

## REVIEW ARTICLE

## Gastrointestinal and Hepatobiliary Manifestations of COVID-19 in Children: A Review

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### Abstract

**Background:** Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is shaking the world heavily. SARS-CoV-2 (COVID-19) infection has a wide variety of presentations as it affects almost every system of body. Gastrointestinal and hepatobiliary symptoms are frequently overlooked especially in children.

**Objectives:** The purpose of this review was to discuss the gastrointestinal and hepatobiliary presentations of COVID-19 in children and compare with non-gastrointestinal presentations.

**Methods:** This study was a narrative review. Recent available literature was searched by keywords. The most recent information from relevant articles were collected and reviewed. This write up was compiled after the review of articles from the last one and half year.

**Results:** About 50.0% symptomatic children with COVID-19 had gastrointestinal manifestations. COVID-19 with gastrointestinal symptoms had delayed diagnosis, delayed hospitalization and worse outcome in compare with Covid-19 with non-gastrointestinal symptoms.

**Conclusion:** Vomiting, diarrhoea, abdominal pain, anorexia, nausea are common gastrointestinal manifestations in children with COVID-19. Elevated transaminasemia is not uncommon.

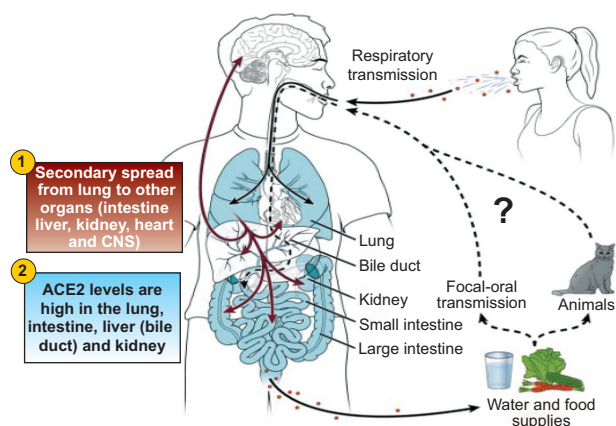
**Keywords:** COVID-19, Children, Gastrointestinal, Hepatobiliary

### Introduction

Coronavirus is an enveloped, single stranded positive-sense RNA virus of the Coronaviridae family, order Nidovirales. It is a zoonotic virus which infects both humans and animals. There are only 7 human Corona viruses identified, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) is the last one. SARS-CoV-2 belongs to the beta Coronavirus family.<sup>1</sup> SARS-CoV-2 is a round or oval-shaped virus with a diameter of 60-100 nm and genomic size 29.9 kb.<sup>2</sup> Its nucleocapsid is buried inside a phospholipid bilayer and covered by two different types of protein. Spike protein gives its crown appearance.<sup>2</sup>

SARS-CoV-2 was first isolated in Wuhan, Hubei province of China.<sup>3,4</sup> First outbreak was on December 19 as a respiratory pathogen that's why the World Health Organization (WHO) named this virus as Coronavirus disease 2019 (COVID-19).<sup>5,6</sup>

By the time it has been evolved into a pandemic, involving almost all countries in the world, threatening the lives of almost all age group populations. COVID-19 infected over 75 million cases and over 1.6 million deaths since the start of the pandemic.<sup>7</sup> It has created tremendous bad effect on global health, economy and social life.



**Figure 1:** Modes of transmission of SARS-CoV-2 in humans.<sup>8</sup>

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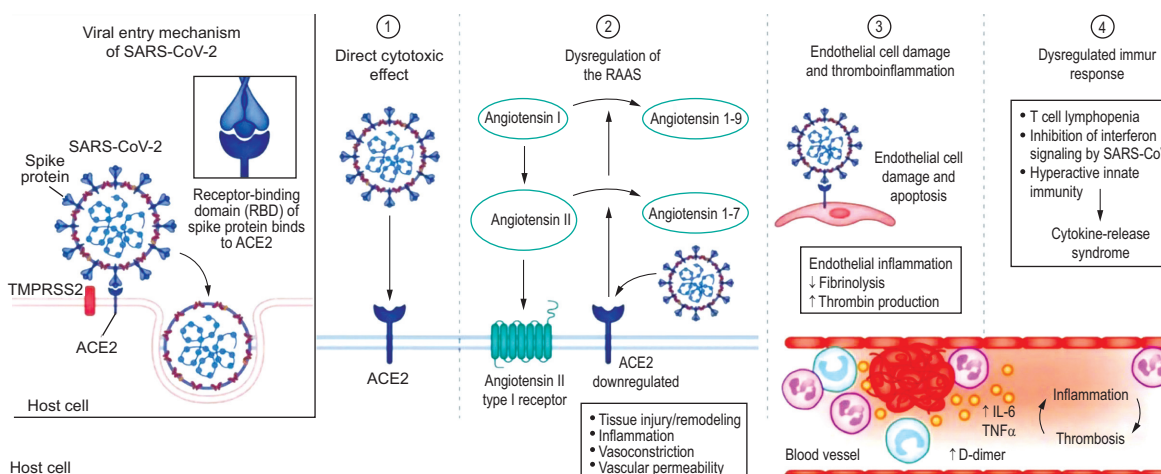
**Modes of Transmission:** SARS-CoV-2 is transmitted from person to person by respiratory droplet, direct contact, and faeco-oral transmission (figure 1).<sup>2,8,9</sup> Incubation period is 2 to 14 days.<sup>10</sup> All ages are susceptible to COVID-19 infection. The youngest baby infected with COVID-19 was preterm 26 weeks gestational age.<sup>11</sup>

**Pathogenesis:** SARS-CoV-2 primarily infects the epithelium of upper respiratory tract. Coronavirus spike protein engages Angiotensin-converting enzyme-II (ACE II) as an entry receptor and cellular serine protease TMPRSS2 or other proteases, facilitate the cellular entry. After entry into the cell, viral RNA genome is released into the cytoplasm and is translated into polyprotein and structural proteins, which triggers the viral replication leading to viremia. ACE-II receptor is expressed in the following cells such as type 2 pneumocyte in the lungs, nasal goblet secretory cells, hepatocyte, cholangiocytes, esophageal keratinocytes, gastrointestinal (GI) epithelial cells, pancreatic beta cells, proximal renal tubules, and podocytes. Coronavirus exerts its notorious effect on targeted tissue by direct viral toxicity, endothelial cell damage, thromboinflammation, dysregulation of the immune response and dysregulation of the renin-angiotensin-aldosterone system. This explains how COVID-19 causes multiple organ injury (figure 2).<sup>8,12,13</sup>

Evidence of GI COVID-19 infection is provided by the isolation of virus RNA from GI epithelial cell and intracellular staining of viral nucleocapsid protein. COVID-19 causes dysfunction of the enterocyte of the colon and ileum.<sup>14</sup> Drug that causes modulation of pH and by interfering with mucosal immunity can potentially prolong the inflammation.<sup>15</sup>

The mechanisms postulated for causation of diarrhoea in COVID-19 infection are: (1) direct virus entry through ACE-2 receptor causing malabsorption, unbalanced intestinal secretion, and activated enteric nervous system; (2) direct/indirect damage to the intestinal epithelium by the inflammatory response; (3) antibiotic and/or antiviral drug-induced intestinal dysbiosis; (4) virus-induced disorders of the intestinal flora; (5) "gut-lung axis" disturbances wherein respiratory flora alteration affects the digestive system by immune regulation.<sup>16</sup>

Studies have shown that COVID-19 can be detected in stool up to 83% of patients.<sup>17</sup> This faecal shedding of viral RNA can last for several weeks after diagnosis.<sup>18</sup> This can be a source of faeco-oral transmission of COVID-19 especially for infants and children who are not toilet trained. It is a special concern for community spread in children in child daycare centres, schools and also in the home.<sup>19</sup>



**Figure 2:** SARS-CoV-2 enters host cells through interaction of its spike protein with the entry receptor ACE2 in the presence of TMPRSS2 (farleft). Proposed mechanisms for COVID-19 caused by infection with SARS-CoV-2 include (1) direct virus-mediated cell damage; (2) dysregulation of the RAAS as a consequence of downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thromboinflammation; and (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNF $\alpha$ .<sup>13</sup>

**Gastrointestinal and hepatobiliary manifestations:** More than 90% of children with COVID-19 are asymptomatic and mild to moderate cases. The severity is less than in the adults.<sup>20</sup> In adults, more than 50% patients have GI symptoms.<sup>18</sup> Paediatric patients experience gastrointestinal symptoms almost similar to that of adults.<sup>18,21,22</sup> Paediatric cases can present with nausea, vomiting, abdominal discomfort, abdominal pain and diarrhoea along with or without fever, cough, respiratory distress, breathlessness, or other symptoms. About 10% of patients presented with gastrointestinal symptoms alone without respiratory features.<sup>21</sup>

A recent paper by Tian et al reviewing studies to date on gastro-intestinal manifestations and COVID-19 infection investigated the incidence of specific symptoms in both children and adults. Diarrhoea was the most common symptom in both children and adults, lasting approximately four days. There were a higher proportion of children who exhibited vomiting compared to adults. Furthermore, other symptoms noted were anorexia (39.9%–50.2%), vomiting (3.6%–66.7%), nausea (1.0%–29.4%), abdominal pain (2.2%–6.0%), and gastro-intestinal bleeding (4.0%–13.7%).<sup>22</sup> Additional studies have characterised similar results amongst COVID-19 patients.<sup>23-33</sup> Hoang et al. had different findings like abdominal pain, diarrhea in 6.5% and vomiting, nausea in 5.4% children.<sup>11</sup>

A systematic review and meta-analysis by Mao et al showed that, prevalence of digestive symptoms were 15% with nausea or vomiting, diarrhoea, and loss of appetite being the three most common symptoms. Subgroup analysis showed patients with severe COVID-19 had higher rates of gastrointestinal symptoms.<sup>21</sup>

Yasuhara et al found, 13.4% and 6.3% children experienced diarrhea and vomiting respectively.<sup>34</sup>

Patients with GI symptoms experience a higher rate of fever, fatigue, shortness of breath, headache and worse outcome.<sup>21,35</sup> Patients with the GI symptoms have the longer hospital stay, vice versa they have delayed hospital admission.<sup>21,36</sup>

Diarrhoea is usually loose watery, non-bloody.<sup>37</sup> The first critically ill paediatric patient, was admitted with intermittent diarrhoea and vomiting.<sup>38</sup> Haematochezia/intussusception may be a presentation of COVID-19 infection manifestation.<sup>39</sup> Bloody diarrhoea may also be due to concomitant clostridium difficile infection.<sup>40</sup>

Children may present with severe acute abdominal pain mimicking acute appendicitis.<sup>41</sup> Anosmia, dysgeusia may be concomitantly present.<sup>14</sup>

Multisystem inflammatory syndrome in children (MIS-C) due to COVID-19 may also present with abdominal pain, vomiting, diarrhoea, elevated transaminases with or without other organ failures.<sup>43</sup> A recent systematic review by Yasuhara et al found that, 15% presented as MIS-C and 53% symptoms were gastrointestinal symptoms and older children have more chance to develop MIS-C.<sup>34</sup>

Another systematic review by Radia et al showed, patients with MIS-C were noted to have a high frequency of gastrointestinal symptoms (71%) including abdominal pain (34%), diarrhoea (27%) and vomiting (25%).<sup>44</sup> Hoang et al had similar findings.<sup>11</sup> Abramset al found much higher prevalence of gastrointestinal symptoms (87%) in MIS-C than the other study.<sup>45</sup>

Nausea, vomiting may also occur due to hepatic involvement, evidenced by jaundice, mildly raised ALT, AST (15-50%).<sup>46-48</sup> Mao et al found, children with COVID-19 had a similar risk of liver injury to that of adult patients (9% [95% CI 3-21] vs 21% [9-43];  $p=0.0516$ ). However, children were less likely to present with increased ALT and AST compared with adult patients.<sup>21</sup> Yasuhara et al found, 16.4% and 22.2% children have raised ALT and AST respectively.<sup>34</sup>

In severe cases, ALT/AST maybe high, which indicates it may be due to subsequent drug-induced, sepsis, or shock-related liver injury.<sup>8</sup> In the presence to the abnormal liver function test or recent development of encephalopathy, concomitant other liver diseases like hepatitis B, hepatitis C, autoimmune hepatitis (AIH), non-alcoholic steatohepatitis (NASH), chronic liver disease should be considered, especially when ALT level is more than 500 IU/L.<sup>9</sup>

Postmortem finding of the liver biopsy showed moderate microvesicular steatosis and mild lobular and portal activity inflammation of the cholangiocyte.<sup>49</sup>

Abdominal pain may result from acute pancreatitis evidenced by raised amylase, lipase.<sup>18</sup> On imaging study, ascites and evidence of ileitis may be found.<sup>50</sup> In young infants, poor feeding along with other symptoms are modes of the presentation.<sup>37</sup> The drug

used during the treatment of COVID-19 also can cause anorexia, nausea and vomiting. Prolong anorexia, nausea, vomiting, anosmia, dysgeusia and acute onset pro-inflammatory cytokines lead to sarcopenia and malnutrition.<sup>51</sup>

Investigations like stool routine examination, OBT (occult blood test) may be abnormal (9%). Stool may remain positive for viral RNA several weeks after the nasopharyngeal swab become negative. In bloody diarrhoea, Clostridium difficile, intussusception should be ruled out.<sup>40</sup> In patients with severe abdominal pain, ultrasonography and CT scan should be considered. This may show lymphadenopathy and the presence of inflammatory fat throughout the mesentery with thickening of the terminal ileum. It will also help to rule out acute pancreatitis and intussusception.<sup>41</sup>

### Conclusion

Vomiting, diarrhoea, abdominal pain, anorexia, nausea are common gastrointestinal manifestations in children with Covid-19. Elevated transaminasemia is not uncommon. So, during the evaluation of a child in this pandemic situation, we should not forget about the gastrointestinal and hepatobiliary presentation of COVID-19, as it influences both diagnosis and outcome.

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