Managing COVID-19 in children

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SARS-CoV-2 infection, which can lead to severe disease known as COVID-19, differs in children compared with adults. The differences are not only in the clinical presentation and severity of disease, but also, consequently, in its management. When managing SARS-CoV-2 infection in paediatric patients in the community, it is important to be able to identify those children who may have an increased risk of severe disease and to be aware of the treatments that may be offered.

We now recognise that children and adults have an equivalent risk of being infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, unlike adults, over two-thirds of children who are infected with SARS-CoV-2 experience mild symptoms or are asymptomatic.[1] If the need for hospitalisation is used as a marker of more severe or complicated infection, 98 to 99% of SARS-CoV-2 infections in children are mild or uncomplicated.[2] In Australia, vaccination against SARS-CoV-2 is recommended in children older than 5 years of age or in at-risk groups (those with medical comorbidities) older than 6 months of age, primarily to reduce the frequency of severe disease.

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Although uncommon, severe disease resulting in hospitalisation or death can still occur in children, especially in at-risk children for whom preventative therapies or early initiation of treatment may be beneficial. In addition, children are uniquely at risk of developing paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)/multisystem inflammatory syndrome in children (MIS-C). A small proportion of children are also recognised to experience prolonged symptoms following infection.

This article provides an overview of the children who are at increased risk of severe disease, infection management approaches in children, treatments that may be indicated in children, when to use these treatments, and post-coronavirus disease (COVID-19) complications in children.

Vaccination in children

Since the introduction of vaccination against SARS-CoV-2, there has been a reduction in the incidence of severe COVID-19 in both children and adults. Vaccination remains the most effective preventative intervention against hospitalisation, severe disease and death. Vaccination not only further reduces the risk of severe COVID-19 in children but may also play a role in reducing transmission of the virus between children and between children and adults, although these benefits are notably limited in the Omicron variant era.[3] COVID-19 vaccination may also be effective in protecting against the development of PIMS-TS/MIS-C.[4,5]

The Australian Technical Advisory Group on Immunisation (ATAGI) recommends vaccination with a COVID-19 vaccine approved for children in:

- all children aged 5 years and older
- children aged between 6 months and 5 years with an increased risk of severe disease who are severely immunocompromised or have a disability
- those who have complex or multiple health conditions that increase the risk of severe COVID-19.[6-8]

A single booster dose six months after infection or vaccination can be considered in at-risk children aged older than 5 years. A booster is currently not recommended in children aged younger

than 5 years or children aged older than 5 years in Australia who do not have an increased risk of severe disease. Guidelines on the timing and number of booster vaccine doses are regularly reviewed and updated, with the most up-to-date information available from ATAGI.[7] Where possible, COVID-19 vaccination in children should be separated by seven to 14 days from other vaccines to reduce the risk of adverse events, such as fever, but can be coadministered if required.[9]

COVID-19 vaccination is generally considered safe in children aged older than 6 months, although they may experience mild side effects at a similar frequency to that in adults; these include fever, fatigue and local injection site reactions or pain.[10-13] An increase in myopericarditis following mRNA-based (e.g. Pfizer and Moderna vaccines) vaccination is well documented, especially after the second dose and usually in men aged 40 years or younger. In children, this risk seems to be highest in adolescents aged older than 12 years.[14]

There does not appear to be an increased risk of myopericarditis following vaccination in children aged between 6 months and 5 years compared with baseline population rates, and there is a small increase in risk in those aged between 5 and 11 years.[15,16] Symptoms usually occur within seven days after vaccination, although they have been reported up to 14 days postvaccination. Adolescents and children presenting with chest pain, dyspnoea, palpitations, syncope or dizziness within 14 days of receiving an mRNA-based COVID-19 vaccine should be assessed thoroughly and further expert guidance should be sought.[17] COVID-19 vaccination with mRNA-based vaccines has been shown to be safe in pregnant women, and evidence is emerging of associated protection in young infants via transplacental antibody transfer.[18]

Prevention beyond vaccines

Prevention of SARS-CoV-2 infection is ultimately the best approach to reduce morbidity and mortality. Beyond vaccination, other measures include limiting viral exposure through regular hand hygiene, physical distancing and mask wearing. However, as SARS-CoV-2 has continued to become more prevalent in society, the risk of incidental exposures increases.

Treatment designed to reduce the risk of infection before (pre-exposure prophylaxis) and after (postexposure prophylaxis) exposure, particularly with monoclonal antibodies, has been studied to varying degrees in adult populations.[19] At the time of writing, there is no consensus on the recommendation for the use of any agent to prevent disease (either pre- or post-exposure) in children, regardless of the underlying risk factors. In part, this is because of evidence suggesting the limited ability of registered monoclonal antibodies in neutralising Omicron variants and the considerably lower rates of severe disease in children.[20]

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Management of mild infection in children

Mild SARS-CoV-2 infection in children often presents with similar symptoms to those of other common upper respiratory tract infections, such as rhinorrhoea, fever, cough and headache. Children with mild infection have no or mild respiratory symptoms, including no or mild increased work of breathing (commonly in younger children) or breathlessness (commonly in older children). Those with mild infection should also be feeding normally or have slightly reduced food intake and have a normal state of consciousness. Given the similarities of SARS-CoV-2 infection in children to other common paediatric illnesses, diagnostic differentiation requires specific SARS-CoV-2 testing.

A positive SARS-CoV-2 PCR test result with sampling by an experienced healthcare worker is the gold standard for diagnosis; however, a reduction in the availability of PCR tests and the widespread increase in availability of commercial rapid antigen test (RAT) kits has led to a shift towards the use of RATs over PCR tests. It is important to note, however, that the sensitivity of RATs is considerably lower than that of PCR testing, and this may be impacted further by the limited user experience of sampling in children. If there is ongoing clinical concern for SARS-CoV-2 infection with a negative RAT result, consider repeat testing with a subsequent RAT or, preferably, a PCR test.

Children without risk factors

Mild SARS-CoV-2 infection in children without risk factors for severe disease can be managed in the community in most cases. Like other respiratory viral infections in children, mild SARS-CoV-2 infection in children often only requires supportive care in the form of ensuring adequate hydration with regular fluid intake, managing pain or discomfort with simple analgesics, and maintaining self isolation, especially from other at-risk individuals where possible. In most cases, this care can be achieved at home; however, it is important to consider social and geographical factors and how these may impact the care provided at home, follow up or escalation of care if required when managing SARS-CoV-2 infection in children in the community.

Children with risk factors

Children with risk factors have an increased risk of severe COVID-19 or death and thus need closer monitoring and follow up. In addition to being unvaccinated or partially vaccinated, factors that can increase the risk of COVID-19 in children include immunosuppression, a complex of severe chronic diseases, young age and the presence of obesity (Box 1). Infection in children who have

these risk factors but have symptoms of mild disease can be managed at home or in the community with increased monitoring and support. The RACGP has developed home care guidelines for managing COVID-19 (https://www.racgp.org.au/clinical-resources/covid-19-resources/clinical-care/covid-19-home-care-guidelines/determining-the-appropriate-monitoring-protocol-1), and the National Clinical Evidence Taskforce for COVID-19 also has resources on caring for people with COVID-19 (https://clinicalevidence.net.au/covid-19/).

When to consider severe COVID-19

Severe COVID-19 in children often presents with similar symptoms to those of severe illness with other common respiratory infections. Children with more severe COVID-19 will often have abnormal vital signs for their age, including tachycardia, tachypnoea, moderately or severely increased work of breathing, subjective breathlessness in older children, reduced oxygen saturation and apnoea in infants. Fever lasting more than five days is an important additional red flag. There will often be a history of reduced feeding (less than half of the normal fluid intake) with the inability to maintain hydration without additional feeding or fluid support. Early recognition of warning signs of severe disease in children, with appropriate escalation to hospital-level support, is essential. Children with severe disease may have an altered state of consciousness, and in very severe cases, may present with shock, with haemodynamic instability and multiorgan involvement.

Treatments

The treatment options for COVID-19 in children are somewhat limited compared with those for adults, given the lack of high-quality trials involving children for many of the available medications. The benefits and safety profile for most medications have been extrapolated from adult data; therefore, caution should be used when considering these available treatments. Therapeutic options for children are reserved for those who are symptomatic with risk factors for severe disease, and usually if more than one risk factor is present. The available therapeutic agents for use in children are outlined in the Table.[21,22] Both inhaled corticosteroids and nirmatrelvir plus ritonavir could be prescribed by GPs for use in the community where indicated. Treatment with remdesivir will likely involve further consultation with local hospital services as it requires intravenous administration. Postexposure chemoprophylaxis is not recommended routinely in asymptomatic children regardless of their vaccination status.

Postinfectious complications in children

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2/multisystem inflammatory syndrome in children

PIMS-TS/MIS-C is a rare but important post-SARS-CoV-2 complication that occurs in less than one in 3000 children (although this risk seems to be lower again with the Omicron variant), usually two to six weeks after infection with SARS-CoV-2. PIMS-TS/MIS-C should be considered in unwell children (especially those with known recent SARS-CoV-2 infection) who have persistent fever (persisting for more than three days), systemic inflammation (raised levels of inflammatory markers), rash, gastrointestinal symptoms (e.g. abdominal pain, vomiting, diarrhoea) or evidence of organ dysfunction.[23]

There may be some overlap in the clinical presentations of PIMS-TS/MIS-C, Kawasaki disease and toxic shock syndrome. Specialist opinion should be sought early for suspected cases of PIMS-TS/MIS-C, as therapy includes admission to a hospital, close inpatient monitoring and the administration of corticosteroids alone or in combination with human intravenous immunoglobulin, aspirin or other anticoagulants.[24,25]

1. RISK FACTORS FOR SEVERE COVID-19 IN CHILDREN

Immunosuppression

- Primary or acquired immunodeficiency
- Post-organ transplant (within 24 months)
- Current or recent chemotherapy and whole-body radiotherapy
- Use of high-dose corticosteroids (greater than 0.5 mg/kg daily for more than two weeks)

Complex or severe chronic diseases

- Severe respiratory disease (including severe asthma)
- Reliance on respiratory support devices (CPAP, BiPAP, home oxygen)
- Chronic organ-specific disease (such as chronic cardiovascular, renal, neuromuscular, metabolic or gastrointestinal disease)
- Severe nutritional deficiencies
- Diabetes

Age*

- Younger than 3 months corrected age

Obesity

- Body mass index greater than the 95th percentile for age

Abbreviations: BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure.

* Adolescents may present with a more 'adult-type' phenotype of disease.

Long COVID

Long COVID (also known as post-COVID condition or post-acute sequelae of COVID-19) is being recognised increasingly among children and adolescents. Prolonged and even nonspecific symptoms following SARS-CoV-2 infection should not be ignored. A number of definitions for long COVID in children have been published and are the subject of ongoing discussions.[26,27] Overall, children and adolescents likely have a lower risk (estimated around fivefold lower) of developing long COVID than adults, but the exact prevalence remains unclear.[28] Fatigue, headache, mood changes and sleep disturbance appear to be the most frequent symptoms in

TABLE. THERAPEUTIC AGENTS AND THEIR INDICATIONS FOR USE FOR COVID-19 IN CHILDREN[21,22]

Treatment	Indicated cohort	Time to commence	Dosage	Considerations
Outpatient treatments				
Inhaled corticosteroids (budesonide)	• Age older than 4 years • Symptomatic SARS-CoV-2 infection without an oxygen requirement AND with risk factors for severe disease	Within 14 days of symptom onset	Twice daily via dry powder inhalation for ten days at: • 400 mcg (age 4 years and older) • 800 mcg (age 12 years and older)	• Rinse mouth after use to reduce the risk of oral candidiasis • Can consider fluticasone with a spacer as an alternative in young children • Inhaled corticosteroids are not TGA approved for this indication
Nirmatrelvir plus ritonavir	• Age older than 12 years and body weight greater than 40 kg • Symptomatic SARS-CoV-2 infection without an oxygen requirement AND with at least one risk factor for severe disease*	Within five days of symptom onset	Twice daily for five days at 300 mg nirmatrelvir plus 100 mg ritonavir	• Not TGA approved for this indication in children because of a lack of safety and efficacy data in those aged younger than 18 years • Multiple drug interactions† • Requires dose adjustments in those with renal impairment
Remdesivir	• Age older than 28 days and body weight greater than 3 kg • Mild to moderate disease as pre-emptive therapy for those who have a high risk of severe disease and other are treatments not available	Within seven days of symptom onset	Intravenous for three days at: • 200 mg loading dose and 100 mg daily (age 12 years and older with a body weight of 40 kg and greater) • 5 mg/kg loading dose and 2.5 mg/kg daily (age younger than 12 years with a body weight less than 40 kg)	• Requires intravenous administration • Can cause renal and hepatic impairment and severe bradycardia
Inpatient treatments				
Remdesivir	• Age older than 28 days and body weight greater than 3 kg • Hospitalised and with risk factors for severe disease who do not require invasive or non-invasive ventilation if other therapies are not indicated	Within seven days of symptom onset	Intravenous for five days at: • 200 mg loading dose and 100 mg daily (age 12 years and older with a body weight of 40 kg and greater) • 5 mg/kg loading dose and 2.5 mg/kg daily (age younger than 12 years with a body weight less than 40 kg)	• Requires intravenous administration • Can cause renal and hepatic impairment and severe bradycardia
Corticosteroids (dexamethasone)‡	• All ages • Hospitalised with hypoxaemia secondary to SARS-CoV-2 infection	N/A	0.15 mg/kg, per oral, intravenous, up to a maximum 6 mg daily for up to 10 days	Consider intravenous hydrocortisone as an alternative if dexamethasone is not available
Tocilizumab	Hospitalised with moderate or severe COVID-19 and oxygen requirement in discussion with a specialist, particularly if systemic inflammation is persisting or escalating despite the use of corticosteroids	N/A	Single dose of: • 12 mg/kg (body weight: less than 30 kg) • 8 mg/kg (30 to 40 kg) • 400 mg (greater than 40 kg to 65 kg) • 600 mg (greater than 65 kg to 90 kg) • 800 mg (greater than 90 kg)	• Immunosuppressive • No established dose for this indication in children and adolescents • Use in conjunction with corticosteroids
Baricitinib	• Age older than 2 years • Hospitalised with moderate or severe COVID-19 requiring noninvasive or invasive ventilation	N/A	Per oral daily for 14 days or until discharge (whichever occurs first) at: • 2 mg (age two to nine years) • 4 mg (age 10 to 18 years)	• Immunosuppressive • May cause cytopenia • Requires dose adjustments in those with renal impairment

* Many expert opinions suggest two or more risk factors given the overall low risk of severe disease in children.
† Refer to the Liverpool COVID-19 drug checker (https://www.covid19-druginteractions.org/checker) for full details.
‡ Used with high-level evidence to treat severe COVID-19 in adults that is inflammatory; consider systemic inflammatory state in a child and timing of severe disease relative to infection onset.

2. PRACTICE POINTS FOR GPs ON COVID-19 IN CHILDREN

- SARS-CoV-2 infection is either asymptomatic or presents with mild symptoms in most children, similar to other respiratory viral infections.
- Risk factors for severe disease include the presence of obesity (body mass index-for-age greater than the 95th percentile), diabetes, immunosuppression or complex or chronic diseases, and age younger than 3 months.
- Vaccination is recommended in children older than 5 years and in those aged between 6 months and 5 years with an increased risk of severe disease because of medical comorbidities.
- Symptoms and signs of more severe disease include breathlessness, abnormal observations for the child's age, increased work of breathing, an oxygen or respiratory support requirement, reduced feeding, dehydration and an altered level of consciousness.
- Treatment may be indicated for symptomatic children with risk factors for severe disease, although the evidence and safety data for use of the available agents in children is limited.
- Routine postexposure chemoprophylaxis is not recommended for children, regardless of the vaccination status.
- Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 is a rare but serious postinfectious, Kawasaki disease-like illness that may occur in children, usually two to six weeks after infection. The risk is notably lower following infection of some variants, such as Omicron.
- Long COVID remains poorly defined in children and poses a low risk compared with adults. Reassuringly, according to longitudinal studies, most postinfectious symptoms in children resolve entirely within three to six months.

children.[29] Despite this, the symptoms of long COVID in children and adolescents seem to resolve within six months of onset in most cases.[30,31] The potential implications of recurrent infections of SARS-CoV-2 in children and the impacts of these on developing long COVID or other post-COVID sequelae are unknown and remain an area for further research. Resources are being developed in Australia to support GPs and paediatricians in assessing and managing long COVID in children and adolescents. Currently, resources from the UK's National Health Service can be used as a good starting point (https://www.yourcovidrecovery.nhs.uk/children-and-young-people-with-covid/).

Conclusion

In most children, SARS-CoV-2 infection will be asymptomatic or present with mild symptoms, similar to other common viral upper respiratory infections. The disease in these children can almost always be managed at home. Children who have risk factors for severe disease, such as those who are immunocompromised, have chronic conditions, are obese or are very young infants, are most likely to have mild disease. These children require additional support and monitoring, wherein GPs play a pivotal role. Children with mild infection and the presence of one or more risk factors for severe disease, especially if they are unvaccinated, should be considered for for treatment with either nirmatrelvir plus ritonavir, inhaled corticosteroids or, rarely, early use of remdesivir if they fulfil the other criteria for these treatments. Children with symptoms of severe disease should be referred to a hospital for assessment and support.

PIMS-TS/MIS-C remains a rare but important diagnosis to consider in children presenting with fever and signs of systemic inflammation, usually two to six weeks after SARS-CoV-2 infection. Additionally, children and adolescents are increasingly being reported to develop persistent and prolonged symptoms following SARS-CoV-2 infection, often called long COVID; reassuringly, although some children and adolescents may be significantly impacted, these symptoms do not often seem to last for more than six months.

Vaccination remains the best method of prevention of severe disease and other manifestations of COVID-19 and is recommended in children older than 6 months of age with risk factors for severe disease, and in all children older than 5 years of age. Vaccination is also recommended and safe to use in pregnancy, which protects infants younger than 6 months of age. There is no consensus for recommendations of the use of pre- or postexposure prophylaxis. Practice points for GPs are presented in Box 2. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: None.

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