

In brief

Disease modifying treatments for COVID-19 in children

11 February 2022

Summary

- Most of the trials on disease modifying treatments for COVID-19 are focused on adults, and many of the recommendations made for children cite these adult studies. The few studies on children are limited to small observational studies and case reports.
- A systematic review and meta-analysis on COVID-19 treatment in children found anti-inflammatory agents, such as corticosteroids, and antivirals, such as remdesivir, have the most promising evidence for use with severe cases of COVID-19 in children.¹
- Remdesivir has been reported in observational studies after use on compassionate grounds. The drug was well tolerated with a low incidence of serious adverse events.^{2,3}
- Australian and international guidance outlines recommendations for the use of disease modifying treatments for COVID-19 in children. Full recommendations are included in Table 1.
- There are several local guidelines in Australia, including those produced by children's hospitals such as the Royal Children's Hospital in Melbourne. These guidelines give specific guidance in various settings.⁴

Peer reviewed literature

- A [systematic review and meta-analysis](#) on COVID-19 treatment in children found that anti-inflammatory agents such as corticosteroids and antivirals such as remdesivir have the most promising evidence for use in the treatment of severe cases of COVID-19 in children.¹ A further [systematic review](#) found children with severe COVID-19 disease received antimicrobials, inotropes and anti-inflammatory agents.⁵
- It has been reported in [observational studies](#) that when [remdesivir](#) has been used on compassionate grounds it was well tolerated with a low incidence of serious adverse events.^{2,3}
- An [observational study of 40 children](#) with COVID-19 who were treated with different drugs found the average hospital stay was 10.4 days. All children received interferon- α nebulization and 90% were co-administered with budesonide. Other drugs were also administered in some patients. Multivariable analysis showed none of the covariates were related to the cure rate at 14 days with different drug treatments.⁶
- [Favipiravir](#) was well tolerated when used in children with COVID-19 who had an acute kidney injury. A small observational study showed the drug was well tolerated with no major side effects.⁷
- The National COVID-19 Clinical Evidence Taskforce in Australia has made 20 [recommendations specific to children and adolescents](#). In summary these are:
 - Corticosteroids are recommended as first-line treatment for acute COVID-19 in children and adolescents who require oxygen.
 - Tocilizumab could be considered but remdesivir should not be administered routinely in this population.

- Non-invasive ventilation or high-flow nasal cannulae should be considered in children and adolescents with hypoxaemia or respiratory distress unresponsive to low flow oxygen. But assess whether appropriate infection control measures can be used.
- Children and adolescents with paediatric inflammatory multisystem syndrome (PIMS-TS) should be managed by a multidisciplinary team. Intravenous immunoglobulin and corticosteroids, with concomitant aspirin and thromboprophylaxis, should be considered for treatment.⁸
- Guidance on [monoclonal antibody therapy](#) in children from May 2021 suggests against routine administration of monoclonal antibody therapy (bamlanivimab, or casirivimab and imdevimab), for treatment of COVID-19 in children or adolescents. They found disease in these patients is typically mild, and there is no evidence for the safety and efficacy of monoclonal antibody therapy in this population.⁹
- Guidance from early in the pandemic includes:
 - September 2020, Italy: Guidance from the [Italian Society of Pediatric Infectious Disease](#) recommends remdesivir for severe cases (hydroxychloroquine OR lopinavir/ritonavir if this is not available). Immunomodulating therapy is considered for ARDs or multisystem inflammatory syndrome.¹⁰
 - April 2020, United States: [Guidance on antivirals](#) for children suggested supportive care alone for most cases due to the mild course of disease in children. A decision-making framework for antiviral therapies is suggested for the rare cases of severe disease, where remdesivir is the preferred agent.¹¹
 - April 2020, India: [Guidance on management of children](#) found no antivirals had been proven to be effective and presented clinical indications for starting virus-suppressive therapy (hydroxychloroquine or lopinavir/ritonavir) which are not routinely recommended.¹²
 - [February 2020, China](#). Updated [April 2020](#): Interferon-α can reduce the viral load in the early stage of infection. The safety of lopinavir/litonavir is yet to be determined.¹³
- The RECOVERY trial protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day dexamethasone for children, but it is unclear whether any children were included in the trial.⁸
- The RECOVERY trial is recruiting children and adolescents with PIMS-TS for their trial of tocilizumab. Trials are also underway in which children over 12 years of age are eligible for inclusion for sotrovimab.⁸

Grey literature

Table 1: Treatment recommendations from national and international guidance

Note: Recommendation wording has been copied directly from source material.

Treatment	Recommendation
Budesonide	National COVID-19 Clinical Excellence Taskforce <ul style="list-style-type: none"> ● Consider using inhaled budesonide for the treatment of symptomatic COVID-19 in children and adolescents who do not require oxygen and who have one or more risk factors for disease progression.

Treatment	Recommendation
<p>Casirivimab plus imdevimab (Ronapreve/REGEN-COV)</p>	<p>National COVID-19 Clinical Excellence Taskforce</p> <ul style="list-style-type: none"> Consider using, in exceptional circumstances, casirivimab plus imdevimab within seven days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40 kg with mild COVID-19 who are at high risk of deterioration. Do not use casirivimab plus imdevimab in children under 12 years of age without risk factors for deterioration who have mild or asymptomatic COVID-19 outside of randomised trials with appropriate ethical approval. Consider using, in exceptional circumstances, casirivimab plus imdevimab in seronegative children and adolescents aged 12 years and over and weighing at least 40 kg with moderate to critical COVID-19 who are at high risk of disease progression. Do not use casirivimab plus imdevimab in seropositive children and adolescents hospitalised with moderate to critical COVID-19. <p>NICE COVID-19 Rapid Guideline</p> <ul style="list-style-type: none"> For people aged 12 and over with COVID-19 who are not in hospital and are thought to be at high risk of progression to severe COVID-19. For people aged 12 and over hospitalised because of COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative). Do not offer to people aged 12 and over hospitalised because of COVID-19 who have detectable SARS-CoV-2 antibodies (seropositive) or whose serostatus is unknown. <p>National Institutes of Health (NIH)</p> <ul style="list-style-type: none"> Based on adult studies, bamlanivimab plus etesevimab or casirivimab plus imdevimab may be considered on a case-by-case basis for non-hospitalised children who meet Emergency Use Authorization (EUA) criteria for high-risk of severe disease, especially those who meet more than one criterion or are aged ≥ 16 years. The Panel recommends consulting a paediatric infectious disease specialist in such cases.
<p>Corticosteroids</p>	<p>National COVID-19 Clinical Excellence Taskforce</p> <ul style="list-style-type: none"> Consider using dexamethasone daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in children and adolescents with acute COVID-19 who are receiving oxygen (including mechanically ventilated patients). Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19 in children and adolescents who do not require oxygen. <p>UpToDate</p> <ul style="list-style-type: none"> Administration of glucocorticoids ideally should occur in the context of a clinical trial. For select children with severe or critical COVID-19 who cannot participate in a clinical trial (i.e., those who require mechanical ventilation or

Treatment	Recommendation
	<p>those who require supplemental oxygen and have risk factors for disease progression), low-dose glucocorticoids may be warranted.</p> <p>NICE COVID-19 Rapid Guideline</p> <ul style="list-style-type: none"> For children with a greater than 44-week corrected gestational age, follow the risk criteria set out in Royal College of Paediatric and Child Health guidance for assessing children admitted to hospital with COVID-19. <p>National Institutes of Health (NIH)</p> <ul style="list-style-type: none"> Recommends using dexamethasone for hospitalised children with COVID-19 who require high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation. <p>The Royal Children's Hospital (RCH) Melbourne</p> <ul style="list-style-type: none"> Consider for children requiring ongoing supplemental oxygen (including mechanically ventilated patients). Starting dose dexamethasone (IV or oral) 0.15 mg/kg/day (max dose 6 mg)⁴
Baricitinib	<p>National COVID-19 Clinical Excellence Taskforce</p> <ul style="list-style-type: none"> Do not use baricitinib for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval. <p>UpToDate</p> <ul style="list-style-type: none"> It should ideally be used in the context of a clinical trial.
Sarilumab	<p>National COVID-19 Clinical Excellence Taskforce</p> <ul style="list-style-type: none"> Do not use sarilumab for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval. <p>National Institutes of Health (NIH)</p> <ul style="list-style-type: none"> Recommends against the use of sarilumab for hospitalised children with COVID-19 or MIS-C, except in a clinical trial (AIII).
Tocilizumab	<p>National COVID-19 Clinical Excellence Taskforce</p> <ul style="list-style-type: none"> Consider using tocilizumab for the treatment of COVID-19 in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation. <p>UpToDate</p> <ul style="list-style-type: none"> It should ideally be used in the context of a clinical trial. <p>NICE COVID-19 Rapid Guideline</p> <ul style="list-style-type: none"> Consider tocilizumab for children and young people who have severe COVID-19 or paediatric inflammatory multisystem syndrome only if they are one year and over, and only in the context of a clinical trial. <p>National Institutes of Health (NIH)</p>

Treatment	Recommendation
	<ul style="list-style-type: none"> There is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab in hospitalised children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C).
Remdesivir	<p>National COVID-19 Clinical Excellence Taskforce</p> <ul style="list-style-type: none"> Use of remdesivir in children and adolescents with COVID-19 outside of a trial setting should not be considered routinely. If treatment is considered—in exceptional circumstances—it should be in consultation with a clinical reference group, such as the ANZPID COVID-19 Clinical Reference Group. <p>UpToDate</p> <ul style="list-style-type: none"> When a decision is made to use antiviral therapy in a child who cannot be enrolled in a clinical trial, suggest remdesivir rather than other antiviral agents. <p>NICE COVID-19 Rapid Guideline</p> <ul style="list-style-type: none"> Consider remdesivir for up to five days for COVID-19 pneumonia in young people 12 years and over weighing 40 kg or more, in hospital and needing low-flow supplemental oxygen. Do not use in young people and children in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of a clinical trial. <p>National Institutes of Health (NIH)</p> <ul style="list-style-type: none"> Remdesivir is recommended for: <ul style="list-style-type: none"> hospitalised children aged ≥ 12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen. hospitalised children aged ≥ 16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risks factors for severe disease. In consultation with a paediatric infectious disease specialist, remdesivir can be considered for hospitalised children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen.
Sotrovimab	<p>National COVID-19 Clinical Excellence Taskforce</p> <ul style="list-style-type: none"> Do not routinely use sotrovimab outside of randomised trials with appropriate ethical approval for the treatment of COVID-19 in children and adolescents under 12 years of age and without high risk factors for deterioration. Consider using, in exceptional circumstances, sotrovimab for the treatment of COVID-19 within five days of symptom onset in children and adolescents aged 12 years and over and weighing at least 40 kg who do not require oxygen and who are at high risk of deterioration.

Treatment	Recommendation
	<ul style="list-style-type: none"> Consider using sotrovimab only in unvaccinated or partially vaccinated children and adolescents, or those who are immunosuppressed regardless of vaccination status. Do not routinely use sotrovimab in fully vaccinated patients unless immunosuppressed. Decisions to provide sotrovimab to a child or adolescent should be based on the individual's combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.
Hydroxychloroquine and chloroquine	<p>UpToDate</p> <ul style="list-style-type: none"> Recommend not using them for the treatment of COVID-19 in children.
Lopinavir-ritonavir	<p>UpToDate</p> <ul style="list-style-type: none"> Do not recommend routine use.

To inform this brief, the PubMed and Google searches were conducted using terms related to (child OR paediatric) AND COVID-19 drug treatment on 28 January 2021.

References

- Panda PK, Sharawat IK, Natarajan V, et al. COVID-19 treatment in children: A systematic review and meta-analysis. *J Family Med Prim Care*. 2021 Sep;10(9):3292-302. DOI: 10.4103/jfmpc.jfmpc_2583_20
- Goldman DL, Aldrich ML, Hagmann SHF, et al. Compassionate Use of Remdesivir in Children With Severe COVID-19. *Pediatrics*. 2021 May;147(5). DOI: 10.1542/peds.2020-047803
- Méndez-Echevarría A, Pérez-Martínez A, Gonzalez Del Valle L, et al. Compassionate use of remdesivir in children with COVID-19. *Eur J Pediatr*. 2021 Apr;180(4):1317-22. DOI: 10.1007/s00431-020-03876-1
- The Royal Children's Hospital Melbourne. COVID-19 [internet] Australia: The Royal Children's Hospital Melbourne; Sep 2021 [cited 9 Feb 2022] Available from: https://www.rch.org.au/clinicalguide/guideline_index/COVID-19/.
- Irfan O, Muttalib F, Tang K, et al. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. *Arch Dis Child*. 2021 Feb 16;106(5):440-8. DOI: 10.1136/archdischild-2020-321385
- Li M, Wang Y, Xu H, et al. Existing drug treatments cannot significantly shorten the clinical cure time of children with COVID-19. *J Infect Dev Ctries*. 2020 Sep 30;14(9):963-7. DOI: 10.3855/jidc.13491
- Ozsurekci Y, Oygur PD, Gürlevik SL, et al. Favipiravir use in children with COVID-19 and acute kidney injury: is it safe? *Pediatr Nephrol*. 2021 Nov;36(11):3771-6. DOI: 10.1007/s00467-021-05111-x
- Fraile Navarro D, Tendal B, Tingay D, et al. Clinical care of children and adolescents with COVID-19: recommendations from the National COVID-19 Clinical Evidence Taskforce. *Med J Aust*. 2021 Oct 24. DOI: 10.5694/mja2.51305
- Wolf J, Abzug MJ, Wattier RL, et al. Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of Coronavirus Disease 2019 in Children and Adolescents. *J Pediatric Infect Dis Soc*. 2021 May 28;10(5):629-34. DOI: 10.1093/jpids/piaa175

In brief documents are not an exhaustive list of publications but aim to provide an overview of what is already known about a specific topic. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

10. Venturini E, Montagnani C, Garazzino S, et al. Treatment of children with COVID-19: position paper of the Italian Society of Pediatric Infectious Disease. Ital J Pediatr. 2020 Sep 24;46(1):139. DOI: 10.1186/s13052-020-00900-w
11. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter Initial Guidance on Use of Antivirals for Children With Coronavirus Disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2. J Pediatric Infect Dis Soc. 2020 Dec 31;9(6):701-15. DOI: 10.1093/jpids/piaa045
12. Sankar J, Dhochak N, Kabra SK, et al. COVID-19 in Children: Clinical Approach and Management. Indian J Pediatr. 2020 Jun;87(6):433-42. DOI: 10.1007/s12098-020-03292-1
13. Shen K, Yang Y, Wang T, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr. 2020 Jun;16(3):223-31. DOI: 10.1007/s12519-020-00343-7

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