostasis of the intestinal microbiome. The mouse model knock-out for ACE-2 frequently develop colitis subsequently to SARS-CovV-2 infection, suggesting that the virus may cause enzymatic changes, increased susceptibility to intestinal inflammation and diarrhea.

Further studies are needed to clarify the mechanisms underlying diarrhea and to define the correlation between respiratory and gastrointestinal symptoms. The virus also appears to alter the intestinal microbiome even when only the respiratory mucosa is involved through the regulation of the mucosal immune system (the "gut-lung axis").⁴

Is fecal-oral transmission possible?

In several studies in pediatric and adult populations, the fecal elimination of SARS-CoV-2 was found to be prolonged for several weeks, which has led to speculating a possible fecal-oral transmission.^{14,15} The fecal-oral transmission route has also been previously demonstrated for other coronaviruses, such as MERS-CoV. However, it has been argued that the positivity of reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 on rectal swab or stool does not imply that it is vital and able to infect other subjects. A study by Wang et al. including 205 patients with SARS-CoV-2 infection (more than one thousand samples from blood, sputum, feces, urine, nasal swab, and other biological samples) is particularly noteworthy.¹⁶ Fecal samples were positive in 29% of cases; moreover, four samples revealed a vital virus after culture, possibly transmitting the infection.

In adults, RT-PCR positivity on stool samples in patients diagnosed with COVID-19 varies between 6 and 53.4% across studies. It is interesting that in some case-series, around 20% of the fecal samples resulted posi-

tive even after that RT-PCR on pharyngeal swab had turned negative.¹⁵ Therefore, a fecal-oral transmission might also be possible in asymptomatic or convalescent patients.

Similar findings have been observed in children. In a Chinese study, 8 out of 10 children were still positive for RT-PCR on the rectal swab for a few days after RT-PCR negativization on nasopharyngeal swabs.¹⁶ Some authors suggested that serial rectal swabs should be performed over time before declaring the child non-infectious. In a recent case series, including 22 children with documented SARS-CoV-2 infection, fecal RNA shedding was observed in 68% of patients independently from gastrointestinal symptoms. The estimated positivity on day 14 from symptom onset was 52% for a nasopharyngeal swab and 31% for stool swab.¹⁷ In another Italian study, two pediatric cases with RT-PCR positivity on stool were reported. The pediatric literature available at publication date was reviewed, including overall 13 children affected by SARS-CoV2 infection with a positive RT-PCT on the stool and/or rectal swab.⁹ Authors suggest that negativity in both nasopharyngeal and stool samples might be a standard requirement for the cessation of mandatory isolation.

Conclusion

Gastrointestinal symptoms are common findings in children with SARS-CoV-2 infection. Moreover, fecal shedding in asymptomatic children and prolonged fecal elimination, lasting several days after negativization of RT-PCR on respiratory swabs, have been reported with variable frequency in children with COVID-19. All these observations raise the question regarding the role of children in spreading the infection, in particular when they appear to be asymptomatic or with gastrointestinal symptoms and no respiratory involvement, as well as during their convalescent phase.

References

1. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report (MMWR). Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. Available at the website site web: www.cdc.gov/mmwr. Last accessed 2020 May, 15.
2. 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, April 22. Online ahead of print.
3. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020 May 13. Online ahead of print.
4. Matthai J. Coronavirus Disease (COVID-19) and the Gastrointestinal System in Children. *Indian Pediatr*. 2020, Apr 12. Online ahead of print.
5. D'Amico F, Baumgart DC, Danese S, et al. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. *Clin Gastroenterol Hepatol*. 2020, Apr 8. Online ahead of print.
6. Hosoda T, Sakamoto M, Shimizu H, Okabe N. SARS-CoV-2 enterocolitis with persisting to excrete the virus for approximately two weeks after recovering from diarrhea: A case report. *Infect Control Hosp Epidemiol*. 2020;41:753-754.
7. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut*. 2020;69:997-1001.
8. Liguoro I, Pilotto C, Bonanni M, et al. SARS-COV-2 infection in children and newborns: a systematic review. *Eur J Pediatr*. 2020, May 18. Online ahead of print.
9. Donà D, Minotti C, Costenaro P, et al. Fecal-oral transmission of Sars-Cov-2 in children: is it time to change our approach? *Pediatr Infect Dis J*. 2020 Apr 16. Online ahead of print.
10. Song Y, Liu P, Shi XL, et al. SARS-CoV-2 induced diarrhoea as onset symptom in patients with COVID-19. *Gut* 2020;69:1143-1144.
11. Xiong X, Wong K, Chi S, et al. Comparative Study of the Clinical Characteristics and Epidemiological Trend of 244 COVID-19 Infected Children With or Without GI Symptoms. *Gut* 2020 May 19. Online ahead of print.
12. Parri N, Lenge M, Buonsenso D, et al. Children With Covid-19 in Pediatric Emergency Departments

in Italy. *New Engl J Med* 2020 May,1. Online ahead of print.

13. Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. *J Gastroenterol Hepatol* 2020;35:744-748
14. Chen C, Gao G, Xu Y, et al. SARS-CoV-2–Positive Sputum and Feces After Conversion of Pharyngeal Samples in Patients With COVID-19. *Ann Intern Med.* 2020 Mar 30;M20-0991.
15. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens *JAMA* 2020;e203786
16. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent faecal viral shedding. *Nat Med* 2020;26:502-505.
17. De Ioris MA, Scarselli A, Ciofi Degli Atti ML, et al. Dynamic Viral SARS-CoV-2 RNA Shedding in in Children: Preliminary Data and Clinical Consideration of Italian Regional Center. *J Pediatric Infect Dis Soc* 2020 May 23. Online ahead of print.

Table 1. Proportions of subjects presenting with vomiting or diarrhoea reported in pediatric case-series including at least ten children (modified and updated from ref. 8)

Author	Total	vomiting	diarrhoea	vomiting	diarrhoea
	(n)	(n)	(n)	(%)	(%)
CDC-MMWR	291	31	37	10,7	12,7
Xiong	244	23	15	9,4	6,1
Lu	171	15	11	8,8	6,4
Garazzino	110	9	22	8,2	20,0
Parri	100	10	9	10,0	9,0
De Ceano Vivas	58	9	7	15,5	12,1
Tagarro	41	2	2	4,9	4,9
Qiu	36	2	2	5,6	5,6
Wang	34	0	0	0,0	0,0
Zhang	34	4	4	11,8	11,8
Wang	31	3	0	9,7	0,0
Chen	31	0	0	0,0	0,0
Zheng	25	3	2	12,0	8,0
Xia	20	3	1	15,0	5,0
Feng	15	0	0	0,0	0,0
Cai	10	0	0	0,0	0,0
Xu	10	3	0	30,0	0,0
Tan Y.	10	1	0	10,0	0,0
TOTAL	1271	118	112	9,3	8,8