

# Progress in the Diagnosis and Treatment of COVID-19 in Children: A Review

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**Abstract:** Coronavirus disease 2019 (COVID-19) has been circulating in many countries around the world, characterized by long incubation period, strong infectivity, strong variability, high population susceptibility and diversified transmission methods. Its causative agent is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Compared with adult patients, the clinical manifestations of COVID-19 in children are often dominated by mild or asymptomatic infections, but children are also important virus carriers and play an important role in the transmission of the virus. In addition, some children will show excessive inflammatory response and experience serious complications such as multisystem inflammatory syndrome in children (MIS-C). At present, the research on COVID-19 in children is still imperfect. This article will review epidemiological characteristics, the mechanism of action, variant characteristics, clinical manifestations, auxiliary examinations and treatment of children with COVID-19, in order to provide help for the diagnosis, treatment and research of children with COVID-19.

**Keywords:** children, COVID-19, mutation, clinical manifestations, treatment

## Introduction

SARS-CoV-2 was identified in Wuhan, China in December 2019.<sup>1</sup> The disease caused by this virus is called COVID-19. COVID-19 is highly infectious.<sup>2</sup> It has now developed into a global pandemic, affecting more than 214 countries and regions around the world. As of July 2021, the cumulative number of confirmed cases worldwide has exceeded 190 million, and the cumulative number of deaths has exceeded 4 million. COVID-19 has become a major public health threat in the world today. However, even with the emergence of a global pandemic, causing serious global harm, current research on COVID-19 is still imperfect, especially in pediatric groups.

Compared with adult patients, pediatric patients have a smaller number, lower incidence, milder symptoms, and lower mortality (about 0–0.2%), better prognosis.<sup>3–5</sup> In pediatric infected individuals, the incidence of common symptoms with COVID-19 was low. Among them, 59.9% (80% in adults) had fever; 55.9% (84% in adults) had cough; 20% (38.4% in adults) had runny nose.<sup>6</sup> Currently, there is increasing evidence that individuals in the pre-symptomatic phase carry a large number of viruses with a greater risk of transmission than those in the symptomatic phase,<sup>7,8</sup> while asymptomatic infected individuals have also been demonstrated to play an important role in the transmission of the virus.<sup>9</sup> This means that children with COVID-19 who have mild symptoms and few symptoms are more likely to have transmission of the virus due to misdiagnosis and missed diagnosis.<sup>10</sup>

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Existing studies show that approximately 5% are infected SARS-CoV-2. Children can become critically ill or critically ill COVID-19,<sup>11</sup> some children will show excessive inflammatory response and experience MIS-C.<sup>12,13</sup> Children with MIS-C are characterized by persistent fever, systemic excessive inflammation, and multiple organ involvement, and many have severe gastrointestinal symptoms as well as symptoms similar to toxic shock syndrome (TSS) such as cardiogenic shock and hypotension, most of which are severe and require pediatric intensive care unit care.<sup>14</sup> Therefore, deepening the understanding of children with SARS-CoV-2 infection, improving the detection rate of children with COVID-19, and rapidly identifying and treating children with critical symptoms such as MIS-C are important tasks in the current world. This article reviews the progress in the epidemiological characteristics, mechanism of action, variation characteristics, clinical symptoms, auxiliary examination and treatment of COVID-19 in children, with a view to providing help for the diagnosis, treatment and research of children with COVID-19.

## Epidemiological Characteristics of COVID-19 in Children

Children are infected mainly through contact with those infected with SARS-CoV-2. The incubation period of the virus can be as long as 24 days.<sup>15</sup> The virus is mainly spread through respiratory droplets and close contact.<sup>3</sup> Most children with COVID-19 can excrete the virus through feces, and aerosols or contact with body fluids may also lead to infection in children when feces and urine cause environmental pollution.<sup>3,16</sup> At the same time, there are reports showing that viruses can be cultivated from wastewater samples, which suggests a possible water transmission route.<sup>17</sup> Starting from the newborn, children of all ages are likely to be infected with COVID-19.<sup>18</sup> Existing data show that the main source of infection for children is SARS-CoV-2-positive adults living in the family.<sup>19</sup> Therefore, timely isolation of adults with a history of epidemiological exposure in the family helps protect children from infection.<sup>20</sup> In general, compared with adults, children are less likely to transmit SARS-CoV-2,<sup>21</sup> and children are less susceptible to SARS-CoV-2 with longer incubation period and viral excretion time in feces.<sup>17</sup> Children have fewer outdoor activities and fewer international travels, and the virus infection rate may be reduced accordingly.<sup>22</sup> Data also show that

children under 5 years of age are less likely to be infected with SARS-CoV-2 than children over 5 years of age, though there is no clear reason for this finding.<sup>23</sup> At present, the effect of caesarean section on the vertical transmission of COVID-19 is not clear.<sup>24</sup> Cases of coinfection with SARS-CoV-2 in newborns born to mothers perinatally infected with SARS-CoV-2 are rare.<sup>25</sup> However, because mothers who have been infected with SARS-CoV-2 at the time of delivery are still infectious, newborns are still at risk of contracting the virus from their mothers.<sup>26</sup> In order to protect newborns from SARS-CoV-2, perinatal clinicians also need to emphasize the importance of focusing on infection control and preventive measures in the family to SARS-CoV-2-infected mothers, requiring mothers and other nursing staff to meet non-infectious indicators.<sup>26</sup>

Children are generally susceptible to the SARS-CoV-2.<sup>18</sup> However, the severity of disease after infection is lower than in adults.<sup>21</sup> In China, children account for approximately only 2% of all COVID-19 infection cases.<sup>27</sup> Children with underlying diseases (such as type 1 diabetes, congenital abnormalities of heart and circulation, obesity, essential hypertension, epilepsy, neuropsychiatric disorders, asthma, malnutrition, Down syndrome, etc.) are at risk of developing severe cases.<sup>28–30</sup> Data suggest that children with complex chronic diseases are three times more likely to have severe disease than children without chronic diseases.<sup>31</sup> Immunocompromised children have a 2.89-fold increased risk of contracting SARS-CoV-2.<sup>32</sup> On the other hand, as children age, the risk posed by a history of malnutrition to children with severe COVID-19 decreases only slightly and is highest in younger children (under 5 years of age).<sup>29</sup> At the same time, the length of hospital stay was significantly prolonged in children with other viral (such as adenovirus, rhinovirus, enterovirus, etc.) infections.<sup>33</sup>

## Pathogenesis of COVID-19 in Children

### Mechanism of Cell Invasion by SARS-CoV-2

SARS-CoV-2 is one of the types of human coronaviruses and belongs to the Beta coronavirus genus. SARS-CoV-2 is mainly composed of membrane, envelope, nucleocapsid and spike glycoprotein (S protein), which plays an important role in the packaging of viral RNA genome and the process of viral infection.<sup>34</sup> SARS-CoV-2 recognizes cells through the S protein on its surface and enters cells after

binding to angiotensin converting enzyme 2 (ACE-2) of cells. Therefore, the body's sensitivity to infection is related to the number of ACE-2.<sup>22,34</sup> ACE2 in pediatric individuals is mainly located in type II alveolar cells and can also be expressed in nasal mucosa, upper respiratory tract, heart, kidney and enterocytes.<sup>35</sup> Therefore, children can present with systemic symptoms of viral infection.<sup>35</sup> At the same time, ACE-2 can process angiotensin-2 into angiotensin-1, 3-7, resulting in vasoconstriction, leukocyte migration, decreased expression of inflammatory cytokines, and activation of fibrinogen, thereby counteracting part of the inflammatory effect.<sup>36</sup> ACE-2, while showing a bidirectional regulatory role during SARS-CoV-2 infection in children, is more evidence that highly expressed ACE-2 expression can protect patients with lung injury from disease exacerbation.<sup>10,37</sup> After infection of host cells with SARS-CoV-2, viral RNA is released into the cytoplasm and uses cellular mechanisms for replication, translation.<sup>35</sup> Newly synthesized viral proteins and RNA genomes bind in the endoplasmic reticulum and Golgi apparatus and release cells through exosomes,<sup>35</sup> which continuously infect new cells and cause severe tissue damage. In addition, it has been shown that transmembrane serine proteinase-2 (TMPRSS2) can promote S protein association with ACE-2 and facilitate SARS-CoV-2 entry into host cells.<sup>38</sup> And the androgen receptor, as the transcription promoter of TMPRSS2, can increase the expression of the TMPRSS2 gene.<sup>38</sup> Therefore, body androgen levels can regulate viral infection through the TMPRSS2/S protein. This may also be the reason why male children have higher admission rates in the Pediatric Intensive Care Unit.<sup>13</sup> CD147 expressed on the cell membrane surface can be used as an alternative receptor for SARS-COV-2, allowing SARS-COV-2 to invade ACE2-deficient T cells, resulting in SARS-COV-2 infection in children, which may provide research direction for the specific treatment of children with SARS-COV-2 infection.<sup>39</sup>

## Immune Damage Caused by SARS-CoV-2 Infection

Children infected with SARS-CoV-2 will produce corresponding immunopathological responses, involving innate immunity (the role of type I interferon (IFN) and pro-inflammatory cytokines) and adaptive immunity (the production of neutralizing antibodies against virus-specific antigens by B cells plays a key role in the clearance of

SARS-CoV-2) as well as autoimmunity.<sup>40</sup> The immune response is bidirectionally regulated after SARS-CoV-2 infection, and its outcome is affected by the degree of immune cell activation and cytokine imbalance.<sup>41</sup> In addition, host-specific factors also determine to some extent whether an individual develops severe disease.<sup>40</sup>

Studies have found that COVID-19 patients have immunological manifestations such as lymphopenia, antibody-dependent enhancement (ADE), and reduced or delayed type IFN. Decreased lymphocytes in children mainly include CD8<sup>+</sup> T cells, CD4<sup>+</sup> T cells and natural killer cells (NK).<sup>42</sup> SARS-CoV-2 may directly infect T cells via ACE2 expressed on T cells, leading to T-cell death, and may also contribute to lymphocyte dysfunction by destroying the secondary lymphoid tissue of the spleen and lymph nodes.<sup>43,44</sup> In addition, animal models suggest that lymphopenia may be attributed to an increase in the number of regulatory T cells.<sup>45</sup> B cells are now known to protect against SARS-CoV-2 infection by producing specific antibodies to block ACE2 receptors to prevent viral entry.<sup>46</sup> However, it has been shown that the severity of COVID-19 is associated with increased IgG reactivity.<sup>47</sup> This may be related to the ADE, the presence of specific antibodies in humans that can bind to SARS-CoV-2 virus and, through their Fc segment, bind to certain FcR-expressing cells thereby mediating viral entry into these cells and enhancing viral infectivity.<sup>48</sup> Interferons are an important part of antiviral immunity, in which type I IFNs (IFN- $\alpha$  and IFN- $\beta$ ) are widely expressed in humans. Viral infection can induce IFN production, which in turn triggers the transcription of IFN-stimulated genes, which have a variety of antiviral functions. The type I IFN response has been found to be severely impaired in critically ill and critically ill COVID-19 patients (as indicated by IFN- $\beta$  deletion and low IFN- $\alpha$  expression, low activity), which is linked to sustained blood viral load and exacerbated inflammatory response.<sup>49</sup> Therefore, we should monitor the immune status of SARS-CoV-2 infected children and interfere promptly to avoid pathological damage caused by immune imbalance.

## Serious Complications in Pediatric Infected Individuals – MIS-C

Overall, children with COVID-19 have milder symptoms and a good prognosis relative to adults. On the one hand, children have less ACE2 receptor expression in respiratory cells and some are undifferentiated and mature, so the risk of SARS-CoV-2 infection is low.<sup>50,51</sup> On the other

hand, there is a phenomenon of elevated physiological lymphocyte levels, particularly NK cell levels, in the blood of children, and this phenomenon persists after SARS-Cov-2 infection.<sup>10</sup> Therefore, pediatric patients are less affected by lymphopenia and decreased white blood cell count.<sup>22,52</sup> In addition, compared with adults, children are less likely to experience uncontrolled immune activation, less inflammatory cytokine (eg, Interleukin-6 (IL-6)) production, and more anti-inflammatory cytokine (eg, Interleukin-10 (IL-10)) production.<sup>10</sup> Therefore, children have mild symptoms and a good prognosis after viral infection.

Although the prevalence and severity of COVID-19 are low in children, some pediatric patients develop a serious complication similar to Kawasaki disease or TSS, namely MIS-C, and the peak of this case often occurs weeks after the peak of COVID-19.<sup>53,54</sup> MIS-C cases often present with positive SARS-Cov-2 antibodies and negative RT-PCR results, so MIS-C is considered to be an immune-mediated post-infectious syndrome. MIS-C may be explained by an abnormal immune or inflammatory response triggered by SARS-CoV-2 infection.<sup>55</sup> The ratio of neutrophils to lymphocytes can be used as an inflammatory marker to assess the condition of COVID-19 patients with MIS-C.<sup>52</sup> When the immune system is activated to a certain degree or even out of control, there is an extreme immune attack on the host. When SARS-CoV-2 further invades children, it prompts the human body to secrete cytokines such as interleukin-8, IL-6, IL-10, and tumor necrosis factor- $\alpha$  and produce a cytokine storm, which leads to an excessive inflammatory response and destroys blood vessels, causing MIS-C.<sup>56</sup> Vascular endothelial injury and vasculitis are important lesions in MIS-C and may also be induced by immune complexes.<sup>57</sup> S protein-IgG immune complexes highly expressed in children with MIS-C cause inflammatory responses and vascular injury through Fc $\gamma$  receptor signaling, neutrophil activation and phagocytosis.<sup>58,59</sup> After global autoantibody screening of children with MIS-C, autoantibodies were found to bind to proteins involved in immune cell signaling as well as structural proteins in the heart and blood vessels.<sup>60</sup> This suggests that autoimmunity may be greatly involved in the pathological progression of MIS-C such as myocarditis and vasculitis. In addition, the efficacy of intravenous immunoglobulin (IVIG) also supports the hypothesis that autoimmune reactions are involved in the pathogenesis of MIS-C.<sup>61</sup>

## The Mutation of the New Coronavirus Types of Mutations

Studies have shown that over time, the SARS-COV-2 produces mutations, and as the accumulation of the number of mutations, eventually certain mutational features will dominate, allowing mutational viral outbreaks.<sup>34</sup> So far, there are 4 globally recognized variants: Alpha or pedigree B.1.1.7 (UK), Beta or pedigree B.1.351 (South Africa), Gamma or pedigree P.1 (Japan/Brazil), and Delta or pedigree B.1.351 (South Africa) pedigree B.1.617.2 (India).<sup>62</sup> The S protein contains two subunits: S1, which contains the receptor binding domain (RBD), and S2, which mediates virus-host cell fusion.<sup>63</sup> The most common mutation in the viral genome is the substitution of D614G (Asp 614→Gly) in S1, which increases the affinity of the virus to the ACE2 receptor, leading to increased host susceptibility and increased transmission.<sup>63,64</sup>

## Significance of Mutations

Viruses obtain more effective functions such as virus replication, transmission and evasion of host defense functions through mutation and natural selection.<sup>63</sup> Among the people infected with the mutant strain, about 80% have only mild symptoms, these patients are ignored by early clinical screening because they have only mild symptoms but no typical early clinical symptoms such as fever, cough and upper respiratory tract infection, and about 20% with severe symptoms of “cytokine storm”.<sup>65</sup> Due to the recognition and binding of S protein, S protein and its RBD are expected to become vaccine targets for SARS-CoV-2.<sup>65</sup> The neutralizing antibodies in serum mainly target RBD domain motifs, in which mutations will significantly affect the neutralization of antibodies.<sup>65</sup> Major viral mutations reduced the neutralization sensitivity of recently vaccinated individuals to convalescent plasma antibodies.<sup>63</sup> Investigating emerging, rapidly spreading variants and ongoing assessment of the phenotype for neutralization of post-vaccination sera should be a high priority for monitoring the impact of vaccine efficacy.<sup>63</sup> There are data showing that SARS-CoV-2 mutants in some patients are 5-fold less sensitive to neutralization by convalescent plasma antibodies.<sup>63</sup> In addition, the D614G mutation did not affect the virus replication or viral particle infectivity in Vero E6 cells, but the infectivity and stability of SARS-CoV-2 produced by the human lung cell line increased after the mutation, while the D614G mutation had the potential to change the conformation of the spike protein, thereby

affecting the neutralization of monoclonal antibodies in an epitope-specific manner.<sup>66</sup> More and more evidence show that immune escape mutations and a variety of fast-spreading mutations will appear in long-term SARS-CoV-2 infections.<sup>63</sup> We should focus on these mutations and variants in these infections and study them accordingly.<sup>63</sup>

Within 5 weeks after the first identification of the Delta variant, the main virus variant in Mesa County, Colorado is the Delta variant, which is now the main variant in the United States.<sup>67</sup> The intensive care unit admissions and case fatality rate in this county suggests that infection with the Delta variant may cause more serious results.<sup>67</sup> Although the vaccine can reduce the transmission potential of SARS-CoV-2 and reduce the risk of virus infection in humans, the Delta variant affects the effect of the vaccine and may increase the risk of virus transmission.<sup>68</sup> Although the specific mechanism of action of the variants on the vaccine has not been elucidated, more importantly, the ability of antibodies to neutralize the Delta variant is reduced compared to the Alpha variant, and the Delta variant is more transmissible and attenuates 10-fold the immune protection of the human body.<sup>69</sup> But in most cases, the level of neutralizing antibodies induced by the vaccine is sufficient to protect them.<sup>69</sup> In order to prevent the further emergence of immune escape variants, a comprehensive global vaccination and prevention strategy is needed to reduce the spread of SARS-CoV-2,<sup>63</sup> the safest and most controllable way to prevent COVID-19.<sup>35</sup> Where children have frequent contact with grandparents, measures to vaccinate children are beneficial in reducing the possibility of transmission of SARS-CoV-2 to the elderly.<sup>70</sup> On the other hand, children's vaccination facilitates their return to school and return to normal life.<sup>71</sup> Given the evolutionary nature of the SARS-CoV-2 genome, drug and vaccine developers should continue to be alert to the emergence of new variants or substrains of the virus.<sup>64</sup> Recent data show that some vaccines have weaker resistance to B.1.351 variants, which requires further research.<sup>63</sup> However, the reduced sensitivity of antibodies to new variants does not essentially prove that the vaccine is less effective.<sup>63</sup>

## Clinical Characteristics of COVID-19 in Children

### Clinical Manifestations

Mild or asymptomatic infection is the main clinical manifestation in pediatric patients, mainly manifested as fever,

sore throat, shortness of breath and pneumonia.<sup>72</sup> Compared with adults, vomiting and diarrhea are more common in pediatric patients, while the incidence of fever and pulmonary symptoms is lower,<sup>22</sup> and anosmia and taste are less common.<sup>73</sup> Children with cancer, children undergoing hematopoietic cell transplantation, children undergoing solid organ transplantation and other children taking immunosuppressive agents mostly present with asymptomatic or mild gastrointestinal symptoms due to low immune function and weak immune response after infection with COVID-19,<sup>32,74</sup> with a low risk of death.<sup>75</sup> The frequency of dyspnea and mortality in immunocompromised adults hospitalized may be due to their incidence of complications (such as hypertension, cardiovascular disease and diabetes).<sup>32</sup> Children have relatively fewer neurological complications after infection with SARS-CoV-2 compared with adults.<sup>76</sup> Neurological symptoms are mainly non-specific symptoms such as headaches, and the incidence of severe symptoms and specific complications is only about 1%.<sup>76</sup> This also causes respiratory Children with insignificant symptoms are easily misdiagnosed and missed.<sup>77</sup> Children with severe infections may develop acute respiratory distress syndrome, septic shock, metabolic acidosis and coagulopathy.<sup>22</sup> The results of the study showed that the hospitalization and intensive care time, lymphocytosis, and abnormal CT findings (ground-glass opacities and consolidation) of children in the critically ill group were higher than those in non-critically ill children, which are the most reliable factors related to the severity of COVID-19.<sup>78</sup>

Some children with progressive disease may develop serious complications MIS-C. The complications are prominent in cardiovascular lesions with clinical manifestations similar to macrophage activation syndrome, symptoms of staphylococcal and streptococcal TSS, sepsis.<sup>79</sup> Other systems also affected include the respiratory system (eg, manifestations of respiratory distress), urinary system (eg, anuria, oliguria), hematologic (eg, active bleeding and thrombosis), digestive system (eg, diarrhoea, liver involvement), nervous system (eg, irritability, confusion), etc.<sup>13</sup> Compared with children without MIS-C, children with MIS-C had less sore throat and respiratory symptoms, inflammation (such as fever and rash) and gastrointestinal (such as vomiting and diarrhea) symptoms.<sup>72</sup> In addition, neurological complications that are rarely seen in children infected with SARS-CoV-2 are particularly likely to occur in SARS-CoV-2 infected children with MIS-C, among which encephalopathy is more

common, sometimes accompanied by transient symptomatic seizures, but without long-term neurological sequelae.<sup>76</sup> Therefore, the possibility of being one of the clinical manifestations of MIS-C should be considered in any child presenting with primary neurological symptoms, accompanied by fever and mild or no respiratory symptoms in an endemic area of COVID-19. In addition, serum albumin levels<sup>13</sup> and croup<sup>80</sup> can also be closely monitored as predictive indicators of MIS-C. Due to most children with MIS-C have mild or no symptoms when initially infected with COVID-19, and high vigilance is needed for MIS-C.<sup>81</sup>

## Imaging Manifestations

Chest computed Tomography (CT) can be used for screening diagnosis of COVID-19 infection, showing disease progression, and has great promise in adult symptom screening applications.<sup>82,83</sup> However, because the clinical symptoms of children with COVID-19 are relatively mild, difficult to detect by CT, and CT will produce high-dose radiation, the necessity of chest CT should be proposed by pediatricians according to clinical needs.<sup>83</sup> The most common CT abnormalities in children with COVID-19 pneumonia are peripheral and/or subpleural mixed ground-glass opacities and consolidation.<sup>84</sup> In more than half of the children with abnormal CT examinations, the “halo” sign is seen, that is, focal consolidation, surrounded by ground glass shadows, and bronchial wall thickening and peribronchovascular opacity are more frequent in children than in adults.<sup>84</sup> If multiple lobular lesions appear in the lungs and white lungs of children, it indicates a high inflammatory response.<sup>82</sup> After active treatment of children, lung lesions can be absorbed to varying degrees.<sup>82</sup> Chest X-ray and CT findings of infants are atypical, and still need to further research and summary.<sup>82</sup>

86.4% of pediatric patients with COVID-19 infection can be correctly diagnosed by lung ultrasound (LUS).<sup>85</sup> In the absence of reliable, highly sensitive diagnostic tests or when there are too many requests for nasal swab, the LUS can be used to diagnose children with suspected COVID-19 and persistent cough, because ultrasound can highlight the interstitial lung lesions caused by COVID-19 and can be used to strengthen the diagnostic ability in children with suspected COVID-19 pneumonia.<sup>86</sup> Standardized LUS protocols combine ultrasound probability patterns with clinical phenotypes, and both LUS high likelihood patterns and LUS moderate likelihood patterns are very sensitive to the exclusion of interstitial pneumonia, which

increases in sensitivity when the child’s clinical symptoms worsen.<sup>87</sup> During the COVID-19 pandemic, LUS can quickly identify children with or without COVID-19 pneumonia infection, which helps clinicians to quickly guide the management of children to use hospital resources more efficiently.<sup>87</sup> On the other hand, CT, although the gold standard in the assessment of pneumothorax, is limited by the inconvenience of transporting critically ill patients and their high dose of radiation.<sup>88</sup> Nursing lung ultrasound can reduce the exposure of ionizing radiation, so it has become an effective auxiliary means for the diagnosis of pneumothorax in the post-diagnosis follow-up of children with SARS-CoV-2.<sup>88</sup> However, there are still reports showing that LUS incorrectly diagnosed COVID-19 in 45% of uninfected individuals, so LUS needs to be used reasonably in clinic.<sup>85</sup>

## Laboratory Auxiliary Examination

Prompt diagnosis of children infected with SARS-CoV-2 is not only important for individuals, but also essential to reduce the spread of the virus during the pandemic.<sup>89</sup> Abnormal results of COVID-19 laboratory tests in children are less common than in adults.<sup>90</sup> Cases of lymphopenia are very common in adults with COVID-19, while only 5.5% of children present with this test result.<sup>90</sup> Children are less likely to have leukopenia, and C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), alanine aminotransferase levels, lactate dehydrogenase levels, and aspartate aminotransferase levels are not significantly increased, while phosphocreatine isoenzyme levels are often significantly increased.<sup>90</sup> The level of procalcitonin in most children is normal, and the number of D-dimer and ferritin in the blood of severely ill children increases, and the number of lymphocytes gradually decreases.<sup>3</sup> The number of neutrophils in children with ordinary COVID-19 can be reduced, but the number of neutrophils in severely ill children is significantly increased.<sup>52</sup> For example, in children with progressive inflammation, they often present with lymphopenia, hypoalbuminemia, hypertriglyceridemia, and elevated IL-6, ESR, lactate dehydrogenase, CRP, fibrinogen, procalcitonin, D-dimer, and serum ferritin.<sup>13</sup> The levels of bilirubin and liver enzymes can be used to diagnose the severity of childhood diseases.<sup>22</sup> In short, SARS-COV-2 can cause abnormal hematological parameters in children, which is different from adult examination results. This finding is conducive to early diagnosis and treatment of COVID-19 in children.

## Treatment of COVID-19 in Children

### General Treatment

It is recommended that most children with COVID-19 use supportive care.<sup>91</sup> Effective oxygen therapy measures can be given under hypoxia, and nasal high-flow oxygen ventilation, non-invasive or invasive mechanical ventilation, prone position ventilation therapy or lung recruitment and extracorporeal membrane oxygenation can be taken, when necessary, according to the child's situation.<sup>3</sup> For children with high fever, convulsions or epileptic seizures, the corresponding drugs should be used to control the condition first to ensure that the airway is unobstructed before treatment.<sup>3</sup>

### Antiviral Treatment

Antiviral drugs (eg, remdesivir) can be used to treat critically ill or critically ill children (age  $\geq 12$  years, weight  $\geq 40$  kg) who require oxygen supplementation, or invasive mechanical ventilation or extracorporeal membrane oxygenation.<sup>92</sup> COVID-19 monoclonal antibody therapy is not recommended for children, but infliximab can effectively treat children with Crohn's disease and prevent the systemic inflammatory response in children.<sup>93</sup> Other drugs including chloroquine, hydroxychloroquine, azithromycin, or lopinavir/ritonavir are also not recommended for the treatment of COVID-19 in children.<sup>92</sup> Drug development has focused on targets for viral entry into the host and on viral RNA-dependent RNA polymerases.<sup>94</sup> Due to the emergence of SARS-CoV-2 variants, effective and broad-spectrum antiviral drugs against SARS-CoV-2 and its variants need to be investigated, such as fusion inhibitors targeting the conserved heptapeptide repeat region 1 in the S2 subunit of the S protein.<sup>95</sup>

### Traditional Chinese Medicine Treatment

Traditional Chinese Medicine (TCM) bases on syndrome differentiation and treatment.<sup>96</sup> Through the analysis of signs and prescriptions, it can prevent COVID-19, which reflects the idea of "prevention and treatment", and has an integrated mechanism of anti-virus, anti-inflammatory, immunomodulatory and organ protection.<sup>96</sup> It can improve the cure rate, delay the course of the disease, reduce mortality, and treat COVID-19.<sup>96</sup> In terms of prevention, herbal fragrances, Chinese herbal decoctions, moxibustion, food therapy, Chinese medicine substitutes for tea, and Chinese herbal foot baths can be used, thus cutting off the route of transmission.<sup>97,98</sup> In terms of TCM treatment,

Chinese medicine decoctions and Chinese patent medicines can be used for treatment, and the corresponding Chinese patent medicines can be used according to the clinical manifestations.<sup>97</sup> At the same time, acupuncture therapy can regulate the human immune system, and different acupoints are used in different clinical stages.<sup>97</sup> Acupuncture is expected to become a safe and effective adjuvant therapy.<sup>97</sup> According to reports, integrated traditional Chinese and western medicine can shorten the treatment time of COVID-19 patients, improve the clinical cure rate, and play a huge role in fighting the COVID-19 pandemic.<sup>99</sup> Because the disease spectrum of children is different from that of adults, the effectiveness and safety data of TCM in treating children are not comprehensive, and this method needs further study.<sup>100</sup>

### Adjuvant Treatment

Vitamin C has the potential to control inflammation, but there is still no evidence to prove that vitamin C supplementation can effectively reduce the risk of SARS-CoV2 infection.<sup>101</sup> Vitamin D can play a role in preventing or treating SARS-CoV2 infectious diseases by improving the immune response of children to the virus.<sup>102</sup> Folic acid is also a potential treatment for COVID-19.<sup>103</sup> In addition, the COVID-19 virus spike protein uses TMPRSS2 to invade the host.<sup>104</sup> Androgen receptor is the transcription promoter of TMPRSS2.<sup>38</sup> Therefore, androgen can promote the entry of COVID-19 virus into host cells. TMPRSS2 inhibitors or ACE2 receptor binding competitive inhibitors are the active ingredients to prevent the new coronavirus, so it is possible to treat COVID-19 by inhibiting androgens, while bromhexine, a drug with both favorable and safe properties, gives clinicians a better treatment strategy, and the specific therapy is still under investigation.<sup>104</sup>

### Treatment for MIS-C

Supportive intensive care, immune modulation (steroids and intravenous immunoglobulins), and organ support therapy (including hemodynamic support) are effective in children with MIS-C.<sup>55</sup> In the pediatric MIS-C treatment consensus, intravenous immunoglobulin is recommended as the first-line treatment, corticosteroids as the second-line drugs, and anticoagulants according to the child's condition.<sup>105</sup> At present, the most widely recommended is intravenous immunoglobulin drugs,<sup>106</sup> the drug helps restore the systolic function of the left ventricle.<sup>107</sup> In addition, the length of hospital stay of

children is shortened after applying corticosteroids to MIS-C treatment.<sup>108</sup> For example, low-dose prednisolone can shorten the length of hospital stay in children with moderate to severe COVID-19.<sup>109</sup> There have been cases of MIS-C that have fully recovered with oral steroid therapy alone.<sup>110</sup> Another report also indicated that the risk of cardiovascular dysfunction was lower in MIS-C children with cardiac insufficiency treated with IVIG in combination with corticosteroids compared with IVIG treatment alone,<sup>111</sup> shorter time to recovery of cardiac function.<sup>112</sup> However, because corticosteroids may slow the rate of viral clearance and increase the risk of infection in children, and the optimal dose and duration of corticosteroid therapy in children with MIS-C have not been clarified.<sup>113</sup> Therefore, the use of corticosteroids should be used with caution according to the clinical condition of the child.

## Treatment of Immunocompromised Children

Immunocompromised children mainly include: children with congenital immunodeficiency, children with acquired immunodeficiency caused by immunosuppressive therapy and children with immune dysfunction caused by related chronic diseases (such as organ dysfunction or failure or severe inflammatory diseases).<sup>114</sup> Immunosuppression appears to be a protective factor, making immunocompromised children at lower risk of developing critical illness.<sup>115</sup> Therefore, a certain dose of immunosuppressive agents should be maintained in children on long-term immunosuppressive therapy to prevent recurrence of underlying diseases. On this basis, attempts at antiviral therapy in immunocompromised children can control viral invasion and improve the prognosis of children.<sup>75,115</sup> For children who do not respond to antiviral therapy, IVIG shows good efficacy without significant complications for the time being.<sup>115</sup> Moderate anti-inflammatory therapy (such as anti-IL-6 or corticosteroids) may also be tried in children with progressive pneumonia.<sup>116</sup> In summary, The treatment of immunocompromised children should be decided based on their clinical manifestations.<sup>117</sup>

## Other Treatments

Blood purification therapy can be used to remove inflammatory factors and block the “cytokine storm”; bronchoscopy and lavage can ensure normal airway ventilation and

prevent obvious airway obstruction;<sup>3</sup> the use of convalescent plasma therapy to treat severely ill children is safe and effective,<sup>118</sup> and there is evidence that this therapy does not increase the risk of thromboembolism in children with COVID-19,<sup>119</sup> appropriate antibiotics (such as azithromycin) can be used control secondary bacterial infections.<sup>120</sup>

## Abbreviations

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MIS-C, multisystem inflammatory syndrome in children; TSS, toxic shock syndrome; S protein, spike glycoprotein; ACE-2, angiotensin converting enzyme 2; TMPRSS2, transmembrane protease serine 2; IFN, interferon; ADE, antibody-dependent enhancement; NK, natural killer; IL-6, interleukin-6; IL-10, interleukin-10; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RBD, receptor binding domain; CT, computed tomography; LUS, lung ultrasound; TCM, traditional Chinese medicine; IVIG, intravenous immunoglobulin.

## Summary

As a special group, most children with COVID-19 present asymptomatic or with mild symptoms and are less affected in the COVID-19 pandemic, but children are also important virus carriers and may also die due to missed diagnosis and misdiagnosis or combined serious complications. For most children with COVID-19, only general supportive therapy is sufficient. However, for critically ill children with serious complications such as MIS-C or underlying immunocompromised patients, after comprehensive evaluation, rational use of IVIG, steroids and antiviral therapy and other measures can reduce the occurrence of serious hemodynamic complications and improve the prognosis of critically ill children. Current research on children infected with SARS-CoV-2 is still imperfect and there are still few available drugs. Clinicians should maintain a high degree of vigilance for children with the risk and potential symptoms of SARS-CoV-2 infection, pay attention to the clinical diagnosis, treatment and prognosis of pediatric COVID-19 patients, reduce the risk of virus transmission caused by missed diagnosis, and reduce the mortality of pediatric COVID-19.

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Wei Lin and Zhenlang Lin contributed equally to this work and should be considered co- corresponding author.



## Disclosure

The authors report no conflicts of interest in this work.

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