



Clinical Management of Appendicitis and Inflammatory Bowel Disease in Children with COVID-19

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Abstract

The novel coronavirus that swept the world into a pandemic in 2019 has affected many aspects of health care. COVID-19 has infected about 263 million people across the globe and led to the death of 5.2 million people. Its impact on various organs is still vague and requires further research. The increase in hospital visits and administrations has accordingly increased exposure and risk of obtaining the coronavirus. Patients previously hospitalized and being treated with immunosuppressants tend to be very susceptible to serious respiratory infections from the novel virus. Amongst the diseases that require hospitalization are ulcerative colitis and appendicitis. Hospitalization from such diseases inevitably increases the risk and exposure to COVID-19 infection. This study analyzed the management and procedures taken in patients with inflammatory bowel disease and appendicitis during the COVID-19 pandemic. Similarly, the effects of the pandemic on the pediatric ward and admitted children were also discussed and compared.

Keywords: COVID-19, Pandemic, Inflammatory Bowel Disease, Children, Pediatrics

1. Context

In December 2019, the World Health Organization (WHO) named the disease caused by a newly discovered coronavirus as COVID-19. Subsequently, COVID-19 had spread globally within months and has caused a serious pandemic (1, 2). The WHO has reported around 263 million confirmed COVID-19 cases and more than 5.2 million deaths (3).

The pandemic has had direct and indirect effects on all parts of the health care system and has led to fundamental changes in clinical decisions (4). The high in-patient flow demands hospital management and challenging decisions to choose the most appropriate approach for patients that requires intensive care. The unnecessary hospitalizations expose the patients to COVID-19, and wrongful discharge can endanger the life of patients (5). The prevalence and burdens of other chronic inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) and Crohn's disease (CD), has grown in the previous decades, especially in newly industrialized countries (6). The COVID-19 pandemic affects anxiety, depression, or psychological symptoms in both CD and UC patients (7).

Although immunosuppressants are a common treat-

ment for IBDs and are in favor of controlling inflammatory effects of COVID-19, several other treatments, including corticosteroids, lopinavir/ritonavir, hydroxychloroquine, oseltamivir, etc. were also used to treat this novel disease (8). On the other hand, the essential hospitalization during administration and a decline in the immune system increase the risk of exposure to infection as well (9-11). Therefore, although IBDs do not influence COVID-19, more efficient management would be required to pass the pandemic and prevent the effects of IBDs on different societies worldwide.

Appendicitis is an obstructive gastrointestinal tract due to bacterial growth or mucus production (12). Acute appendicitis (AA) is one of the most urgent surgical conditions among children. COVID-19 has caused significant delays in all usual, essential, and even urgent visits and provided several troubles (13). On the other hand, the observed differences between adults and children in the prevalence and difficulties of management would result in the demand for novel protocols to reduce the risk of COVID-19 alongside providing the most accessible health care (14). However, there are many contradictions in this case, which have shown it to be either unchanged (15), increased (16), and in some articles, decreased several times compared to

the previous year (17).

Here, we aimed to review the management studies on appendicitis and IBD that had been conducted during the COVID-19 pandemic to evaluate the applied methods. We also analyzed the difference between children and adults and the effects of the pandemic on appendicitis in pediatric wards.

2. UC and COVID-19

2.1. Difference Between Adults and Children with COVID-19 Infection

The risks and difficulties of the management of adults and children with UC have several differences. Although the risk of COVID-19 in adults with IBD (AIBD) is significantly more than in children, the effects of COVID-19 on children with IBD (CIBD) are relatively more difficult and extensive (14). Therefore, different recommendations suggest that the children would require a higher dose of biological agents and immunomodulators to achieve favorable outcomes (18). Fortunately, this situation would provide an appropriate condition to control both the cytokine storm of COVID-19 and the adverse effects of IBD symptoms (19).

2.2. Management of UC Occurring with COVID-19

The health care systems have to provide several procedures to follow the CIBDs. First, it is essential to reduce their hospitalization and restrict the clinical session to the inevitable procedures. The staff should obey the pandemic protocols and use surgical masks to mitigate risks related to COVID-19 exposure (20). Besides, full-time caregivers are required to consider their hygiene and supervise the treatment procedure (21). Although the vaccination of both adult and pediatric patients is important, protecting children against respiratory infection is of great importance. Therefore, complete childhood vaccination, including influenza and pneumococcus, is recommended (22). On the other hand, some routine drugs, such as 6-MP, prednisone, azathioprine, and methotrexate, face a contradiction in CIBDs with positive COVID-19 test (23).

3. Appendicitis and COVID-19

3.1. Pathophysiology of Appendicitis

The etiology of appendicitis is multifactorial (eg, fecaliths, foreign bodies, malignancy and tumors, lymphoid hyperplasia, and parasites). The appendix in the neonatal period is about 4.5 cm long. At the age of 1 - 2 years, increment in susceptibility to inflammation can be detected due to the appendix becoming similar to adults. In young

children, the omentum is undeveloped. For that reason, it is not able to limit the purulent material in perforation. Therefore, diffuse peritonitis after perforation in young children is more likely (24).

The location of obstruction can be at any point. The stimulation of visceral afferent thoracic nerves (8th - 10th) causes peri-umbilical pain that usually lasts 5 hours (1st stage). When the intraluminal pressure starts to increase, the perfusion of the appendiceal wall decreases because of arterial insufficiency (2nd stage). In the next step, tissue ischemia and compromised mucosa can be detectable (3rd stage). The invasion of bacteria is predictable in the luminal wall, leading to transmural inflammation (4th stage). As the transmural inflammation develops beyond the appendix, the adjacent organs and parietal peritoneum become inflamed. In the final stage, the pain perception moves from the peri-umbilical to the right lower quadrant in the abdominal region. The associated symptoms, including anorexia, fever, nausea, and vomiting, can be detected (22, 25). Considering all the above, mortality and morbidity, including wound infection rate and intra-abdominal abscess rate, diagnosing AA, perforation rate in children is similar to those in adults (26). Raised amount of serological reaction to fecal calprotectin and microbial antigens are noticeable in both UC (ulcerative colitis) and CD (Crohn's disease) patients. The combination of these landmarks provides noninvasive and useful tools for the diagnosis of inflammatory bowel disease (IBD) (27). Fecal calprotectin is regarded to be an accurate examination for ruling out (IBD) in youths with chronic gastrointestinal manifestations in specialized health care for additional diagnostic work-up, with a low danger of missing youth with IBD (28). A significant increase in fecal calprotectin was found in IBD patients. Fecal calprotectin links with fecal 111 indium-labeled neutrophils, indicating that fecal calprotectin is obtained from these neutrophils (29).

3.2. Difference Between Adults and Children with COVID-19 Infection

Some studies have indicated that children are more susceptible to gastrointestinal symptoms of COVID-19 than adults. Among these symptoms, diarrhea is the most prominent in both adults and children (30). Compared with adults, children seem to get a milder COVID-19 infection and mostly represent common adverse effects of respiratory tract infections, such as cough and fever. Also, about 20% of COVID-19 positive children are asymptomatic carriers (31). On the other hand, approximately 20% of symptomatic children show serious gastrointestinal adverse effects of COVID-19 (32, 33).

3.3. Management of Appendicitis Occurring with COVID-19

COVID-19 significantly impacted diagnostic IBD practice. Recovery, planning, and funding are critical to reducing secondary morbidity. Pediatric centers face several challenges in medical fields, such as management, treatment, and the effects of COVID-19 on IBDs (34). While the pandemic affects children's lifeless than others, it has made major changes in the management of different childhood disorders to adult protocols (35). Considering the fast spread of COVID-19, some health care providers decided to develop non-operative management (NOM) (36). Specifically, this procedure is regarded as a successful one for controlling the aerosolization of infectious particles, such as COVID-19, during an appendectomy (37). However, recent findings have shown that the virus would not exist in the peritoneal fluid. Therefore, practitioners should be aware of the advantages and disadvantages of the procedures that they apply, and multiple factors are required to be considered for an appendectomy or NOM during the COVID-19 pandemic (38).

Another challenge is that the diagnosis of appendicitis, concurrent with COVID-19, would become complicated due to rare cases with unusual symptoms (39). Unfortunately, children are susceptible to these events. A study in South Asia revealed that after COVID-19, physicians prefer to use NOM more than before to treat AA. Some studies challenged the procedure whether this procedure is effective enough, but COVID-19 forced medical caregivers to employ NOM as an alternative treatment since the burden of infection still exists. This alteration in the usage of NOM may remain after the pandemic since the economic recovery is probably slower than expected (40). A recent study conducted by Colvin and Lawther revealed that almost all AA cases treated with antibiotic therapy (one of the novel NOMs) achieved complete outcomes, but using these procedures for patients with CA decreases the efficiency of this treatment lower than 50%. Therefore, early hospitalization of AA cases would prevent the incidence of CA and ascend the NOM achievements (41).

Evaluation of children with appendicitis could be challenging, and different strategies have been developed to upgrade the precision of pre-operative diagnosis. Ultrasound and computed tomography (CT) are extensively used, but they have remained controversial in several studies. Although CT scan is superior to ultrasound in precision for diagnosis of appendicitis, the ionizing radiation (from CT) and risk of radiation-induced malignancy (RIM) are some particular concerns in children (42). MIS-C can significantly influence the diagnosis of appendicitis, post-operative recovery, and prevention of further infections. As a result, when a pediatric patient comes to the clinic

with appendicitis during the pandemic, the surgeons need to be familiar with all of the features of MIS-C (43).

Application of appropriate management protocols, such as NOM, or using prior practice strategies in the best way for AA, can remarkably prevent further damages (44). However, surgery has been the choice of several practitioners for some cases with complicated appendicitis (CA) during the pandemic because the surgeons tend to decrease the hospitalization of pediatrics and the exposure to COVID-19 (15). In possible situations, low-intensive surgeries, such as laparoscopy, would decrease both the term of hospitalization and exposure to further infections (45).

3.4. Impact of COVID-19 on Appendicitis in Children

The investigation of complex appendicitis incidence during the COVID-19 indicated no difference among self-quarantined children (46). But the, other studies have reported a higher rate of CA, hospitalization, and longer procedures in children with AA (47). Considering the fear of COVID-19, Demir et al. suggest that late arrival at hospitals would cause an increase of CA cases (48). Also, a retrospective cohort study showed that the number of children with perforated appendicitis (PA) in the pediatric surgery service had remarkably increased during the pandemic. Since a delay in presentation is notably related to PA, it has been concluded that the higher rate of children with PA is associated with delays in health care that are mostly caused by hesitance to seek care due to fear of exposure to COVID-19 (49). However, there is a chance that the incidence of multi-system inflammatory syndrome in children (MIS-C) caused by COVID-19 affects these outcomes (50). Some COVID-19 positive children that were admitted to the hospital with abdominal pain, fever, and evidence of MIS-C could be diagnosed as appendicitis cases. For example, an inflamed lymph node in the iliac fossa caused by COVID-19 would mimic AA and deceive the physician (51).

Certain receptors are located at the end of the ileum, which are candidates for viral entry. Therefore, when ileitis has been proven by clinical diagnostic procedures, we still have to confirm the etiology of this complication (resulting from the viral entrance through receptors of angiotensin-converting-enzyme-2 or lumen obstruction) (52). Also, as we know much evidence about clinical manifestations of adults with COVID-19, often our information about children is limited to mild cases except for some cases that show evocative of Kawasaki and MIS-C (53). These two complications are related to vasculitis of the appendicular artery. Also, other reports showed that no fecaliths were observed in appendectomy cases (45). Accordingly, vasculitis would be an important pathogenic mechanism in this condition. It is necessary to perform several tests and imaging for accurate diagnosis and management of

the condition, though they are limited during the COVID-19 pandemic (43).

Recent reports have revealed that MIS-C could be a fatal complication in COVID-19-positive children. MIS-C can involve many organs, like the gastrointestinal tract. Clinically, the symptoms may indicate AA. Therefore, further investigation is required to rule out this condition. Centers for Disease Control and Prevention and World Health Organization have published preliminary case definitions for MIS-C (54, 55). As a result, MIS-C should be differentiated from appendicitis when the patient presents with abdominal pain (30).

Although we discussed the downstream effects of the COVID-19 pandemic on appendicitis and how its complications can mimic appendicitis symptoms, the direct effects of the virus on clinical manifestations of AA are still questionable. This relation may be crucial in the management and treatment of these cases (39). A few cases of concomitant COVID-19 with AA were explained during the pandemic. Some COVID-19 positive patients manifest the typical symptoms of AA, including abdominal pain, leukocytosis, and focal tenderness. But there are rare cases with unusual signs, like leukopenia, elevated CRP, and no diffuse tenderness, rebound tenderness or guarding. It should be noted that there is insufficient evidence that COVID-19 caused these manifestations (39). A single-center study in Germany confirmed that the frequency of PA in COVID-19 negative children has increased during the pandemic (2).

3.5. Environmental Changes

Like every pandemic, the COVID-19 has had significant consequences on the world. Furthermore, multiple governments have employed different strategies to encounter this disease since the virus became a global problem. These actions have included severe stay-at-home orders, restrictions on traveling, wearing masks, and other tough health policies. All of these factors contributed to the increment of fear about this novel virus and made difficult challenges related to the disease. The point is that these complications may interrupt the process of early admission to the hospital; thus, a mild disease can progress to a higher stage and lead to more severe problems (49).

Social life has significantly changed over the pandemic (56). COVID-19, like an emerging disease, influenced multiple aspects of human life. In addition to effects on social life and economics, hospitalization protocols have improved to facilitate the situation according to the pandemic difficulties (40).

4. Conclusions

In conclusion, the management of UC and appendicitis during the COVID-19 pandemic was brought to attention and analyzed from a variety of perspectives. It was noted that although adult patients with UC tend to have a higher risk for COVID-19, children with UC signify a greater and more severe set of symptoms. As a primary methodology, hospitals are urged to operate only on inevitable patients and thus conformed to discharging or admitting those with non-critical surgical needs. This ultimately increased exposure and susceptibility to COVID-19 infection. Respiratory tract infection prevention via vaccination was deemed to be crucial in children in order to protect them from various pathogenic organisms and diseases.

As for appendicitis, children showed greater susceptibility to gastrointestinal disorders, such as diarrhea, fever, and cold. However, it was also depicted that adults expressed a greater severity of the same symptoms. As depicted, the symptoms in adults and children varied and required different treatment plans. As some studies have shown, COVID-19 infection in pediatric patients causes fatal complications with gastrointestinal diseases, including appendicitis.

Courses of treatment and managing patient symptoms are important stages in helping patients with diseases. Diagnostic criteria can vary and become difficult to apply when diseases come in complex multilevel forms and show a broad spectrum of symptoms. The novel coronavirus that has now resulted in a pandemic can affect various organs throughout the human body. This makes diagnostic, treatment, and recovery plans susceptible and ultimately put the patient in a fatal position. Understanding the effects of this virus on each organ and thus, is an inevitable requirement for physicians and health care workers.

Footnotes

Authors' Contribution: Study concept and design: M.R.; Acquisition of data: M.R., D.A, M.S., H.P., A.H., M.A.; Analysis and interpretation of data: M.R., D.A, M.S., H.P., A.H., M.A.; Drafting of the manuscript: M.R., D.A, M.S., H.P., A.H., M.A.; Critical revision of the manuscript for important intellectual content: A.H.; Statistical analysis: M.R., D.A, M.S., H.P., A.H., M.A.; Administrative, technical, and material support: M.R., D.A, M.S., H.P., A.H., M.A.; Study supervision: M.R.

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