

COVID-19 infection in children and adolescents

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Abstract

The COVID-19 pandemic has predominantly affected the adult population. The disease is less well-defined in children (≤ 18 years). This review summarises the current understanding of the epidemiology, clinical manifestations, and management of COVID-19 in children and adolescents. The prevalence of COVID-19 is significantly lower in children than adults, but paediatric disease is likely underdiagnosed as a result of the high numbers of asymptomatic or mild cases. Children are vulnerable to family cluster outbreaks, but are unlikely to be index cases within a household. Vertical transmission or breast milk transmission are yet to be proven. Between 10 and 90% of paediatric COVID-19 cases are asymptomatic. Symptomatic cases typically present with mild symptoms, including cough, fever and sore throat. Intensive care admission and mortality are rare. Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 is a rare, but severe, newly emerging phenotype. At present, there is no specific treatment for COVID-19 in adults or children; management is usually supportive. For severe or critical disease, including paediatric multisystem inflammatory syndrome temporally associated with COVID-19, the decision to start antiviral or immunomodulatory therapy should be on a case-by-case basis; in the UK, this should be done within a clinical trial. Further research is needed into both the disease course and treatment of paediatric COVID-19.

Key words: Adolescents; Children; COVID-19 infection; Epidemiology of COVID-19 infection in children; Management of COVID-19 infection in children

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Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), originated in Wuhan, China in December 2019 and has spread globally. The pandemic has had devastating consequences: as of 5 June 2020, 6 722 408 confirmed cases and 393 934 deaths have been reported worldwide (Dong et al, 2020a). The burdens of morbidity, and certainly mortality, lie chiefly in the adult population (Wu and McGoogan, 2020), while COVID-19 in children has been observed to run a milder, less well-defined course.

This review summarises current understanding of the epidemiology, clinical manifestations, and management of COVID-19 in children and adolescents (aged ≤ 18 years).

Epidemiological features

Internationally, the prevalence of confirmed COVID-19 is significantly lower in children than in adults. In February 2020, a Chinese case series of 72 314 patients with suspected or confirmed COVID-19 found that only 2.2% of the 44 672 confirmed cases were aged 19 years or younger: 0.9% were less than 10 years old and 1.3% were 10–19 years old (Wu and McGoogan, 2020). A further study sought to identify all hospitalised infants (under 1 year old) with COVID-19 in China and found only nine cases from December to February (Wei et al, 2020). Data from Italy show that children accounted for only 1.2% of 22 512 COVID-19 cases in March (Livingston and Bucher, 2020). In the USA, in April, hospitalisation rates as a result of COVID-19 (per 100 000) were 0.3 and 0.1 in ages 0–4 years and 5–17 years respectively, vs 2.5, 7.4, and 13.8 in ages 18–49 years, 50–64 years and ≥ 65 years respectively (Garg et al, 2020). In Australia, as of 26 April, 1% of all COVID-19 cases were aged under 10 years, and 3% aged 10–19 years (COVID-19 National Incident Room Surveillance Team, 2020).

There are a number of theories to explain the lower incidence of COVID-19 in children. One is that differences in angiotensin-converting enzyme 2 receptors, to which SARS-CoV-2 binds, in the fetal lung compared to mature lung tissue may provide protection;

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another is that exposure to other respiratory viruses common in childhood may convey cross-protection (Mustafa and Selim, 2020). It is also likely that the true number of paediatric cases is unknown, as a greater proportion of children have asymptomatic disease (Ludvigsson, 2020a).

Epidemiological data suggest that children are vulnerable to family-aggregated infection, but unlikely to drive it. The majority (85%) of all reported paediatric cases have had exposure to a household positive contact or been within a family cluster outbreak (Liguoro et al, 2020). A study that identified all patients aged under 16 years with confirmed COVID-19 in Switzerland found that in 79% of family cluster cases an adult household contact developed suspected or confirmed COVID-19 before the child (Posfay-Barbe et al, 2020). A systematic review found that children were unlikely to be the index case in a household cluster (Ludvigsson, 2020b).

It has been observed that the incubation period is likely longer in children than in adults, leading them to present with symptoms after adult relatives who were contemporaneously exposed (Cai et al, 2020). The longer incubation time in children may be because they experience milder disease (Lauer et al, 2020).

The SARS-CoV-2 virus spreads via human-to-human transmission through direct contact, droplets and surfaces. Some studies also suggest the potential for faecal–oral transmission (Ge et al, 2020). The possibilities of viral shedding into maternal breast milk and vertical transmission from mother to newborn are yet to be proven, as studies thus far have involved only small sample sizes (Mustafa and Selim, 2020).

A systematic review found no evidence that sex influences the incidence of paediatric COVID-19 infection (Mustafa and Selim, 2020), and there is a paucity of evidence for the effects of comorbidities in children (Castagnoli et al, 2020). No research into the role of ethnicity in children has been published thus far.

Clinical features and differences per age group

In some children, COVID-19 infection can be completely asymptomatic (estimated to vary from 10% (Qiu et al, 2020) to 90% (Dong et al, 2020b) of infected children), while the majority of symptomatic cases have mild disease. A meta-analysis found that the following clinical manifestations (Figure 1) were most common: cough (49%), fever (47%), sore throat (36%), diarrhoea and/or vomiting (17%), and rhinorrhoea (9%). Pneumonia was recorded in 60% of cases (Mustafa and Selim, 2020).

A review concluded that the clinical manifestations of disease in adolescents differed from younger age groups: adolescents were more likely to suffer from dizziness, chills and myalgia, while these symptoms were rare in younger children (Leung, 2020).

A retrospective study of 2141 children with confirmed or suspected COVID-19 found that severe or critical illness was most prevalent in the infant group; the prevalence was 10.6% in infants, 7.3% in pre-school children, 4.2% in school children (aged 6–10 years), 4.1% in 11–15 years and 3.0% in 16–17 years (Dong et al, 2020b).

Diagnosis and testing

The real-time reverse transcriptase-polymerase chain reaction test remains the gold standard for the diagnosis of SARS-CoV-2. In children, this is usually done by nasopharyngeal or throat swab (Castagnoli et al, 2020; Mustafa and Selim, 2020).

Stool samples or rectal swabs have also been used for reverse transcriptase-polymerase chain reaction: two studies have identified cases in which rectal swabs remained positive after nasopharyngeal or throat swabs became negative, suggesting persistent viral shedding into the gastrointestinal tract (Cai et al, 2020; Xu et al, 2020a).

Imaging (chest X-rays and computed tomography scans) in symptomatic children with COVID-19 infection is predominantly characterised by bronchial thickening, ground-glass opacities, or inflammatory lung lesions (Castagnoli et al, 2020).

Serological immunoassays have not yet been widely used for diagnostic purposes in paediatric studies, other than in children who develop multisystemic inflammatory involvement. The most common blood test abnormalities seen are shown in Figure 2 (Mustafa and Selim, 2020).

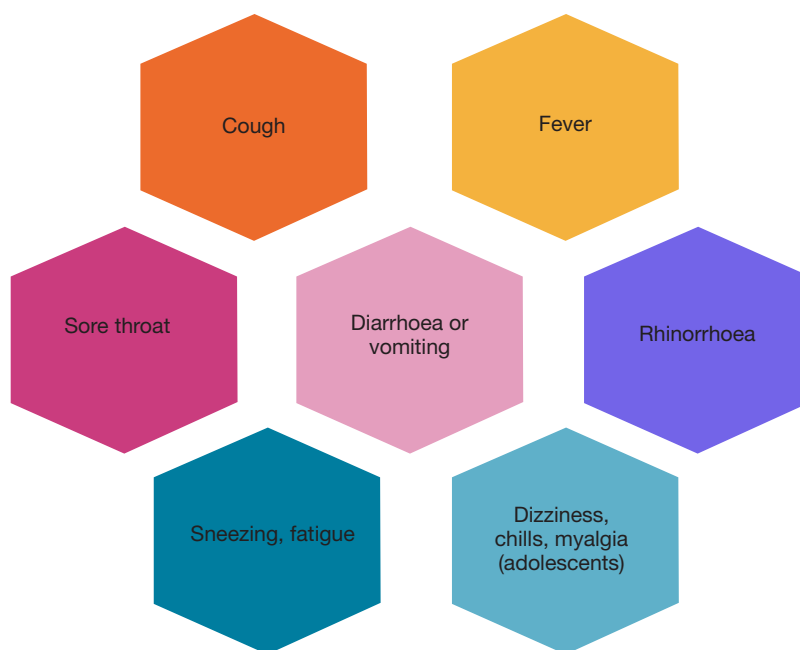


Figure 1. Common clinical manifestations of symptomatic COVID-19 infection in children.

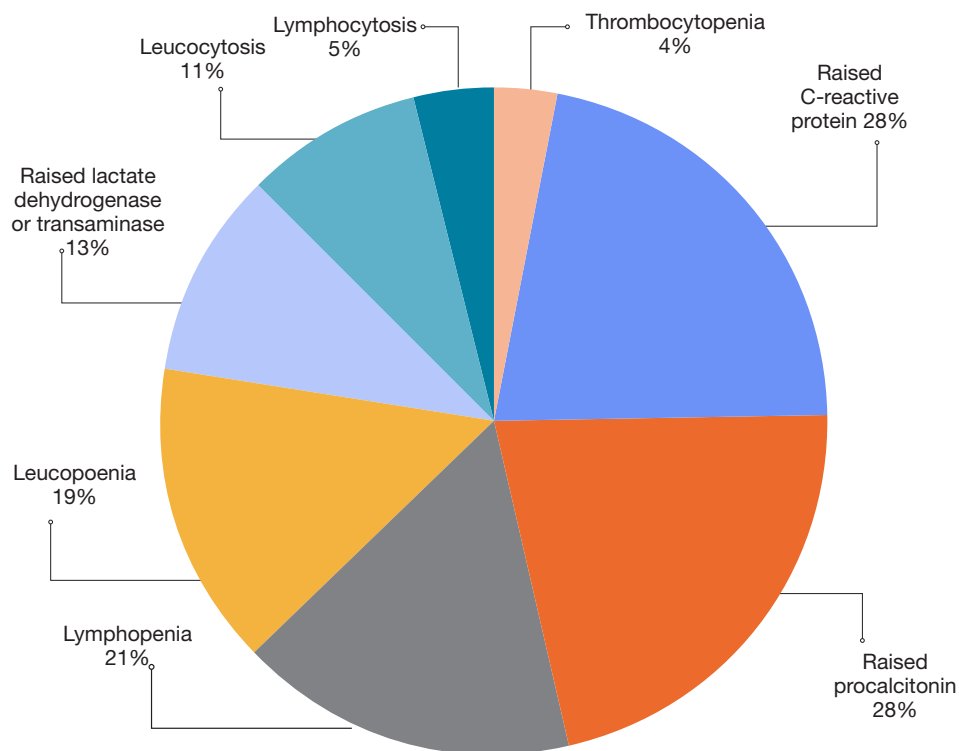


Figure 2. Common laboratory results in children with COVID-19 infection. Adapted from Mustafa and Selim (2020).

Intensive care unit admission rates

Admission to paediatric intensive care as a result of COVID-19 is rare. In a Chinese study of 171 confirmed cases, three children (1.8%) required paediatric intensive care admission and invasive ventilation: all three had underlying health conditions (Lu et al, 2020). A larger study of 2143 children found that 0.6% of patients developed ‘critical’ disease, defined by the authors as development of acute respiratory distress syndrome or respiratory failure, and in some cases shock and organ dysfunction (including encephalopathy, myocardial dysfunction, abnormal coagulation, and acute kidney injury) (Dong et al, 2020b).

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Mortality rates

There have been very few deaths in children with COVID-19. An analysis of all confirmed COVID-19 cases of all ages in China up to 11 February reported 1023 deaths (out of 44 672 cases; 2.3% case fatality rate); of these, there were no deaths in children aged 0–9 years (of 416 cases), and one death in a child aged between 10–19 years (of 549 cases; 0.2% case fatality rate) (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020).

Newly emerging clinical phenotype: paediatric multisystem inflammatory syndrome temporally associated with COVID-19

Although, as described, the majority of paediatric cases of COVID-19 are asymptomatic or mild, a small number of children develop a significant multisystemic inflammatory response, termed paediatric multisystem inflammatory syndrome temporally associated with COVID-19. This shares features with other paediatric inflammatory conditions such as Kawasaki disease, toxic shock syndromes, bacterial sepsis, and macrophage activation syndromes. It may also present with unusual abdominal symptoms and raised levels of inflammatory markers (Royal College of Paediatrics and Child Health, 2020a). **Table 1** summarises the clinical features of paediatric multisystem inflammatory syndrome temporally associated with COVID-19.

A case series from London described eight previously well children (aged 4–14 years) who developed features similar to atypical Kawasaki disease, Kawasaki-like disease shock syndrome, or toxic shock syndrome. All eight children tested negative on bronchoalveolar lavage or nasopharyngeal aspirates but subsequently had positive SARS-CoV-2 antibodies. They presented with persistent fevers (>38°C), rash, conjunctivitis, peripheral oedema, extremity pain and gastrointestinal symptoms. Five developed small effusions (pleural, pericardial and/or ascitic) suggestive of a diffuse inflammatory process. All developed shock and eventually required inotropic support. Seven children required invasive ventilation for cardiovascular stabilisation and developed a degree of myocardial dysfunction. One child developed a giant coronary aneurysm. A 14-year-old patient died from a large ischaemic

Table 1. Clinical features in children with paediatric multisystem inflammatory syndrome temporally associated with COVID-19

Frequency seen	Clinical feature
All	Persistent fever >38.5°C*
Most	Hypotension
	Oxygen requirement
Some	Conjunctivitis*
	Rash*
	Mucous membrane changes*
	Swollen or hard hands and feet*
	Lymphadenopathy*
	Neck swelling
	Sore throat
	Abdominal pain, diarrhoea or vomiting
	Headache, confusion or syncope
	Cough or respiratory symptoms

*Features that overlap with diagnostic criteria for Kawasaki disease. Adapted from Royal College of Paediatrics and Child Health (2020a).

cerebrovascular infarction after developing arrhythmia with refractory shock requiring extracorporeal life support (Riphagen et al, 2020).

An Italian case series identified ten patients (aged 7.5 ± 3.5 years) who presented with Kawasaki-like symptoms. There was a high clinical suspicion of COVID-19 infection in all ten patients. When compared to patients with classical Kawasaki disease seen in the same centre before the pandemic, this cohort had a more severe disease course, which was refractory to intravenous immunoglobulin, more often requiring adjunctive steroid treatment. Furthermore, a higher proportion of patients developed Kawasaki-like disease shock syndrome and macrophage activation syndrome (Verdoni et al, 2020).

The majority of patients in both of these studies had positive antibodies to SARS-CoV-2 and negative viral reverse transcriptase-polymerase chain reaction results. This indicates that paediatric multisystem inflammatory syndrome temporally associated with COVID-19 is likely to be a post-infectious inflammatory syndrome, likely immune complex- or antibody-mediated, and may occur after an asymptomatic primary infection (Viner and Whittaker, 2020).

Management and treatment

At present, there is no specific treatment for COVID-19 infection in children or adults. The Royal College of Paediatrics and Child Health (2020b) issued treatment recommendations tailored according to symptom severity and consensus recommendations for treatment of acute respiratory distress syndrome in children (Paediatric Acute Lung Injury Consensus Conference, 2015).

In addition, a Chinese group of paediatric experts published and reviewed consensus criteria for management of COVID-19 infection in paediatric population (Shen et al, 2020). Thus, the authors present general management recommendations for COVID-19 infection in children, using a combination of available publications (Figure 3) (Royal College of Paediatrics and Child Health, 2020b,c; Shen et al, 2020; Zimmermann and Curtis, 2020).

Mild and moderate symptoms (upper respiratory tract symptoms)

As discussed earlier, the majority of paediatric COVID-19 cases are asymptomatic or mild. The general recommendations focus on medical isolation and supportive therapy, as most patients in this category can be managed at home.

Suspected cases should be isolated in a single room, while confirmed cases can be accommodated in the same room (Royal College of Paediatrics and Child Health, 2020b).

Supportive care includes adequate fluid and calorie intake, maintaining water electrolyte balance and homeostasis, and provision of psychotherapy support for older children. Treatment with paracetamol is recommended for fever (Royal College of Paediatrics and Child Health, 2020b).

Severe symptoms (mild–moderate acute respiratory distress syndrome) requiring hospitalisation

Supportive treatment aims to prevent severe acute respiratory distress syndrome, organ failure and secondary nosocomial infections. Based on experience with other viral respiratory diseases most children, even with additional lung involvement, are unlikely to develop respiratory failure (Zimmermann and Curtis, 2020).

In addition to supportive care (see below), the following treatment recommendations apply to this category of patients:

- Low flow nasal cannula oxygen to treat hypoxia
- If hypoxia persists despite low flow nasal cannula, trial of high flow nasal cannula
- Antibiotics should be prescribed based on usual grounds and clinical judgement (with prior urine and/or blood cultures, throat swab, +/- lumbar puncture as appropriate) in the following situations:
 1. Unwell on admission, febrile or deteriorating
 2. Blood tests suggestive of bacterial infection, such as raised C-reactive protein level and neutrophil count
 3. Chest X-rays suggestive of lobar pneumonia (with clinical correlation)

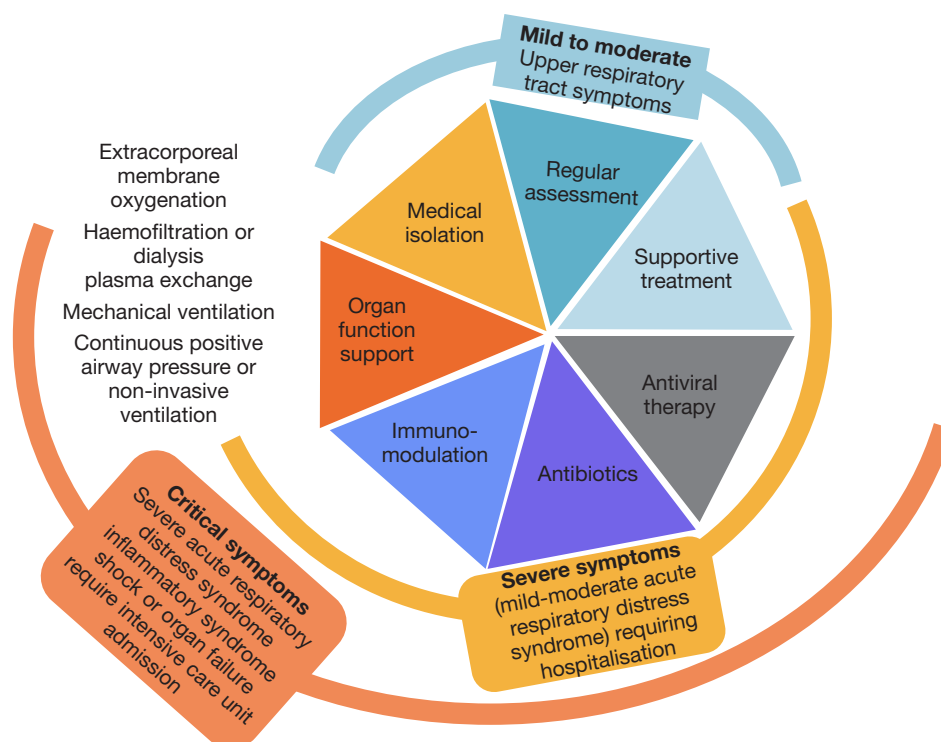


Figure 3. Management recommendations for COVID-19 infection in children and adolescents.

4. An alternative or coincidental diagnosis is suspected
 5. Clinical features of sepsis (taking into account atypical or overlapping features).
- In children with acute wheeze or asthma exacerbations, prompt treatment with salbutamol and systemic steroids is recommended within 1 hour of arrival at hospital
 - The decision to use antiviral and immunomodulatory medication should be based on signs of progressive respiratory deterioration regardless of comorbidity, with the recommendation that, as far as possible, all patients in the UK should only receive antiviral or immunomodulatory treatments for COVID-19 within a clinical trial.

Critical symptoms

Children with critical symptoms as a result of COVID-19, such as severe acute respiratory distress syndrome, septic shock, altered consciousness or multi-organ failure, paediatric multisystem inflammatory syndrome temporally associated with COVID-19, should receive supportive care as above, and organ support if there is evidence of organ failure. Treatment with antiviral and immunomodulatory therapy may be considered.

There is currently limited evidence of efficacy of antiviral and immunomodulatory therapy for COVID-19 in adults (Beigel et al, 2020; Luo et al, 2020), and no evidence in children. The decision to start treatment should be made carefully on a case-by-case basis.

Antiviral treatment

Antiviral treatment is most effective if initiated quickly upon clinical presentation or before clinical deterioration (Royal College of Paediatrics and Child Health, 2020b).

There are several treatment options:

- Lopinavir (LPV)-ritonavir (RTV) (Kaletra) + ribavirin for 7 days: LPV/RTV 400/100 mg in 5 ml liquid formulation (1–3 ml 12-hourly, based on body weight), ribavirin 10 mg/kg (max 900 mg) 12-hourly
- Although treatment with chloroquine and hydroxychloroquine was initially recommended, the preliminary results of clinical trials of these agents in adults with COVID-19 infection have shown no efficacy, so they are not currently indicated (Kupferschmidt, 2020)
- Remdesivir (GS-5734) for 10 days: 5 mg/kg loading dose, then 2.5 mg/kg once daily for 10 days

Immunomodulatory treatment

This is recommended if there is evidence of an inflammatory syndrome (characterised by raised C-reactive protein, ferritin, interleukin-6 (IL-6), sCD25). Some patients with COVID-19 infection and acute respiratory distress syndrome develop clinical features and serological markers found in hyperinflammatory syndromes, such as secondary haemophagocytic lymphohistiocytosis, sepsis-associated macrophage activation-like syndrome and chimeric antigen receptor T (CAR-T) cell therapy-associated cytokine release syndrome. Inflammatory pathology appears to be mainly localised within the lung tissue in COVID-19 (Wang et al, 2020), and levels of systemic inflammatory markers are generally lower than seen in these other syndromes.

Tocilizumab (a humanised anti-IL6 monoclonal antibody) is an established therapy for cytokine release syndrome following CAR-T cell therapy and has been used to treat hyperinflammation in sepsis-associated macrophage activation-like syndrome as well as COVID-19 infection (Xu et al, 2020b).

The following doses are recommended for COVID-19-associated hyperinflammation (Royal College of Paediatrics and Child Health, 2020b): 12 mg/kg in children \leq 30 kg, and 8 mg/kg (max 800 mg) in children $>$ 30 kg, to repeat after 12 hours if no improvement.

Anakinra is a recombinant antagonist of the human interleukin 1 (IL-1) receptor and is an established therapy in macrophage activation syndrome, and off-licence in secondary haemophagocytic lymphohistiocytosis. It has also demonstrated a survival benefit in sepsis-associated macrophage activation-like syndrome.

Anakinra should be given subcutaneously at a dose of 2 mg/kg once daily, which can be increased by 2 mg/kg per day if unresponsive, up to the maximum dose 8 mg/kg (Paediatric Acute Lung Injury Consensus Conference Group, 2015). The intravenous formulation should be used at a loading dose of 2 mg/kg, followed by a continuous infusion of 0.02 ml/kg/hr (2 mg/kg/day) in children \leq 20 kg or 0.01 ml/kg/hr (2 mg/kg/day) for children $>$ 20 kg. If unresponsive, the dose can be increased by 2 mg/kg/day every 12 hours, up to a maximum dose of 12 mg/kg/day.

Corticosteroids

Although corticosteroids should be avoided in most COVID-19 infections, they may be beneficial in the following situations:

1. Rapidly deteriorating chest imaging and occurrence of acute respiratory distress syndrome
2. Obvious toxic symptoms, encephalitis or encephalopathy, secondary haemophagocytic lymphohistiocytosis and other serious complications
3. Septic shock
4. Wheeze.

Intravenous methylprednisolone (1–2 mg/kg/day) is recommended for 3–5 days, but not for long-term use.

Management of paediatric multisystem inflammatory syndrome temporally associated with COVID-19

Children with symptoms suggestive of paediatric multisystem inflammatory syndrome temporally associated with COVID-19 are characterised by severe clinical manifestations, some of them overlapping with Kawasaki disease; therefore, the treatment recommendations share commonalities. Children suspected or diagnosed with Kawasaki-like disease associated with COVID-19 infection require hospital admission for evaluation, observation and treatment. As with Kawasaki disease, treatment with high-dose intravenous immunoglobulin (2 g/kg) has been used as a first-line management option, and antibiotics, corticosteroids (methylprednisolone), heparin, aspirin, and immunomodulation (such as tocilizumab) have also been used. Intravenous immunoglobulin is effective in reducing the risk of coronary artery disease in Kawasaki-like disease when administered within 10 days of fever onset.

Respiratory support

In the case of respiratory distress that occurs despite nasal cannulae or mask oxygenation, heated humidified high flow nasal cannula non-invasive respiratory support, non-invasive ventilation such as continuous positive airway pressure, or non-invasive high-frequency

ventilation is recommended (Shen et al, 2020). If there is no improvement, mechanical ventilation with endotracheal intubation and a protective lung ventilation strategy should be adopted as a last resort.

Haemofiltration

Continuous haemofiltration should be considered in cases of multiple organ failure (especially acute kidney injury) or fluid overload and life-threatening water, electrolyte, and acid–base imbalance, using continuous veno-venous haemofiltration or continuous veno-venous haemodialysis. In the presence of liver failure, plasma exchange is indicated (Shen et al, 2020).

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation should be considered when mechanical ventilation or haemofiltration are not effective, and in the context of additional cardiopulmonary failure (MacLaren et al, 2020). Extracorporeal membrane oxygenation is indicated in the following situations (Shen et al, 2020):

1. $\text{PaO}_2/\text{FiO}_2 < 50$ mmHg or oxygen index > 40 for more than 6 hours, or severe respiratory acidosis ($\text{pH} < 7.15$)
2. High mean airway pressure during mechanical ventilation, or severe air leakage and other severe complications
3. Circulation cannot be improved with conventional treatment, or large amounts of vasoactive drugs are required to maintain basal blood pressure, or lactate levels continuously rise.

Clinical trials in children with COVID-19 infection

As per Royal College of Paediatrics and Child Health recommendations, access to antiviral and immunomodulatory treatment for children with confirmed COVID-19 infection should be facilitated through recruitment in clinical trials to ensure adequate collection of data to inform future management policies. One of the largest clinical trials in COVID-19 patients in the UK, the RECOVERY trial, is currently recruiting both children and adults. In addition, the British Paediatric Surveillance Unit study is collecting real-life data on patients with paediatric multisystem inflammatory syndrome temporally associated with COVID-19 manifestations.

Conclusions

The phenotype of paediatric COVID-19 infection is milder than that of adults. The incidence of COVID-19 in children has likely been underestimated because of their propensity for asymptomatic or mild disease. Rates of paediatric intensive care admission and mortality as a result of COVID-19 alone in children are low. Treatment is largely supportive, and the use of antiviral or immunomodulatory therapies should only be considered within a clinical trial setting.

The newly emerging post-infectious Kawasaki-like phenotype, paediatric multisystem inflammatory syndrome temporally associated with COVID-19, is rare but severe. Clinicians should be vigilant for the hallmark signs that may point to the development of this syndrome and remember that it may occur some weeks after an asymptomatic infection.

Although prone to contracting the SARS-CoV-2 virus themselves within a family or household cluster, children are unlikely to be index cases and should not be considered a transmission reservoir. Further research into vertical or breast milk transmission is needed.

Future research aimed at further delineating the disease course of both COVID-19 in children and paediatric multisystem inflammatory syndrome temporally associated with COVID-19 are needed, and clinical trials investigating the use of antiviral and immunomodulatory agents are ongoing.

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Key points

- COVID-19 infection is less defined in children and adolescents compared to adults.
- A higher proportion of paediatric cases are asymptomatic or manifest with milder symptoms than adults.
- Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 infection (PIMS-TS) is a very rare and severe disease phenotype.
- Despite there being no specific treatment for COVID-19 infection, children and adolescents are being included in clinical trials of various therapeutic strategies.

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Conflicts of interest

The authors declare no conflicts of interest.

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