© Pediatr Med Rodz 2022, 18 (1), p. 7–17
DOI: 10.15557/PiMR.2022.0001

Received: 22.12.2021
Accepted: 07.02.2022
Published: 31.05.2022

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Abdominal pain and appendicitis in children during the COVID-19 pandemic – do we need to be especially careful?

Ból brzucha i zapalenie wyrostka robaczkowego u dzieci w czasie pandemii COVID-19 – czy trzeba zachować szczególną ostrożność?

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Abstract

COVID-19 (coronavirus disease 2019) in children is relatively mild, so it is easy to make a misdiagnosis in the early stages if it presents only with respiratory symptoms. At the time of the pandemic, testing for SARS-CoV-2 is important in all paediatric patients who have fever and acute abdominal pain with diarrhoea or vomiting, to differentiate acute COVID-19 or possible multisystem inflammatory syndrome in children (MIS-C) from acute appendicitis, and thus avoiding unnecessary surgery. On the other hand, early accurate diagnosis and consequent appropriate surgical and antibiotic treatment of appendicitis are important because they can prevent complications such as abscess formation and other postoperative complications. Delayed diagnosis can lead to significant morbidity that can outweigh the damage caused by COVID-19 alone. The fact that at the time of the COVID-19 pandemic radiological examination also has its limitations and can very often show a false-positive finding in children with MIS-C must also be taken into account. It is very important that paediatric surgeons are aware of the gastrointestinal manifestations of acute COVID-19 or MIS-C, and are able to distinguish this new entity from the surgical pathologies it often mimics.

Keywords: COVID-19, SARS-CoV-2, MIS-C, children, abdominal pain, acute abdomen, appendicitis

Streszczenie

COVID-19 (*coronavirus disease 2019*) u dzieci przebiega stosunkowo łagodnie, stąd łatwo o błędne rozpoznanie we wczesnym stadium choroby, jeżeli stwierdza się wyłącznie objawy ze strony układu oddechowego. W okresie pandemii istotne znaczenie ma wykonywanie testów na obecność SARS-CoV-2 u wszystkich pacjentów pediatrycznych, u których występują gorączka i ostry ból brzucha z towarzyszącą biegunką lub wymiotami, w celu różnicowania ostrego przebiegu COVID-19 lub wieloukładowego zespołu zapalnego u dzieci (*multisystem inflammatory syndrome in children*, MIS-C) od ostrego zapalenia wyrostka robaczkowego, a tym samym zapobiegania ewentualnej niepotrzebnej interwencji chirurgicznej. Z drugiej strony ważne jest odpowiednio wczesne stawianie prawidłowej diagnozy, a następnie wdrażanie właściwego leczenia chirurgicznego i antybiotykoterapii u pacjentów z zapaleniem wyrostka robaczkowego, co pozwala zapobiegać powikłaniom pooperacyjnym, np. tworzeniu się ropni. Opóźnione rozpoznanie może wiązać się ze znaczącą zachorowalnością, która może przewyższać skutki wywoływane przez sam COVID-19. Należy również uwzględnić fakt, że w okresie pandemii COVID-19 badania radiologiczne mają pewne ograniczenia i bardzo często mogą dawać wyniki fałszywie dodatnie u dzieci z MIS-C. Specjaliści chirurgii dziecięcej powinni mieć świadomość objawów żołądkowo-jelitowych w przebiegu ostrego COVID-19 lub MIS-C i potrafić odróżnić tę nową jednostkę chorobową od stanów wymagających interwencji chirurgicznej ze względu na zbliżony obraz kliniczny.

Słowa kluczowe: COVID-19, SARS-CoV-2, MIS-C, dzieci, ból brzucha, ostry brzuch, zapalenie wyrostka robaczkowego

INTRODUCTION

Since it was first reported, the new coronavirus disease (COVID-19) has spread rapidly, and so far, affected more than 400 million people worldwide. COVID-19 in children is relatively mild, so it is easy to make a misdiagnosis in the early stages if it presents only with respiratory symptoms. Delayed diagnosis and treatment of common paediatric conditions, including appendicitis, can lead to significant morbidity that can outweigh the damage caused by COVID-19 alone. Early diagnosis and consequent appropriate surgical and antibiotic treatment are important because they can prevent complications such as abscess formation and other postoperative abnormalities. On the other hand, the exposure surgery in patients with acute COVID-19 infection and especially multisystem inflammatory syndrome in children (MIS-C), has been shown to have a significant negative impact on the outcome of treatment itself[1]. COVID-19 is predominantly a respiratory disease. However, its significant effect on the gastrointestinal system is now known as well. SARS-CoV-2 enters cells via the angiotensin-converting enzyme-2 (ACE-2) receptor, which is expressed not only in lung cells but also in enterocytes. There are a number of aetiopathogenetic mechanisms, including the loss of intestinal absorption, microscopic mucositis, and impaired ACE-2 function, which play a significant role in maintaining intestinal homeostasis. In children, gastrointestinal manifestations include anorexia, nausea, vomiting, diarrhoea, and abdominal pain, which may represent the earliest symptoms of the disease. Significant inflammation of gastrointestinal mucosa has also been reported, such as terminal ileitis mimicking atypical appendicitis, especially in the presence of MIS-C[2,3]. It is important to note that patients with MIS-C may have positive SARS-CoV-2 reverse transcriptase–polymerase chain reaction (RT-PCR) or antibody test results, or recent exposure with no alternate diagnosis, while patients with acute COVID-19 infection have positive RT-PCR test results. MIS-C mainly occurs with a time lag from acute COVID-19[4]. In this review, we discuss the incidence, presentation, and management of paediatric appendicitis at the time of the COVID-19 pandemic.

MATERIALS AND METHODS

A systematic literature search and review were conducted according to the PRISMA guidelines using the PubMed online database on 16 August 2021. The search was performed in all fields, based on the MeSH (Medical Subject Headings) terms including appendicitis, children, COVID, with the use of the Boolean operator AND. Regarding the type of articles, their availability (abstracts, full papers), date of publication, language, gender and age, no limiter was used. After a detailed reading of abstracts and complete articles, papers were selected that dealt in the narrowest sense with the following topics:

- leading symptoms and duration of symptoms;
- incidence and prevalence of appendicitis;
- reasons for reduced or increased incidence;
- incidence of complicated appendicitis (e.g. perforation);
- non-operative appendicitis management and success rate;
- radiological and laboratory features of appendicitis at the time of the pandemic;
- incidence of MIS-C;
- distinguishing appendicitis from acute COVID-19 and MIS-C.

Based on the previous search strategy, a total of 93 studies were obtained from the database. Following careful reading of abstracts and complete papers, with defined topics of interest for discussion, a total of 61 papers were selected (Fig. 1).

RESULTS

Tab. 1 shows the main conclusions and results reported in selected research papers.

Based on the literature review and personal experiences in the course of the pandemic so far, we present the therapeutic management in Fig. 2.

DISCUSSION

Already the first medical cases of children from Wuhan clearly indicated that non-respiratory symptoms could dominate as the first manifestation of a disease caused by the SARS-CoV-2 virus. In four of five patients, gastrointestinal symptoms appeared as the first sign of the disease[2]. In a number of cases, gastrointestinal symptoms, in relation to the respiratory ones, were the leading manifestations[5,6]. Zampieri et al. claim that at the time of COVID-19 there were fewer cases of appendicitis due to a reduced number of potential co-factors. Quarantine has been shown to have played a protective role, especially in terms of avoiding infections. The phenomenon is explained by the fact that during a quarantine preschool children stay at home, without any contact with others, and thus without respiratory or enteric infections, while household hygiene is improved[7,8]. Pines et al. cite as the most worrying finding of their study a significant drop in visits among children with appendicitis, septicaemia and intussusception[9]. On the other hand, La Pergola et al. report that there were no significant differences in the prevalence and occurrence of symptoms of acute appendicitis in the paediatric population during the peak of a pandemic, as compared with non-pandemic periods[10]. Lee-Archer et al. noted that there was no significant change in the number of cases of appendicitis, but complicated appendicitis was significantly more common during the pandemic (60.5% of confirmed cases) compared to the same period of the pre-pandemic year (30.4%)[11]. The reason for the increased number of complicated appendicitis, as suggested by Snapiri et al., were the parents of children, and their reluctantance to visit the hospital. Also, the

DOI: 10.15557/PiMR.2022.0001

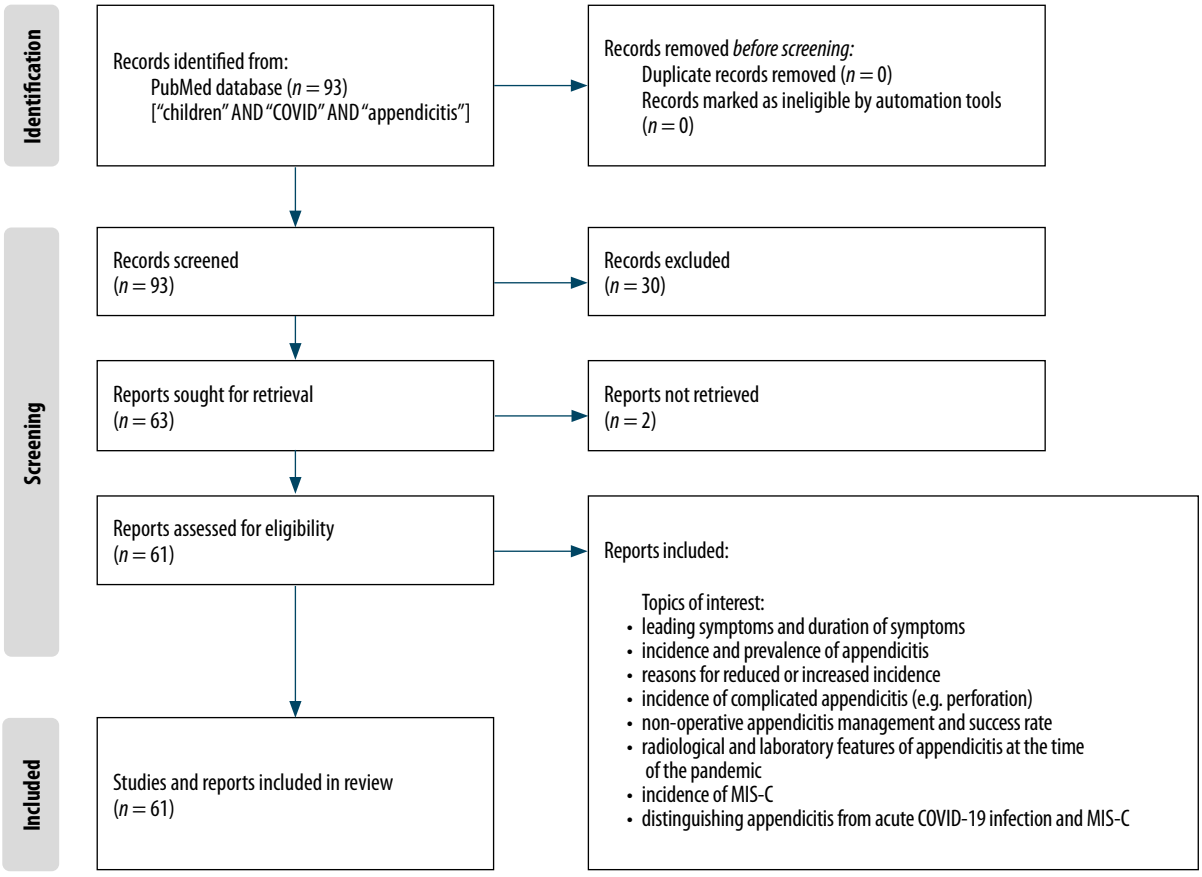

Fig. 1. PRISMA flow diagram

family doctors were not determined to send such children to the hospital in time. In this study, twice as many perforations were observed at the time of the pandemic as in the period before the pandemic, which is a truly worrying fact[12]. In a study by Ali et al., among the complications, perforated appendix was found statistically significantly more at the time of COVID-19 ($p = 0.001$). Therefore, a much larger number of laparotomies had to be performed ($p = 0.008$) due to complications[13]. According to Kumaira Fonseca et al., the number of appendectomies performed during a pandemic decreased by 56%. The average time of symptom onset to hospital arrival was significantly higher (40.6 vs. 28.2 hours, $p = 0.02$), with a significantly higher proportion of complicated cases (33.3% vs. 15.2%, $p = 0.04$). The rate of postoperative complications and the average length of stay were not statistically different[14]. Place et al. reported a 20% increase in the incidence of perforated appendicitis ($p = 0.009$), while Bada-Bosch et al. reported that at the time of the pandemic, 61.5% of appendicitis cases were complicated, compared to 42.4% in the COVID-free period ($p = 0.17$)[15,16]. A study by Schäfer et al. found an increase in perforation rates from 20.7% to 27.8% ($p = 0.0359$). Particularly affected subgroups included children younger than 11.2 years where the perforation rate was significantly higher; 37.6% vs. 22.2% ($p = 0.014$), and boys; 35.0% vs. 21.4% ($p = 0.0165$)[17]. Data from Switzerland show that a number of consultations for acute appendicitis decreased by almost 20 percent during the pandemic periods, with a significant increase in complicated appendicitis (52% vs. 20%, $p < 0.001$). Significant differences were also noted in the duration of symptoms (symptoms >48 h in 61% vs. 26%, $p < 0.001$), intervention time (77 vs. 61 minutes, $p = 0.002$), length of hospital stay (hospitalisation of >2 days; 63% vs. 32%, $p < 0.001$), and duration of antibiotic treatment (antibiotics >3 days; 36% vs. 24%, $p = 0.001$)[18]. According to Delgado-Miguel et al., children at the time of the pandemic who presented with appendicitis had a longer time of symptom progression (46.8 hours; $p = 0.046$), a higher rate of complicated appendicitis (48.4%; $p = 0.004$), a longer average hospital stay (4.9 days; $p < 0.001$), increased cumulative incidence (8.27 cases per 100,000 children per 0.1 year; $p < 0.001$), and increased incidence of complicated appendicitis (83 cases per 100,000 children; $p < 0.001$)[19]. Fisher et al. observed a higher perforation rate (45% vs. 27%, $p = 0.005$) and a longer mean duration of symptoms in children with perforation (71 ± 39 vs. 47 ± 27 h, $p = 0.001$) during the COVID-19 period[20]. Meyer found that perforated appendicitis was statistically more common in children during the first six months of the COVID-19 pandemic (39.5% vs. 20.6%)[21]. Esparaz et al. found a significant increase in cases of perforated appendicitis during three months of the COVID-19 pandemic compared to the previous five months

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Manuscripts	Main conclusions
Cai et al. (2020)[2]	The initial symptoms of the patients may not have been associated with SARS-CoV-2 infection or the symptoms of SARS-CoV-2 infection may have been relatively latent or mild before COVID-19 was confirmed. Four out of five cases had symptoms involving the digestive tract as the first manifestation
Puoti et al. (2021)[3]	SARS-CoV-2 enters cells via the angiotensin-converting enzyme-2 (ACE-2) receptor, which is abundantly expressed on lung cells, but also on enterocytes. In children, gastrointestinal manifestations include anorexia, nausea, vomiting, diarrhoea, and abdominal pain, which may represent the earliest presenting symptoms of the disease
Alsuwailem et al. (2020)[5]	The clinical presentation of complicated appendicitis in association with COVID-19 may not be different from that in the general population
Ekbatani et al. (2021)[6]	COVID-19 must be considered as an equivocal presenting infection in any patients referred to hospital with atypical presentations such as unexplained abdominal pain
Zampieri et al. (2020)[7]	There were less cases of appendicitis due to a reduced number of potential co-factors. Results demonstrate that quarantine had a protective role, especially avoiding infections
Zampieri (2020)[8]	Rural hospitals were associated with higher perforated appendicitis rates, less laparoscopy use, and higher complication rates
Pines et al. (2021)[9]	Paediatric emergency department visits fell more sharply than adult emergency department visits during the COVID-19 pandemic. Declines were also seen for serious conditions, suggesting that parents may have avoided necessary care for their children
La Pergola et al. (2020)[10]	There were no significant differences regarding the prevalence and the onset of symptoms of acute appendicitis in the paediatric population during the peak period of the pandemic
Lee-Archer et al. (2020)[11]	Paediatric emergency department presentations have decreased, as people are reluctant to leave home and risk contracting the virus whilst attending hospital. The observed increase in complicated appendicitis is most likely due to COVID-19
Snapiri et al. (2020)[12]	The main reasons for the delayed diagnosis during the COVID-19 era were parental concern, telemedicine use, and insufficient evaluation
Ali et al. (2020)[13]	Delay in presentation, complications and requirement for extensive surgical procedure are the indirect impacts of the current pandemic on emergency surgical conditions of children
Kumaira Fonseca et al. (2020)[14]	The number of appendectomies during the pandemic decreased significantly. The average time to onset of symptoms until arrival at the hospital was significantly longer. A significantly higher proportion of complicated cases are present. The rate of postoperative complications and the average length of stay did not differ statistically
Place et al. (2020)[15]	The parents showed visible signs of anxiety in the emergency room and openly expressed reluctance to visit the hospital for fear of COVID-19, resulting in an increased number of appendicitis perforations
Bada-Bosch et al. (2021)[16]	Appendicular pathologies were in a more advanced stage than usual, with a clear trend towards open surgery vs. laparoscopy
Schäfer et al. (2021)[17]	The rate of perforated appendicitis in childhood increased significantly, especially in younger children and boys
Burgard et al. (2021)[18]	The COVID-19 pandemic resulted in a decreased number of consultations for acute appendicitis, with a higher proportion of complicated appendicitis cases
Delgado-Miguel et al. (2021)[19]	Delayed emergency department visit of children with acute appendicitis during home confinement leads to an increased rate of complicated appendicitis
Fisher et al. (2021)[20]	Children in the epicentre of the COVID-19 outbreak demonstrated higher rates of perforated appendicitis
Meyer (2021)[21]	The COVID-19 pandemic increased the proportion of patients with perforated appendicitis. It is important to inform children and parents about the poor outcome of delaying hospitalisation
Esparaz et al. (2021)[22]	The COVID-19 pandemic and related orders to stay at home had downstream effects on health care. There was a significant increase in the number of children with perforated appendicitis
Fadgyas et al. (2021)[23]	The cause of the increased number of perforated cases in COVID-19 positive appendicitis patients is unknown. The causes of the high proportion of perforated cases in COVID-19 positive patients and the rising rate of perforated appendicitis cases since 2015 need further studies
Velayos et al. (2020)[24]	The SARS-CoV-2 pandemic influenced the time of diagnosis of appendicitis, as well as its course, and mean hospital stay. Peritonitis was more frequently seen
Maneck et al. (2021)[25]	The lockdown resulted in a decreased number of appendectomies. This affected mainly appendectomies in simple acute and non-acute appendicitis, but not complicated acute appendicitis. The study gives no evidence that the confinement measures resulted in a deterioration of medical care for appendicitis
Raffaele et al. (2020)[26]	During the pandemic, an increase in the average length of time elapsed between the onset of symptoms and surgery was observed. The doubling of the time until admission to the ambulance is reasonably a consequence of the fear of COVID-19, which is why people with early symptoms avoid access to the hospital
Gaitero Tristán et al. (2021)[27]	COVID-19 self-quarantine has not increased the incidence of complicated appendicitis, and children who developed complicated appendicitis did not have worse clinical outcomes
Theodorou et al. (2021)[28]	Paediatric perforated appendicitis rates did not rise during the first six months of the COVID-19 pandemic, and there were no delays in presentation noted. There was a higher rate of CT scans, non-operative management, and longer hospitalisations
Sheath et al. (2021)[29]	Despite presenting later during COVID-19, paediatric patients with appendicitis were treated expediently, with good outcomes
Montalva et al. (2020)[30]	Despite an increase in the number of children with appendicitis, management and outcome remained similar
Gerall et al. (2021)[31]	Patients treated for acute appendicitis during the peak of the COVID-19 pandemic presented with more severe disease and experienced suboptimal outcomes
Bethell et al. (2020)[32]	Non-operative treatment of appendicitis is safe and effective in selected patients

Tab. 1. Brief overview of selected manuscripts

DOI: 10.15557/PiMR.2022.0001

Manuscripts	Main conclusions
Kvasnovsky et al. (2021)[33]	Non-operative treatment can be applied to almost half of patients with acute appendicitis. The same was successfully done, with a reduced follow-up period, thus limiting operations and minimising the length of stay
Farooq et al. (2021)[34]	Conservative treatment of acute appendicitis was more prevalent during the pandemic period, but patients who underwent appendectomies had more complicated appendicitis
Colvin and Lawther (2021)[35]	The use of a non-operative management pathway for paediatric appendicitis during the COVID-19 surge was safe and effective for staff and patients
Emile et al. (2021)[36]	Non-operative management of acute appendicitis in the setting of COVID-19 may be a safe, short-term alternative to surgery with acceptably low failure and complication rates
Polites and Azarow (2020)[37]	With comparable outcomes for operative and non-operative management of uncomplicated appendicitis, hospitals must consider capacity and resources in determining the best course of action
Tankel et al. (2020)[38]	The significant decrease in the number of patients admitted with acute appendicitis during the onset of COVID-19 possibly represents successful resolution of mild appendicitis treated symptomatically by patients at home
Saleem et al. (2020)[39]	More than half of the patients had perforated appendix, which was the highest percentage observed in the group of patients during the period of two months
Mehl et al. (2021)[40]	COVID-19 children requiring surgery have a favourable postoperative course and short-term outcomes compared to the reported adult experience
Rohani et al. (2021)[41]	COVID-19 has many different and mysterious presentations. Gastrointestinal manifestations are among the most important, common presentations
Hwang et al. (2021)[42]	Laboratory criteria, specifically low-normal white blood cell count and thrombocytopenia, appear to be of high relevance in differentiating MIS-C from acute appendicitis, even when the appendix is radiologically dilated
Gerall et al. (2021)[43]	A rash as well as tachycardia and/or hypotension and elevated inflammatory markers out of proportion to the amount of inflammation seen on imaging should be used to differentiate a typical surgical abdomen from MIS-C and prompt testing for active SARS-CoV-2 infection as well as antibodies
Romberg et al. (2021)[44]	CT of COVID-positive patients with severe abdominal pain showed lymphadenopathy, mild thickening of the intestinal wall, and mesenteric oedema
Meyer et al. (2021)[45]	We encourage consideration of testing for SARS-CoV-2 in paediatric patients with severe gastrointestinal symptoms to inform about strategies to alleviate transmission and possible complications due to unnecessary surgical treatment
Rico Espiñeira et al. (2021)[46]	Gastrointestinal symptoms can be the primary manifestation of the new coronavirus infection, which simulates an acute abdomen with a potentially unfavourable evolution. For an accurate diagnosis to be achieved, a good clinical record and a comprehensive physical exploration, as well as complementary tests in search of characteristic findings of COVID-19, should be carried out
Jackson et al. (2020)[47]	MIS-C should be considered in patients with prominent gastrointestinal symptoms and a history of recent SARS-CoV-2 exposure or infection. Long-term follow-up analysing potential sequelae and organ dysfunction will be important for determining the actual severity of disease in COVID-19 and MIS-C
Öcal Demir et al. (2021)[48]	Glucocorticoids have a critical role in the treatment of MIS-C, early recognition and treatment may decrease the need for intensive care by providing rapid recovery
Harwood et al. (2020)[49]	Judicious, repeated clinical assessment, multi-speciality team-working and a low threshold for cross-sectional abdominal imaging are recommended to enable differentiation between paediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2 and acute appendicitis in unwell children with abdominal pain and unremarkable abdominal ultrasonography findings
Guanà et al. (2021)[50]	Routine serological test for SARS-CoV-2 should be performed in infants with unusual abdominal pain and elevation of inflammatory markers and who had no diagnosis of appendicitis, since early detection and treatment of SARS-CoV-2 hyperinflammatory syndrome is vital for prompt management
Garcia-Dominguez et al. (2020)[51]	Various paediatric centres are recognising the various MIS-C phenotypes around the world, with identification of risk factors, pathogenesis, clinical course, and treatment for MIS-C
Shahbaznejad et al. (2020)[52]	Children with COVID-19 may present with symptoms similar to Kawasaki disease and inflammatory syndromes. Paediatric inflammatory multisystem syndrome should be considered in children with fever, rash, seizures, cough, tachypnoea, and gastrointestinal symptoms such as vomiting, diarrhoea, and abdominal pain
Malhotra et al. (2021)[53]	Acute appendicitis in children infected with SARS-CoV-2 may represent a postinfectious hyperinflammatory complication occurring 2 weeks after the early manifestation of acute pneumonia in children
Valitutti et al. (2021)[54]	In children with query acute abdomen, MIS-C should be promptly ruled out in order to avoid unnecessary surgeries that could worsen the already frail outcome of this new syndrome. Nevertheless, it should be considered that MIS-C might well encompass complications (e.g. appendicitis, segmental intestinal ischaemia) which need swift surgical treatment
Al Lawati et al. (2021)[55]	Given the risk of severity and rapid deterioration of children with MIS-C, we recommend that surgeons, emergency physicians and paediatricians have a high index of MIS-C suspicion when managing children and adolescents with fever and acute abdomen during the current pandemic
Borgi et al. (2021)[56]	A patient with MIS-C is considered to have a refractory disease when the child has persistent fever and/or significant end-organ involvement despite initial immunomodulatory treatment
Lee et al. (2021)[57]	Early recognition by disease awareness and prompt management are key to saving the lives of children affected by MIS-C. The benefits of immunomodulatory therapy have been suggested in both MIS-C and severe paediatric COVID-19 patients, even though no guidelines support the use of one immunomodulatory therapy over another
Lishman et al. (2020)[58]	Paediatricians that diagnose MIS-C should be vigilant and continue to carefully evaluate children for surgical complications, including appendicitis and perforation, particularly if abdominal pain is part of the presenting complaint

Tab. 1. Brief overview of selected manuscripts (cont.)

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Manuscripts	Main conclusions
Samprathi et al. (2021)[59]	Normal leukocyte count, low platelets, significantly raised inflammatory markers, and echocardiographic changes can confirm MIS-C
Al Maskari et al. (2021)[60]	Early diagnosis and referral to centres equipped with the required subspecialties are recommended. It should be noted that the severity of the disease is transient, usually resulting in high survival rates with proper supportive treatment. A good evaluation of the possibility of acute abdomen related to MIS-C is essential to prevent unnecessary surgical intervention
Anderson et al. (2021)[61]	Surgeons should have a high index of suspicion for MIS-C in patients with acute appendicitis who become critically ill out of proportion to their surgical findings, especially in cases of high and prolonged fever and hypotension unresponsive to fluid
Yock-Corrales et al. (2021)[62]	Further studies are needed to better characterise children with acute abdomen during COVID-19 or MIS-C, to avoid delay in the diagnosis of surgical conditions and at the same time, minimize unnecessary surgical approaches
Azılı et al. (2021)[63]	The duration of abdominal pain, presence of high-grade and prolonged fever, and evaluation of haemogram in terms of high neutrophil count and low lymphocytes count exhibit high sensitivity and negative predictive value for MIS-C presenting with acute abdominal pain. Where in doubt, inflammatory markers such as CRP, ferritin, D-dimer, and serology for SARS-CoV-2 should be determined to confirm the diagnosis

Tab. 1. Brief overview of selected manuscripts (cont.)

(45.6% vs. 26.4%, $p < 0.001$), but found no significant difference in pain duration ($p = 0.926$)[22]. According to Fadgyas et al., the number of perforated cases was higher in patients who tested positive for COVID-19 than in negative patients ($p = 0.0075$)[23]. The pandemic affected the time of diagnosis of appendicitis, as well as its course and average hospital stay. Peritonitis occurred more frequently, as a result of significant circumstances, delaying the diagnosis and treatment of acute appendicitis[24]. According to a study by Maneck et al., the total number of appendectomies decreased significantly. Appendectomy numbers of complex appendicitis remained unchanged[25]. In a study by Raffaele et al., a histological examination showed a higher prevalence of gangrenous appendicitis (50% vs. 15.4, $p = 0.050$). Advanced stages of appendicitis have been attributed to a longer wait for a swab finding on SARS-CoV-2[26]. A study from Spain indicated that at the time of the epidemic, the incidence of complicated appendicitis was higher (38.9% vs. 28.3%), showing no significant differences. The two groups were homogeneous, with no difference in time between the onset of symptoms and the first visit to the emergency department, the results of laboratory tests, the mean length of stay, admission to intensive care, or patients correctly diagnosed at the first visit[27]. According to a study by Theodorou et al., perforated appendicitis rates were unchanged (40.4% vs. 42.1%, $p = 0.17$). The mean duration of symptoms was two days in both cohorts ($p = 0.90$). The use of computed tomography (CT) increased from 39.8% to 49.4% ($p = 0.002$). Non-operational management increased during the pandemic (8.8% vs. 16.2%, $p < 0.0001$). The length of hospital stay (LOS) was longer (two vs. three days, $p < 0.0001$)[28]. Although there was a trend toward a higher proportion of complicated appendicitis during COVID-19 (22% vs. 10%, $p = 0.6$), this did not translate into poorer outcomes. Despite later presentation during pandemic, paediatric patients with appendicitis were treated expeditiously, with good outcomes[29]. Montalva et al. concluded that during the lockdown, children treated for appendicitis were older (11.1 vs. 8.9 years, $p = 0.003$), and more likely to live more than 5 km from hospital (77% vs. 52%, $p = 0.017$). There was no difference in the length of hospital stay, rate of postoperative intra-abdominal abscess, ambulance visits, and readmissions between the two periods[30]. According to Gerall et al., the findings of complicated appendicitis on radiography, including suspected perforation (41.7% vs. 9.8%, $p < 0.001$) and intra-abdominal abscess (27.1% vs. 7.3%, $p = 0.025$) were higher in patients during the pandemic period. Patients treated during the pandemic had higher rates of non-operative treatment (25.0% vs. 7.3%, $p = 0.044$) which required increased use of antibiotics[31]. Given the new circumstances, surgeons in Great Britain and Ireland were more in favour of a non-operative approach to appendicitis in children who were assessed to have a milder form. The data showed that non-surgical treatment of acute appendicitis was effective and safe[32]. In an effort to conserve resources, minimise surgical procedures, and enable test results at COVID-19, Kvasnovsky et al. investigated the full potential of non-operative treatment of acute appendicitis with antibiotics. 45.5% children were discharged from the hospital after initial non-operative treatment, which showed that as many as half of the patients could be treated in this way[33]. In a study by Farooq et al., conservative treatment of acute appendicitis was more common during the pandemic period (47.5% vs. 28.5%, $p = 0.01$), but patients who underwent appendectomy had more complex appendicitis (63.3% vs. 42.1%, $p = 0.01$)[34]. The use of a non-operative management (NOM) pathway for paediatric appendicitis during the COVID-19 surge in Northern Ireland was safe and effective for staff and patients. For those with simple appendicitis, there was a 96% success rate of NOM on discharge, with a 93% 30-day success rate. For complicated appendicitis, there was a 40% success rate on discharge, with a 30% 30-day success rate[35]. Emile et al., in their review which included 14 studies, assessed the extent of adoption, efficacy, and safety of NOM of acute appendicitis in a COVID-19 setting. The weighted mean rate of NOM application was 50.1% (95% confidence interval, CI: 29.8–70.5%). The application of NOM during the pandemic was significantly more likely than its application before COVID-19 (odds ratio, OR = 6.7, $p < 0.001$). The weight mean failure rate of NOM was 16.4% (95% CI: 9.4–23.4). The weighted mean

DOI: 10.15557/PiMR.2022.0001

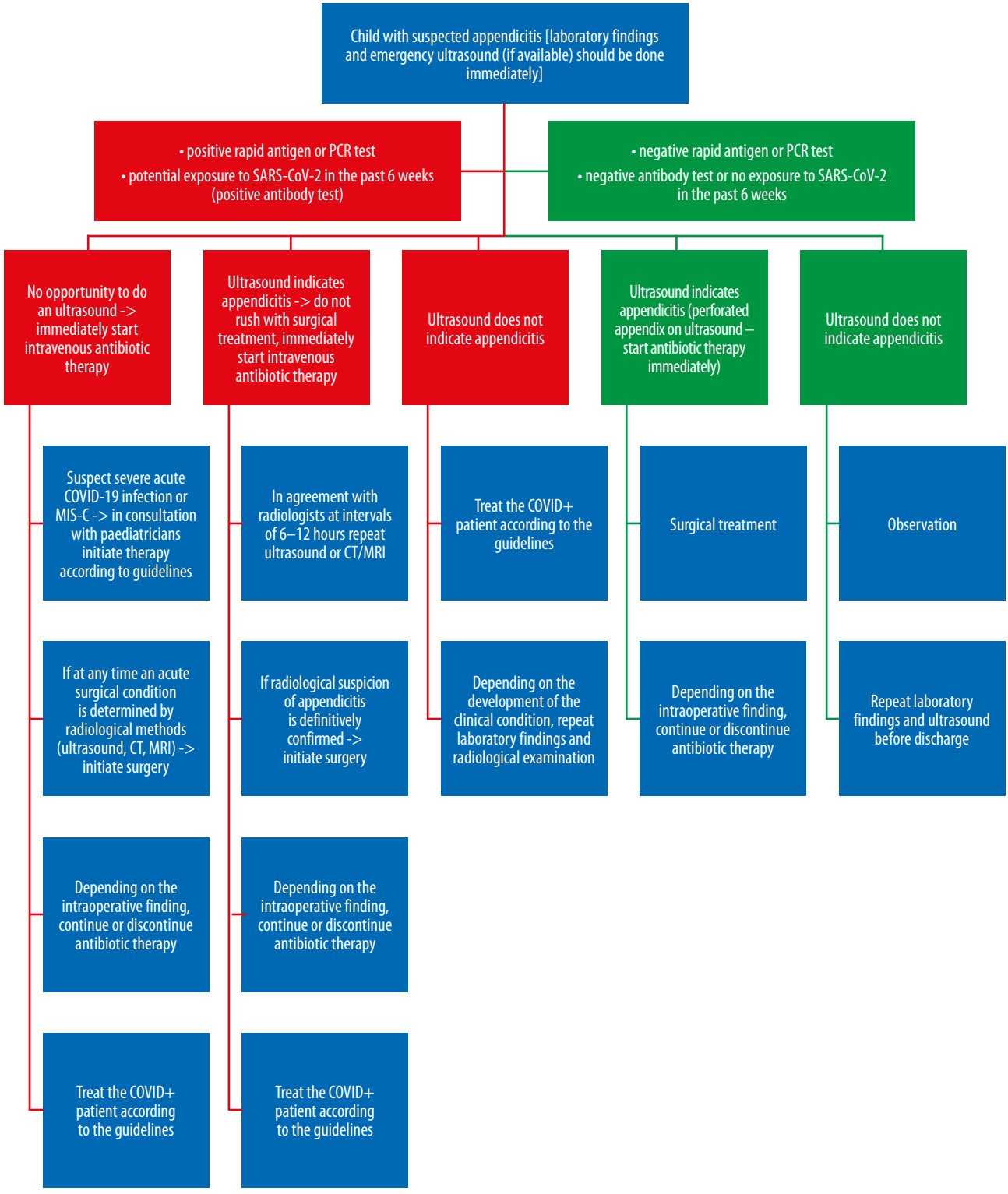

Fig. 2. Treatment of a child with suspected appendicitis during the COVID-19 pandemic (author's own work)

 DOI: 10.15557/PiMR.2022.0001

complication rate after NOM was 4.5% (95% CI: 1.4–7.7). NOM had significantly lower odds for complications than appendectomy (OR = 0.36, $p = 0.03$). However, in order for paediatric surgeons to be able to decide whether they want a non-operative or operative approach, they need to know clearly what resources they have at their disposal. Depending on hospital capacity, they must assess whether early surgery (to discharge the child from hospital earlier) or non-operative antibiotic treatment (which requires longer hospitalisation) is more beneficial[36,37]. According to research from Israel, the difference in the severity of appendicitis did not reach the level of statistical significance. The number of patients who needed postoperative peritoneal drainage did not differ significantly. The incidence of acute appendicitis decreased by 40.7% ($p = 0.02$). They believe that the significant reduction in the number of patients admitted with appendicitis during the onset of COVID-19 is likely due to the successful symptomatic resolution of mild appendicitis at home[38]. Saleem et al. reported that children who did not show clinical or radiological indications of complicated appendicitis were given intravenous antibiotics[39]. In a study by Mehl et al., abdominal pain was identified as the most common preoperative symptom (65%). Twenty-three percent of patients had no symptoms associated with COVID-19[40]. Rohani et al. presented the case of a boy whose initial diagnosis was acute abdomen due to acute appendicitis. The final diagnosis, however, was enterocolitis[41]. A 16-year-old girl presented with a four-day history of abdominal pain, vomiting, fever, headache, myalgia and cough. Physical examination revealed abdominal tenderness in the lower right quadrant. Contrast-enhanced CT showed appendicitis (8 mm). Appendicitis surgery was initiated which macroscopically showed a normal appendix. Pathohistological findings did not show transmural acute appendicitis[42]. Gerall et al. reported a case of a seven-year-old girl with rebound tenderness. She underwent abdominal ultrasound which showed borderline appendicitis. At this time, antibiotics were started in the emergency department for presumed appendicitis, and the surgical team was consulted. Follow-up magnetic resonance imaging (MRI) was performed, and significant for a normal-appearing appendix; however, extensive inflammatory changes were noted within the terminal ileum with surrounding mesenteric inflammatory changes. Early recognition of similar cases is crucial to prevent surgical intervention[43]. Radiologists also reported a patient suffering from COVID-19 and having abdominal pain. CT showed adenopathy, mild thickening of the intestinal wall, and mesenteric oedema. Another COVID-positive patient had abdominal pain, fever, vomiting, and hypotension. Abdominal CT showed minimal lymphadenopathy and traces of free fluid in the abdomen as well as minimal clouding of the basilar pulmonary lung glass[44]. Meyer et al. draw attention to the possible association between COVID-19 and appendicitis. They are of the opinion that testing for SARS-CoV-2 should be performed in paediatric patients with severe gastrointestinal symptoms[45]. In the series Rico Espiñeira et al. of the 14 patients who presented with abdominal pain and a diagnosis of COVID-19, 11 patients were with fever, nine patients with vomiting or diarrhoea, and nine patients with clinically suspected surgical pathology (acute appendicitis or peritonitis). An abdominal ultrasound examination was conducted in all patients, and a CT scan was performed in four patients, showing inflammatory signs in the terminal ileum. In all but one patient, conservative treatment was provided[46]. Jackson et al. reported on the case of a nine-year-old girl who presented with pain in the right lower quadrant. Upon admission, she had positive antibodies. An ultrasound was done at the hospital, showing the blind end of a tubular structure suspected of appendicitis. Appendectomy was started based on the ultrasound findings and clinical picture. However, the pathohistological diagnosis did not indicate appendicitis. The treatment determined that it was in fact MIS-C[47]. According to a study from Turkey, 70% of children treated for MIS-C presented with abdominal pain (symptoms mimicking acute appendicitis and ileus)[48]. Harwood et al., based on their cases, warned that there was diagnostic uncertainty during the COVID-19 pandemic. The authors highlighted that the initial clinical picture of abdominal pain in MIS-C and appendicitis with co-infection with COVID-19 could not be distinguished. Children with MIS-C often have terminal ileitis, with free intraperitoneal fluid in the right iliac fossa. They recommended reasonable, repeated clinical evaluation, multi-specialty teamwork, and a low threshold for cross-sectional abdominal imaging to allow a distinction to be made between MIS-C and appendicitis in COVID-positive children[49]. Guanà et al. presented the case of a seven-year-old boy with MIS-C who presented with a tense and painful abdomen and gave clear instructions on how to recognise the condition. MIS-C definition includes six diagnostic criteria: serious illness leading to hospitalisation, age <21 years, fever lasting for at least 24 h, laboratory evidence of inflammation, multisystem organ involvement, evidence of SARS-CoV-2 infection based on RT-PCR, antibody testing, or exposure to persons with COVID-19 in the past month. It occurs about four to six weeks after acute SARS-CoV-2 infection, developing from an uninhibited immune response to a prior infection rather than an acute manifestation of the viral disease. Among the initial symptoms, high fever and gastrointestinal impairment (that is, abdominal pain, vomiting, and diarrhoea) correlate with high values of C-reactive protein (CRP) (>100 mg/L), requiring the differential diagnosis of acute appendicitis. Abdominal pain is not electively localised in the right iliac fossa; it is more diffuse and often associated with symptoms like vomits and diarrhoea. Abdominal ultrasound shows indirect signs of appendicitis such as mesenteric lymphadenopathy or borderline thickening of the appendicular wall. Early detection and treatment of SARS-CoV-2 hyper-inflammatory syndrome is vital for prompt management[50]. In a series of four MIS-C cases, none of the patients had typical COVID-19 respiratory symptoms. They all had general weakness, asthenia and adynamia. All had a gastrointestinal

DOI: 10.15557/PiMR.2022.0001

symptom (vomiting, diarrhoea and/or abdominal pain). One patient needed emergency surgery on suspicion of appendicitis, which was ultimately diagnosed as mesenteric adenitis. A significant increase in CRP, polymorphonuclear cells, procalcitonin, D-dimers and fibrinogen, as well as lymphopenia and hypoalbuminemia, were observed in the patients[51]. In a study by Shahbaznejad et al., nine out of 10 patients with MIS-C had gastrointestinal symptoms, and seven had abdominal pain. Most patients had anaemia, lymphopenia, and hypoalbuminemia, while all of them had increased CRP[52]. A study from New Jersey indicated that patients with appendicitis had significantly fewer days of fever than did patients with MIS-C. Appendicitis patients presented predominantly with nausea, vomiting, and abdominal pain. MIS-C patients had longer febrile days both before admission and while in hospital. MIS-C patients were also noted to present with gastrointestinal features, similarly to appendicitis patients, but reported a higher frequency of diarrheal symptoms at time of presentation. Appendicitis patients had significantly lower aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) values than did patients with MIS-C, and significantly lower alanine aminotransferase (ALT) values than patients with MIS-C[53]. Valitutti et al. claim that preliminary assessments of troponin, B natriuretic peptide (BNP), D-dimers, ferritin, and echocardiography are definitely valuable for establishing an accurate differential diagnosis in children with acute abdomen[54]. Al Lawati et al. state that gastrointestinal symptoms are increasingly recognised as related to the presentation of MIS-C. The mechanism of appendicitis is not clear, whether it is related to the inflammation resulting from viral entry, reactive lymphoid hyperplasia or vasculitis of the appendicular artery[55]. In a study by Borgi et al., in all eight cases of children with MIS-C, fever and gastrointestinal symptoms were noted. Five patients had severe abdominal pain and were examined by a surgeon for possible appendicitis. Abdominal ultrasound was performed in three cases, and CT of the abdomen showed mesenteric lymphadenitis in two cases. Seven patients had diarrhoea[56]. Lee et al. presented a patient who developed MIS-C approximately three weeks after an initial diagnosis of COVID-19. High fever with abdominal pain mimicking appendicitis was the initial manifestation of MIS-C, which could have been easily missed if the patient's history of COVID-19 was ignored[57]. In a series coming to us from South Africa, three children were initially diagnosed with acute appendicitis and treated surgically, and MIS-C was diagnosed in all three after appendectomy. Although appendicitis was histologically confirmed in all the three children, Lishman et al. clearly point out that special attention must be paid to possible ileitis without appendicitis[58]. Samprathi et al. presented a case of a boy with abdominal pain whose ultrasound showed a thickened, incompressible appendix 7.1 mm in diameter, all of which indicated acute appendicitis. Since he was diagnosed with MIS-C in time, the boy was not operated on. Normal leukocyte counts, low platelets, significantly elevated inflammatory markers, and echocardiographic changes may confirm MIS-C[59]. In a study by Al Maskari et al. it is important to note that two of the six patients, suffering from MIS-C, presented to them with an acute abdomen. An appendectomy was performed on a six-year-old male child, and histopathology showed no evidence of inflammation[60]. In a report by Anderson et al., a nine-year-old girl had uncomplicated appendicitis and underwent laparoscopic appendectomy, but developed postoperative fever and shock. The antibody test was positive and she responded to MIS-C treatment. Histology showed lymphohistiocytic inflammation within the muscularis propria, mesoappendix, and serosa, without the typical inflammation rich in neutrophils and involvement of the mucosa associated with acute appendicitis[61]. In a group of 42 children who had a clinical diagnosis of acute abdomen, four (9.5%) were diagnosed with MIS-C and did not undergo surgery. The remaining 38 children (3.8%) underwent abdominal surgery due to suspected appendicitis, and 34 of them (89.7%) had an intraoperative diagnosis of acute appendicitis, while four had a non-surgical finding. Children with complicated appendicitis were more likely to have fever (85.7% vs. 60%), intestinal distension on abdominal radiographs (7.1% vs. none), leukocytosis (85.7% vs. 40%), and high levels of CRP (35.7% vs. 5%), although the differences were not statistically significant[62]. The duration of abdominal pain, presence of high-grade and prolonged fever, and evaluation of haemogram in terms of high neutrophil counts and low leukocytes count exhibit high sensitivity and negative predictive value for MIS-C presenting with acute abdominal pain[63].

CONCLUSION

Testing for SARS-CoV-2 (rapid antigen, PCR or antibody test) is important in all paediatric patients presenting with fever and acute abdominal pain with diarrhoea or vomiting, to differentiate acute COVID-19 infection or MIS-C from acute appendicitis, and thus avoiding unnecessary surgery. We must interpret the findings of abdominal ultrasound at the time of the pandemic with extreme caution, given that more and more false-positive findings are present. In order to be more confident in the diagnosis, we have to use other diagnostic methods more often, such as CT and MRI. Patients with COVID-19 who underwent surgery were observed to have a complicated postoperative course with an increased rate of acute respiratory distress syndrome, shock, arrhythmia, heart injury, and mortality. It is very important that paediatric surgeons are aware of the gastrointestinal manifestations of the SARS-CoV-2 virus and are able to distinguish this new entity from the surgical pathologies it often mimics. In conclusion, awareness of the high rate of gastrointestinal symptoms in COVID-19 patients is definitely an added value for both paediatricians and paediatric surgeons.

 DOI: 10.15557/PiMR.2022.0001

Conflict of interest

The author does not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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