

The ABCs of COVID-19 in children

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Abstract

Coronavirus Disease 2019 (COVID-19) has become notorious for its transmissibility and virulence among adults and the elderly. However, it is becoming increasingly clear that children are not spared from the grips of this infectious disease. As the six-month anniversary of the pandemic approaches, a notable rise is evident in pediatric COVID-19 cases, particularly severe cases. Yet, coronavirus-related research has been concentrated towards older demographics, the result of which is an insufficient understanding of the disease in children. This makes it more difficult to manage severe pediatric cases in clinical settings. This narrative review presents a summary of COVID-19 literature from a pediatric lens, as it is understood today. It consolidates the range of clinical features observed in child-related cases, evaluates the features unique to pediatric patients and explores the unprecedented spike of multisystem inflammatory conditions coinciding with the pandemic. Regarding the current understanding of COVID-19 in children, three areas requiring further research were identified. First, clinical trials determining the safety and efficacy of remdesivir, and other drug candidates, must be elucidated in pediatric patients. A shift towards larger-scale, multicenter case studies are also needed when examining the poorly understood, child-specific COVID-19 features that have been observed. Further investigation into these features, which include delayed symptoms, prolonged viral presence, and prevalence of asymptomatic cases, may help in achieving a better understanding of the disease pathogenesis in children. Finally, the effectiveness of interventions like aspirin for long-term complications of inflammatory conditions associated with COVID-19, must be established. It is imperative to elucidate the pathogenesis of COVID-19 and gain a better understanding of treatment guidelines for children to manage the mounting rates of infection and cases of increased severity observed in this young demographic.

Introduction

Coronavirus disease 2019 (COVID-19) is a novel respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ Originating from Wuhan, China, this infectious disease swept across the globe in a matter of months and was declared a pandemic by the World Health Organization (WHO) on March 12th, 2020.² During the beginning of the pandemic, the largest rates of infection and mortality were seen in the elderly, followed by the adult demographic.³ These observations stand in contrast to scarce reports of pediatric infection and even fewer instances of child-related mortality.^{4,5} With such a large contrast in the way COVID-19 was affecting the young compared to the old, it was initially understood that children were relatively safe from the disease. They appeared to have lower susceptibility to infection and demonstrated resilience against the effects of COVID-19 when infected, since most cases remained mild in severity.^{6,7}

Now, almost half a year after the declaration of the pandemic, the understanding of COVID-19 in children is evolving. The pe-

diatric demographic still maintains the lowest rates of infection and mortality.⁸ However, child-related cases have been on the rise. A systematic review published in March, estimated that children accounted for 1-5% of diagnosed cases, with the majority of data coming from China.⁵ More recent data from July reported that children represented 8.4% of COVID-19 cases in America, increasing 44% from the beginning to the end of the month.⁹ Even more concerning is the rise in severe child-related cases. This is reflected by soaring rates of pediatric intensive care unit (ICU) admissions as well as the unprecedented increase in multisystem inflammatory conditions associated with COVID-19.^{8,10,11}

However, accompanied by this rise is the current underrepresentation of children in coronavirus research. This is due, in part, to insufficient information gained during the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) outbreaks which occurred in 2002 and 2012 respectively.¹² These coronavirus epidemics saw low numbers of child-related cases, resulting in limited knowledge to help guide pediatric COVID-19 research today.¹² This is further compounded by current research efforts which are focused predominantly on adults and the elderly. While there is a greater need for research targeted towards older demographics in the current climate, it results in gaps of knowledge regarding COVID-19 in children. Given the rise

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in severe child-related cases, it is more important now than ever before to conduct pediatric-focused research. An improved ability to understand and treat the clinical features unique to young COVID-19 patients may help to achieve better clinical outcomes in this demographic.

This article analyzes existing literature to provide an up-to-date account of the ABCs regarding the clinical presentation of COVID-19 from a pediatric perspective so as to elucidate where further research is needed.

Methods

This article is a narrative review. A primary search was conducted on MEDLINE, PubMed, and Google Scholar databases using the following terms: COVID-19 [OR] SARS-CoV-2 [OR] coronavirus [AND] children [OR] pediatric [AND] clinical features [OR] prognosis [OR] Kawasaki disease. Literature was included if it was in English, published before August 17th, 2020 and reported on the clinical features of COVID-19 in children. To increase the comprehensiveness of the review, there were no limitations placed on study methodologies, and preprints were included. A secondary search for grey literature was performed to obtain more timely data and additional information as COVID-19 is a novel disease with limited publications pertaining to children. The same search terms and inclusion criteria were used for the secondary search with the exception of the inclusion date which was extended to August 28th, 2020 to obtain live data from specific databases including clinicaltrials.gov and Virtual Pediatric Systems (myvps.org).

Clinical Features of COVID-19 in Children

Mild - Moderate Clinical Features

Children of all ages, from newborns to adolescents of 17 years can contract COVID-19.¹³ The majority of child-related cases, especially during the beginning of the pandemic, have been reported as mild to moderate in severity and mortality is still currently considered rare.^{4,14-18} In fact, a pediatric case study completed between January and February observed that over 90% of the 2143 cases involved were asymptomatic, mild, or moderate infections.⁷ Most clinical features of viral infection have been observed to last for 1 to 2 weeks and in general, children have presented with symptoms similar to those in adults.¹⁴ This includes the most commonly observed symptoms of fever and cough as well as sore throat, rhinorrhea, sneezing, diarrhea, vomiting, dyspnea on exertion, myalgia and fatigue.^{4,14,16,17,19} Children in particular have been observed to present with co-infection frequently. This has been evident through elevated levels of procalcitonin and the detection of influenza A or B, cytomegalovirus, and respiratory syncytial virus.^{4,14}

Pediatric cohort studies have also often reported children to present with more upper than lower respiratory tract symptoms.¹⁴ Some studies have even recorded an absence of pulmonary problems and abnormalities on chest x-ray results altogether.^{4,16} It is possible that, in children, infection is more likely to be contained in the upper respiratory tract which may explain why viral infection presents mildly in the majority of cases. Of note, not all of the existing data is consistent with this theory. One case in particular reported 3 out of 4 asymptomatic children to present with chest abnormalities in computed tomography (CT) scans.²⁰ As such, there may be other reasons for the high prevalence of mild pediatric cases.

Severe - Critical Clinical Features

While the majority of children experience mild infection, cumulative data on North American cases indicate a rise in severe pediatric infections. At the start of April, there was 1 pediatric intensive care unit (ICU) admission and by the end of August, there was a total of 1253 ICU admissions among this demographic.¹⁰ Furthermore, a recent study by the Centers for Disease Control and Prevention (CDC) reported that 1/3rd of children hospitalized due to COVID-19 were admitted into the ICU.⁸ This mirrors ICU rates of adult cases and indicates that, in the pool of children who do get infected, the proportion of severe cases is now observed to be similar to the proportions seen in adults.⁸

Children who are particularly at a high risk for severe infection include infants and younger children as well as those with a history of congenital or acquired diseases.^{4,14} The severe cases in children have typically developed into pneumonia and have involved a variety of pulmonary symptoms such as moist rales, dyspnea and cyanosis.^{4,17} The further deterioration of cases are typically reflected by a progressive reduction in lymphocyte and platelet count accompanied by an increase in transaminase or creatine kinase levels.^{4,17} These observations have indicated the development of acute respiratory distress syndrome (ARDS), respiratory failure, shock, coagulation disorders, and organ dysfunction and failure.^{7,17} In many severe and critical pediatric cases, children have presented with gastrointestinal symptoms during the onset of their infection.^{7,17} The same observation has been made with adult cases, indicating that gastrointestinal symptoms may be a marker for disease severity.²¹ See Table 1 for a summary of the clinical features of COVID-19 in children.

Pediatric cases that become severe or critical can be especially difficult to treat. Until recently, experimental drug candidates for COVID-19 treatment have only been available to patients involved in the corresponding clinical drug trials, the inclusion criteria for which have mostly been exclusive to specific adult demographics.²² Now, drugs like remdesivir have become available to those outside of clinical trials through expanded access programs and the implementation of emergency use authorization.^{22,23} Clinical trials involving pediatric cohorts have also been increasing since the beginning of the pandemic, and by August 28th there were 165 registered pediatric clinical trials around the world.²⁴ However, compared to the 1785 total clinical trials currently occurring, the inclusion of children only account for 9.2% of ongoing trials.²⁴ Furthermore, only 9 of the 165 trials with pediatric inclusion have completed recruitment to date.²⁴ Given the current situation, the existing body of COVID-19 literature lacks published results on the safety and efficacy of drugs like remdesivir for the pediatric demographic.^{23,25} Therefore, although certain drugs have become more widely authorized for use, physicians do not have a lot of guidance on how to treat the severe cases they encounter.

Peculiar Clinical Features Unique to Pediatric Cases

The following clinical features are peculiar observations which have been made in pediatric cases. Certain observations with no identified cause warrant further investigation which may help to elucidate a better understanding of COVID-19 in children.

Lower Rates and Milder Infection in Children

The main difference between viral infection in children when compared to adults, is the significantly lower rates of infection and milder cases in the pediatric demographic, especially during the beginning of the pandemic.⁷ These are perplexing observations because children are considered to have greater vulnerability to respiratory tract infections due to their developing immune systems.⁴ Children even account for the largest portion of influenza infection rates annually.²⁶ However, as with the previous coronavirus epidemics, SARS and MERS, children appear to be the demographic that is least affected by COVID-19.¹² In current literature, there are a handful of postulations which may provide an explanation for this. It is important to note, however, that the following theories may evolve in the coming months as more cases of greater severity emerge in the pediatric demographic.

1. Children are less mobile than adults and generally have less exposure to virions.¹⁴ In fact, most children are infected through intrafamilial transmission.¹⁴ Furthermore, ribonucleic acid (RNA) viruses including those in the coronavirus family, are prone to mistakes in replication and mutation which decreases their virulence.¹⁶ Therefore, infection from a family member via a second or third generation virus may be less likely.¹⁶
2. Children may have immune systems that are better equipped to fight the virus. The hypothesis is that children have more active innate immune systems which are more effective in producing early responses to fight off infection from COVID-19.¹⁶ This observation was made with the two previous coronavirus outbreaks, SARS and MERS, and may explain why the symptoms of many pediatric patients are observed to remain in the upper respiratory tract.¹⁶ There is, however, an opposing theory that children have weaker innate immune systems which induces less of a response to infection.⁶ This results in less systemic inflammation and subsequent organ damage.
3. Viral entry may occur less often with lower effectiveness in children when compared to adults. SARS-CoV-2 gains entry into host cells primarily through angiotensin-converting enzyme 2 receptors.¹⁵ The expression of this receptor may be lower in children as they are still developing, and this decreases the potential for viral entry.^{6,16} These receptors may also be less developed in children and may not function as well for viral entry as the corresponding receptors in adults.^{6,16}
4. Children have healthier and stronger bodies than adults. They are less likely to have risk factors for COVID-19 including underlying diseases, smoking tendencies, and exposure to pollutants.¹⁴ This means that their chance of catching infection is lower than that of adults, and children that do get infected can fight off the virus with more ease.
5. Co-infections appear to be more prevalent among children when compared to adults.^{4,14} The presence of other viruses may create competition and keep SARS-CoV-2 from proliferating as abundantly when compared to those without co-infection.¹⁴ Furthermore, antibodies formed against concurrent infections may provide additional defenses against SARS-CoV-2.⁶

Delayed Onset of Symptoms and Prolonged Viral Presence

In a study comparing COVID-19 in children to their adult family members, it was reported that symptoms took longer to ap-

pear in 5 of the 6 children compared to adults in the same family.¹⁶ Moreover, the same 5 children tested as COVID-19 positive for a longer duration than adults.¹⁶ These children, who were discharged after 2 negative reverse transcription-polymerase chain reaction (RT-PCR) nucleic acid tests, were even recalled when stool samples tested positive, while no adults were recalled.¹⁶ It is not understood why the onset of symptoms were delayed in the same children that presented with prolonged viral presence.¹⁶ However, this phenomenon supports the hypothesis that the virus has a different pathogenesis in children compared to adults.

Prevalence of Asymptomatic Cases in Children

There are varying reports presenting on the frequency of asymptomatic children. A meta-analysis with case reports mainly from China indicated that 17.4% of children presented as asymptomatic while a study in France involving 438 children found that 45% of patients were asymptomatic.^{27,28} Furthermore, in the study comparing infection in children to that of their adult family members, results indicated a predominance of asymptomatic cases in children.¹⁶ Additionally, 66% of children were asymptomatic while only 28% of adults lacked symptoms.¹⁶ With a range between 17.4% and 66%, asymptomatic COVID-19 cases in children are considered to be prevalent and may have even contributed to the reason why infection rates in children are recorded to be so low. Moreover, data reporting a higher frequency of asymptomatic cases in children suggest that the virus may act differently in children when compared to adults.

See Table 1 for a summary of the peculiar clinical features of COVID-19 that are unique to children.

Kawasaki Disease and Multisystem Inflammation in Children

The understanding of COVID-19 is further complicated by the surge of Kawasaki disease (KD) and similar multisystem inflammatory conditions observed in children during the pandemic. The timing of this influx in cases draws concern over its relation to COVID-19 and calls for the reevaluation of disease severity and post-viral complications in pediatric cases.

Prevalence of inflammatory Conditions During the Pandemic

Following the first diagnosed COVID-19 case in Italy, hospitals reported 30 times more Kawasaki-like, multisystem inflammatory conditions in children than in previous years.²⁹ France reported similarly, with 17 KD cases in 11 consecutive days between the end of April and beginning of May.³⁰ This showed a significant increase from their average of 2 cases per month for the past 2 years.³⁰ In April, American researchers documented the first case study of diagnosed KD concurrent with COVID-19 infection in a 6-month-old infant.¹⁹ By the end of May, however, there were 186 child-related multisystem inflammatory conditions in America.³¹

Clinical Features of Multisystem Inflammatory Conditions

Kawasaki disease is a rare but severe condition which causes multisystem vasculitis, predominantly in previously healthy infants and young children under the age of 5.^{11,19,29} The disease is characterized by persistent fevers lasting over 5 days, accompanied by

rash, conjunctivitis, cracked or dry lips, strawberry tongue, cervical lymphadenopathy, and swelling in the hands and feet.^{19,32} When intervention occurs early enough in the development of the disease, children often make a full recovery.¹¹ However, without intervention, coronary-artery aneurysms will develop in 25% of KD patients, which poses a great risk for myocardial infarction.¹¹

It is important to note that many of the cases resembling KD which have emerged during the pandemic have not been identical to classical KD cases observed pre-pandemic.³³ To distinguish between the similar conditions, cases which did not fulfill the criteria of the classically known KD have been termed Kawasaki-like disease, multisystem inflammatory syndrome in children (MIS-C), pediatric inflammatory syndrome (PID), or pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS).³³ These pseudo-Kawasaki cases are different because they typically involve children and young adults over the age of 5, and the severity of the condition is often greater.^{32,34} For example, MIS-C is diagnosed in adolescents under the age of 21 and presentation may include classical KD symptoms in addition to hypotension, shock, myocardial dysfunction, coagulopathy, and gastrointestinal involvement.^{32,35} MIS-C also shares a similar clinical presentation to multisystem inflammatory conditions in adults; however, these cases remain more prevalent in adults for the time being.³⁵ Nonetheless, the presence of these severe cases in children frequently leads to pediatric ICU admissions and may be a large contributing factor to the high ICU rates among this demographic.³⁶

These clinical features shed new light on the range of severity that pediatric COVID-19 cases can exhibit when complicated by multisystem inflammation, in particular the potential for cardiovascular involvement. See Table 1 for a summary of the clinical features associated with multisystem inflammatory conditions in children.

Cause of Multisystem Inflammatory Conditions

The cause of KD and the newly emerging multisystem inflammatory conditions in children are currently unknown.^{11,19,29} For KD, infectious triggers like coronaviruses have been implicated as possible causes in the past and given the current data, it is likely that COVID-19 is responsible.²⁹ Viral infection from SARS-CoV-2 is known to induce powerful inflammatory responses and mediate endothelial injury which is postulated to provoke the development of KD or similar conditions in children.³² However, while many of the inflammatory conditions have been associated with a positive RT-PCR nucleic acid test for SARS-CoV-2, there have been cases involving negative tests as well.³² This indicates the possibility for other infectious triggers or distinct causes all together.

Possible Post-Viral Complications

The rising rates of multisystem inflammation and pediatric ICU admissions are likely to be accompanied by an increase in children experiencing post-viral complications similar to those observed in severe adult cases. Findings from SARS and MERS as well as limited data on COVID-19 cases indicate that reduced lung function, greater risk for heart conditions and psychological trauma are likely to occur.³⁷ These consequences have the potential to severely alter quality of life in children and produce long-term negative health outcomes. Therefore, it is imperative to establish widely accepted treatment guidelines for these severe cases and elucidate the effectiveness of aspirin and other interventions against long-term complications.³²

Conclusion

Children can exhibit a range of clinical features when infected with COVID-19 and most symptoms resemble those observed in adults. However, children tend to exhibit milder forms of infection with many cases involving symptoms limited to the upper respira-

Table 1. Summary of the clinical features of COVID-19 in children

Category	Description
Mild – Moderate Clinical Features	<ul style="list-style-type: none"> • Fever • Cough • Sore throat • Rhinorrhea • Sneezing • Diarrhea • Vomiting • Dyspnea on exertion • Myalgia • Fatigue • Co-infection
Severe – Critical Clinical Features	<ul style="list-style-type: none"> • Pneumonia with moist rales, dyspnea and/or cyanosis • Reduced lymphocyte and platelet count • Elevated transaminase and creatine kinase levels • ARDS* • Respiratory failure • Shock • Coagulation disorders • Organ dysfunction and failure • Gastrointestinal symptoms during onset of infection • Kawasaki disease <ul style="list-style-type: none"> • persistent fever, rash, conjunctivitis, cracked or dry lips, strawberry tongue, cervical lymphadenopathy, swelling in hands and feet • Other multisystem inflammatory conditions <ul style="list-style-type: none"> • classical Kawasaki disease symptoms, hypotension, shock, myocardial dysfunction, coagulopathy, gastrointestinal involvement
Clinical Features Unique to Children	<ul style="list-style-type: none"> • Lower rates of infection and milder infection • Delayed onset of symptoms and prolonged viral presence • High prevalence of asymptomatic cases

*ARDS = Acute respiratory distress syndrome

tory tract. Co-infection of a bacterial or viral nature is also commonly observed in this demographic. While severe pediatric cases and child mortality associated with COVID-19 are still considered to be rare, the rate of severe cases is on the rise. With the proportion of pediatric ICU admission rates equal to that of adults, it is becoming clear that children may not be as resilient against COVID-19 as initially thought. Although data now indicates that children may have a similar likelihood of developing severe infection to adults, there is an underrepresentation of children in clinical research. Most clinical trials regarding drugs for treatment against COVID-19 have been limited to adult patients. More pediatric-focused research on the efficacy and safety of remdesivir and other interventions is necessary to help guide clinicians through the management of severe pediatric cases.

During the investigation of COVID-19 in children, many studies have reported discrepancies from the typical clinical features of infection observed in adults. Currently, there exist explanations for some features while others lack understanding. Literature suggests that lower susceptibility to infection and milder cases in children are likely due to the smaller epidemiological footprint, superior physiology, and higher likelihood for co-infection in children. Still unknown, however, is the mechanism responsible for a delayed onset of symptoms followed by prolonged infection, though this phenomenon was detected in a small case study with limitations. Therefore, larger, multi-centre case studies involving patients with diverse backgrounds may help to determine if these features reflect the pathogenesis of SARS-CoV-2 in the entire demographic. Further observation on asymptomatic cases in the pediatric population may also be useful in elucidating how COVID-19 develops in children.

Finally, the rise in multisystem inflammatory conditions further demonstrates the increasing prevalence of severe child-related infection. Viral infection complicated by acquired inflammatory conditions can significantly increase the severity of pediatric cases, putting young patients at a risk of cardiovascular damage. These associated conditions even have the potential to induce post-viral damage similar to those seen in adults who recover from severe COVID-19 infection. The negative implications of these complications on the quality of a child's life make it vital to apply research efforts towards establishing widely accepted therapeutic guidelines and validating the effectiveness of interventions against long-term complications.

From the pediatric perspective, a better representation of children in research and literature is needed. An improved understanding of disease pathogenesis and validation of clinical treatments can significantly help in managing severe pediatric cases and it all starts by establishing the ABCs of the clinical presentation of COVID-19 in this younger demographic.

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