



# Therapeutic Management of Hospitalized Children With COVID-19

*Last Updated: August 8, 2022*

This section outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of children (i.e., pediatric patients aged <18 years) who are hospitalized for COVID-19. Throughout this section, the term "COVID-19" refers to the acute, primarily respiratory illness due to infection with SARS-CoV-2. Multisystem inflammatory syndrome in children (MIS-C) refers to the postinfectious inflammatory condition.

## Treatment Considerations for Children With COVID-19

Currently, no pediatric clinical trial results evaluating the treatment of COVID-19 have been published. Data evaluating pharmacologic therapy in children with COVID-19 are limited largely to descriptive reports.<sup>1,2</sup> Therefore, more high-quality randomized trials, observational studies, and pharmacokinetic studies are urgently needed. Whenever possible, clinical trials of therapeutics and multicenter observational cohorts should enroll children with COVID-19.

Published guidance documents on the treatment of COVID-19 in children have been mostly extrapolated from recommendations for adults with COVID-19, recommendations for children with other viral infections, and expert opinion.<sup>3-5</sup> Applying adult data from COVID-19 trials to children is a unique challenge because most children experience a mild course of illness with COVID-19. Relative to adults, children with COVID-19 have substantially lower mortality and less need for hospitalization. Because of these differences in epidemiology and disease severity, the effect sizes for children are likely to be smaller than those observed in adults; therefore, to produce a beneficial outcome, the number needed to treat is higher. Collectively, these factors influence the risk versus benefit balance for pharmacologic therapies in children.

Other challenges are the uncertainty about which comorbid conditions place children at the highest risk of severe COVID-19 and the uncertainty about the absolute magnitude of the increased risk from those comorbid conditions. For children with COVID-19, the number and severity of their comorbid conditions influence decisions about pharmacologic treatment. For more information on risk factors for children with COVID-19, see [Special Considerations in Children](#).

## Recommendations

In the absence of sufficient clinical trial data on the treatment of children with COVID-19, the Panel's recommendations for the therapeutic management of hospitalized children are based largely on adult safety and efficacy data from clinical trials, the child's risk of disease progression, and expert opinion (see Table 3c). For the Panel's recommendations for adults, see [Therapeutic Management of Hospitalized Adults With COVID-19](#).

In general, adult data are most applicable to older children with severe COVID-19 and predominantly lower respiratory tract disease. Extrapolation of adult data to children with SARS-CoV-2 infection who present with clinical syndromes common to other respiratory viruses (e.g., bronchiolitis, croup, asthma) is challenging. No evidence indicates that these syndromes should be managed differently when caused by SARS-CoV-2 infection. Clinical judgment is needed when applying these recommendations to patients, particularly young children.

**Table 3c. Therapeutic Management of Hospitalized Children With COVID-19**

Disease Severity	Panel's Recommendations
<b>Hospitalized for COVID-19</b>	For children aged $\geq 12$ years admitted for COVID-19, use prophylactic anticoagulation unless contraindicated ( <b>BIII</b> ).
<b>Does Not Require Supplemental Oxygen</b>	For children admitted for COVID-19 who are at the highest risk of progression to severe COVID-19, <sup>a</sup> consider using <b>remdesivir</b> <sup>b</sup> for children aged 12–17 years ( <b>CIII</b> ). There is insufficient evidence for using remdesivir in children aged 28 days to <12 years.
	For children admitted for reasons other than COVID-19 who have mild to moderate COVID-19 and are at the highest risk of progression, <sup>a</sup> refer to <a href="#">Therapeutic Management of Nonhospitalized Children With COVID-19</a> .
<b>Requires Conventional Oxygen<sup>c</sup></b>	Use 1 of the following options: <ul style="list-style-type: none"> <li>• <b>Remdesivir</b><sup>b</sup> (<b>BIII</b>)</li> <li>• <b>Dexamethasone plus remdesivir</b><sup>b</sup> for children with increasing oxygen needs, particularly adolescents (<b>BIII</b>)</li> </ul>
<b>Requires Oxygen Through High-Flow Device or NIV<sup>d</sup></b>	Use 1 of the following options: <ul style="list-style-type: none"> <li>• <b>Dexamethasone</b> (<b>BIII</b>)</li> <li>• <b>Dexamethasone plus remdesivir</b><sup>b</sup> (<b>BIII</b>)</li> </ul>
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, <b>baricitinib</b> <sup>e</sup> or <b>tocilizumab</b> can be considered for children aged 12–17 years ( <b>BIII</b> ) and for children aged 2–11 years ( <b>CIII</b> ).
<b>Requires MV or ECMO<sup>f</sup></b>	<b>Dexamethasone</b> <sup>f</sup> ( <b>AIII</b> )
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, <b>baricitinib</b> <sup>e</sup> or <b>tocilizumab</b> may be considered for children aged 12–17 years ( <b>BIII</b> ) and for children aged 2–11 years ( <b>CIII</b> ).
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See <a href="#">Guidelines Development</a> for more information.	

<sup>a</sup> For example, for children who are severely immunocompromised regardless of COVID-19 vaccination status and those who are unvaccinated and have additional risk factors for progression (see [Therapeutic Management of Nonhospitalized Children With COVID-19](#)).

<sup>b</sup> The clinical benefit of remdesivir is greatest if it is initiated within 10 days of symptom onset. Remdesivir should be given for 5 days or until hospital discharge, whichever comes first.

<sup>c</sup> Conventional oxygen refers to oxygen supplementation that is not high-flow oxygen, NIV, MV, or ECMO.

<sup>d</sup> Patients who are receiving NIV or MV at baseline and require a substantial increase in baseline support should be treated per the recommendations for patients requiring new NIV or MV.

<sup>e</sup> **Tofacitinib** is an alternative if baricitinib is not available (**BIII**).

<sup>f</sup> For children who started receiving remdesivir before admission to the ICU, the remdesivir should be continued to complete the treatment course.

**Key:** ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; MV = mechanical ventilation; NIV = noninvasive ventilation

## Rationale for the Panel's Recommendations for Drug Therapies

### *Remdesivir*

Remdesivir is approved by the Food and Drug Administration (FDA) for hospitalized and nonhospitalized pediatric patients aged  $\geq 28$  days and weighing  $\geq 3$  kg.<sup>6</sup> Remdesivir is expected to be active against the Omicron variant of concern, although in vitro and in vivo data are currently limited (see [Remdesivir](#)).<sup>7</sup> For most hospitalized patients, remdesivir should be administered for 5 days or until the patient is ready for discharge, whichever comes first. Treatment may be extended to 10 days for severely ill patients who have not clinically improved or for patients who are severely immunocompromised.

In a trial conducted predominantly among hospitalized patients with COVID-19 who did not receive supplemental oxygen at enrollment, a 5-day course of remdesivir was associated with greater clinical improvement when compared with the standard of care.<sup>8</sup> Remdesivir was also studied in ACTT-1, a double-blind, placebo-controlled, randomized trial for hospitalized adults with COVID-19 who received remdesivir for 10 days (or until hospital discharge) or placebo.<sup>9</sup> The study reported that the remdesivir arm had a shorter time to clinical recovery than the placebo arm (10 days vs. 15 days;  $P < 0.001$ ). A subgroup analysis demonstrated that patients who received conventional oxygen therapy had the greatest benefit. No benefit was detected for patients who did not receive supplemental oxygen or for those who received noninvasive ventilation (NIV) or mechanical ventilation. No statistically significant differences in mortality or in the need for new mechanical ventilation were detected, and the benefit of remdesivir in this study was limited to patients with symptoms for  $< 10$  days.

Three open-label trials in adults compared remdesivir to a local standard of care.<sup>10,11</sup> The World Health Organization's Solidarity trial enrolled hospitalized adult patients with COVID-19 in 35 countries. In the overall cohort, no difference in hospital mortality was demonstrated (14.5% in the remdesivir arm vs. 15.6% in the usual care arm; rate ratio 0.91; 95% CI, 0.82–1.02;  $P = 0.12$ ). However, in the subset of patients receiving supplemental oxygen but not NIV or mechanical ventilation, remdesivir significantly reduced the risk of in-hospital mortality by 13% (14.6% vs. 16.3%; rate ratio 0.87; 95% CI, 0.76–0.99;  $P = 0.03$ ).<sup>10</sup>

The CATCO study demonstrated similar findings. Treatment with remdesivir, when compared with standard care, reduced the need for mechanical ventilation in hospitalized adults with COVID-19 (8% vs. 15%; relative risk 0.53; 95% CI, 0.38–0.75). In this study, 87% of patients in both the remdesivir arm and standard of care arm received dexamethasone.<sup>12</sup> In contrast to these 2 studies, the DisCoVeRy trial demonstrated no difference for any clinical outcome when the use of remdesivir plus usual care was compared to usual care alone.<sup>11</sup>

The efficacy of remdesivir has not been evaluated in clinical trials of hospitalized children with COVID-19. A Phase 2/3, single-arm, open-label study evaluated the safety, tolerability, and pharmacokinetics of remdesivir in 53 hospitalized children with COVID-19.<sup>13</sup> Children weighing 3 kg to  $< 40$  kg received remdesivir 5 mg/kg on Day 1, followed by remdesivir 2.5 mg/kg daily. Adverse events included acute kidney injury (11%) and an increase in alanine transaminase levels (8%). However, this study did not have a placebo group, limiting the ability to draw conclusions regarding the significance of these adverse events. Published observational data are limited to descriptive case series.<sup>1,2</sup>

Findings from the adult trials and the pediatric pharmacokinetic study led the Panel to recommend **remdesivir** for hospitalized children who require conventional oxygen (**BIII**) and to recommend **remdesivir** with **dexamethasone** for children with increasing need for conventional oxygen (**BIII**). The Panel also recommends **remdesivir** in combination with **dexamethasone** for children who require oxygen through a high-flow device or NIV (**BIII**). It is not known if remdesivir offers an additional

clinical benefit to standard care in younger children with SARS-CoV-2 infection who are receiving respiratory support for bronchiolitis, asthma, or croup.

For children hospitalized for COVID-19 who do not require supplemental oxygen, the Panel recommends **remdesivir** for children aged 12 to 17 years who are at the highest risk for progression to severe disease (**CIII**). This recommendation was extrapolated from the findings of the PINETREE study, which demonstrated a reduction in hospitalization among high-risk, unvaccinated adults treated in the outpatient setting.<sup>14</sup> However, there is insufficient evidence for or against the use of remdesivir in children aged 28 days to <12 years and weighing  $\geq 3$  kg who do not require supplemental oxygen. Given the reported clinical experience with the use of remdesivir among younger patients,<sup>13</sup> the use of remdesivir in high-risk, younger children who do not require supplemental oxygen may be considered on a case-by-case basis.

### ***Dexamethasone***

Dexamethasone was evaluated in the RECOVERY trial, which was an open-label, randomized trial conducted in the United Kingdom.<sup>15</sup> The trial compared the use of up to 10 days of dexamethasone 6 mg, administered by intravenous injection or orally, with usual care among hospitalized adults with COVID-19. The primary outcome was all-cause mortality at 28 days, which occurred in 22.9% of patients randomized to receive dexamethasone versus 25.7% of patients randomized to receive usual care (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93;  $P < 0.001$ ). Patients who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO) had the greatest effect size (29.3% vs. 41.4%; rate ratio 0.64; 95% CI, 0.51–0.81). No difference in outcomes was observed for patients who did not require supplemental oxygen (17.8% vs. 14.0%; rate ratio 1.19; 95% CI, 0.92–1.55). For the 28-day mortality outcome, a difference between arms was observed for patients who required supplemental oxygen (23.3% vs. 26.2%; rate ratio 0.82; 95% CI, 0.72–0.94). However, it should be noted that these patients were a heterogeneous group, including those who received either conventional oxygen or NIV. See [Corticosteroids](#) for detailed information.

The safety and efficacy of using dexamethasone or other corticosteroids for the treatment of COVID-19 have not been evaluated in pediatric patients. Given that the mortality for adults in the placebo arm in the RECOVERY trial was substantially greater than the mortality generally reported for children with COVID-19, caution is warranted when extrapolating from recommendations for adults and applying them to patients aged <18 years.

However, because of the effect size observed in the RECOVERY trial, the Panel recommends the use of **dexamethasone** for children who require mechanical ventilation or ECMO (**AIII**). The Panel also recommends the use of **dexamethasone**, with or without concurrent remdesivir, for children who require oxygen through a high-flow device or NIV (**BIII**). The Panel **does not recommend** routine use of **corticosteroids** for children who require only conventional oxygen, but corticosteroids can be considered in combination with remdesivir for patients with increasing oxygen needs, particularly adolescents (**BIII**).

There is evidence demonstrating that the use of corticosteroids does not benefit infants with viral bronchiolitis not related to COVID-19, and current American Academy of Pediatrics guidelines recommend against the use of corticosteroids in this population.<sup>16</sup> There are no COVID-19-specific data to support the use of corticosteroids in children with bronchiolitis due to SARS-CoV-2 infection. Corticosteroids should be used per the usual standards of care in children with asthma and croup triggered by SARS-CoV-2.

The use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated, and there is a potential risk of harm. Therefore, the

use of corticosteroids should be considered on a case-by-case basis in consultation with relevant specialists, and the benefits and risks of the therapy should be weighed. If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be considered. The dexamethasone dose for pediatric patients is 0.15 mg/kg (with a maximum dose of 6 mg) once daily for  $\leq 10$  days.

### ***Baricitinib***

The Janus kinase inhibitor baricitinib was recently approved by the FDA for the treatment of COVID-19 in hospitalized adults. An FDA Emergency Use Authorization (EUA) for baricitinib remains active for the treatment of COVID-19 in hospitalized children aged 2 to 17 years who require supplemental oxygen, NIV, mechanical ventilation, or ECMO.<sup>17</sup>

In the COV-BARRIER trial, adults with COVID-19 pneumonia were randomized to receive baricitinib or standard care. Patients treated with baricitinib showed a reduction in mortality when compared with those who received standard care; the reduction was greatest in patients who received high-flow oxygen or NIV. Similarly, the ACTT-2 trial in adults showed that patients who received baricitinib plus remdesivir had improved time to recovery when compared with patients who received remdesivir alone. This effect was most pronounced in patients who received high-flow oxygen or NIV.<sup>18</sup> In the ACTT-4 trial, 1,010 patients were randomized 1:1 to receive baricitinib plus remdesivir or dexamethasone plus remdesivir. The study reported no difference between the arms for the outcome of mechanical ventilation-free survival.<sup>19</sup>

In the RECOVERY trial, 8,156 patients, including 33 children aged 2 to 17 years, were randomized to receive baricitinib or usual care (95% received corticosteroids).<sup>20</sup> Treatment with baricitinib was associated with a 13% proportional reduction in mortality, with the greatest effect size occurring in patients who received NIV. The RECOVERY investigators included these patients in a meta-analysis and found that treatment with baricitinib was associated with a 20% proportional reduction in mortality (rate ratio 0.80; 95% CI, 0.72–0.89;  $P < 0.0001$ ). See [Kinase Inhibitors: Janus Kinase Inhibitors and Bruton's Tyrosine Kinase Inhibitors](#) and [Therapeutic Management of Hospitalized Adults With COVID-19](#) for additional information. These data in adults indicate that baricitinib is likely to be most beneficial for patients receiving noninvasive forms of respiratory support.

Several open-label trials and cohort studies have evaluated baricitinib in children with autoinflammatory and rheumatic diseases, including many children aged  $< 5$  years, and found the treatment was well tolerated; however, the pharmacokinetics of baricitinib in younger children are not well studied.<sup>21-24</sup> Information on the safety and effectiveness of the use of baricitinib in children with COVID-19 is limited to case reports.

In contrast to the strong recommendation for its use for adults, baricitinib is not considered the standard of care for all children who require high-flow oxygen or NIV because of the low mortality in children with COVID-19 (especially in young children) and the limited data on the use of baricitinib in these children.

Extrapolating from clinical trials among adults with COVID-19, the Panel recommends that:

- For children who require oxygen through a high-flow device or NIV *and* do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib** can be considered for children aged 12 to 17 years (**BIII**) and for children aged 2 to 11 years (**CIII**).
- For children who require mechanical ventilation or ECMO *and* do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib** may be considered for children aged 12 to 17 years (**BIII**) and for children aged 2 to 11 years (**CIII**).

Clinicians should consult with specialists experienced in treating children with immunosuppression (e.g., with pediatric infectious disease, pediatric rheumatology) when considering administering baricitinib to hospitalized children with COVID-19. Data from adults indicate that baricitinib should be initiated promptly; ideally, it should be initiated at the onset of clinical deterioration or respiratory failure.

### ***Tofacitinib***

There are no data on the efficacy of tofacitinib in pediatric patients with COVID-19; the Panel's recommendation is extrapolated from data in adults. The STOP-COVID trial compared tofacitinib to the standard of care in adults hospitalized for COVID-19 pneumonia.<sup>25</sup> The standard of care included glucocorticoids for most patients. The study demonstrated a reduction in mortality and respiratory failure at Day 28 for the tofacitinib arm when compared with the placebo arm. Tofacitinib has been studied less extensively than baricitinib for the treatment of COVID-19. Thus, tofacitinib, as an alternative to baricitinib, is recommended to be used in combination with dexamethasone in adults with COVID-19 who require high-flow oxygen or NIV. See [Kinase Inhibitors: Janus Kinase Inhibitors and Bruton's Tyrosine Kinase Inhibitors](#) and [Therapeutic Management of Hospitalized Adults With COVID-19](#) for additional information.

No trials have evaluated the safety of using tofacitinib in children with COVID-19. Overall, there has been more clinical experience with the use of tofacitinib than baricitinib in children, particularly when used in children with juvenile idiopathic arthritis (JIA) as young as 2 years of age. A Phase 1 study was conducted to define the pharmacokinetics and safety of using tofacitinib in children,<sup>26</sup> and a Phase 3, double-blind, randomized, placebo-controlled trial investigated the efficacy of using tofacitinib in children with JIA.<sup>27</sup> Tofacitinib is available as a liquid formulation for children.

Given the established safety of tofacitinib in the pediatric population, **tofacitinib** can be considered an alternative for children hospitalized for COVID-19 if baricitinib is not available (**BIII**). The dose of tofacitinib that should be used to treat hospitalized children with COVID-19 has not been established. As with baricitinib, the dose of tofacitinib for hospitalized children with COVID-19 likely needs to be higher than the dose typically used to treat pediatric rheumatologic diseases. Therefore, clinicians should consult with specialists experienced in treating children with immunosuppression (e.g., with pediatric infectious disease, pediatric rheumatology) when considering administering tofacitinib to hospitalized children with COVID-19.

### ***Tocilizumab***

Tocilizumab is an interleukin (IL)-6 inhibitor that has received an FDA EUA for the treatment of hospitalized adults and children with COVID-19 who are aged  $\geq 2$  years, receiving systemic corticosteroids, and require supplemental oxygen, NIV, mechanical ventilation, or ECMO.<sup>28</sup> Two large randomized controlled trials (REMAP-CAP and RECOVERY) conducted among hospitalized adults with COVID-19 have demonstrated reductions in mortality with the use of tocilizumab. See [Interleukin-6 Inhibitors](#) and [Therapeutic Management of Hospitalized Adults With COVID-19](#) for additional information.

The RECOVERY trial was an open-label study that included hospitalized adults who had an oxygen saturation of  $<92\%$  on room air or were receiving supplemental oxygen therapy; patients also had C-reactive protein levels  $\geq 75$  mg/L.<sup>29</sup> Patients were randomized to receive tocilizumab plus usual care or usual care alone. Mortality at 28 days was significantly lower in the tocilizumab arm compared to the usual care arm. The REMAP-CAP trial included adults with suspected or confirmed COVID-19 who were admitted to an intensive care unit and received either respiratory (i.e., NIV or mechanical ventilation) or cardiovascular organ (i.e., vasopressor/inotrope) support.<sup>30</sup> Patients were randomized within 24

hours of organ failure to receive either tocilizumab or sarilumab (the majority received tocilizumab) or to receive standard care. The median number of organ support-free days was higher for those who received tocilizumab than for those who received standard care, and in-hospital mortality was lower in the combined tocilizumab or sarilumab arm than in the standard care arm. In both studies, the majority of patients received dexamethasone (82% in the RECOVERY trial and 93% in the REMAP-CAP trial).

Studies have evaluated the use of tocilizumab for the treatment of non-COVID-19 conditions in children, including JIA<sup>31-35</sup> and chimeric antigen receptor T cell-related cytokine release syndrome.<sup>36</sup> The FDA approved tocilizumab for use in children aged  $\geq 2$  years for these indications.<sup>31-35</sup> The use of tocilizumab for children with severe cases of COVID-19 has been described only in case series.<sup>37-39</sup>

Extrapolating from clinical trials among adults with COVID-19, the Panel recommends that:

- For children who require oxygen through a high-flow device or NIV *and* who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **tocilizumab** can be considered for children aged 12 to 17 years (**BIII**) and for children aged 2 to 11 years (**CIII**).
- For children who require mechanical ventilation or ECMO *and* who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, if tocilizumab has not been started, addition of **tocilizumab** may be considered for children aged 12 to 17 years (**BIII**) and for children aged 2 to 11 years (**CIII**).

Data from REMAP-CAP and RECOVERY are most likely to be applicable to high-risk adolescent patients. Clinicians should consult with specialists experienced in treating children with immunosuppression (e.g., with pediatric infectious disease, pediatric rheumatology) when considering the use of tocilizumab in younger children with COVID-19.

### ***Sarilumab***

Sarilumab, a monoclonal antibody that blocks IL-6 receptors, is not authorized by the FDA for the treatment of COVID-19. Data evaluating the efficacy of sarilumab for the treatment of COVID-19 hyperinflammation are limited, and there is a lack of pediatric dosing information. Therefore, the Panel **recommends against** the use of **sarilumab** in hospitalized children with COVID-19, except in a clinical trial (**AIII**).

### **Anticoagulation for Children With COVID-19**

Limited data characterize the risk of thromboembolic disease in children with COVID-19. In a multicenter, retrospective cohort study that included 814 pediatric patients with COVID-19 or MIS-C,<sup>40</sup> thromboembolic events were detected in 2.1% of patients with COVID-19 and in 6.5% of patients with MIS-C. No trials to define the optimal approach to anticoagulation have been conducted among children. Therefore, the Panel recommends prophylactic anticoagulation for children aged  $\geq 12$  years who are hospitalized for COVID-19, unless there are contraindications (**BIII**). There is insufficient evidence for the Panel to recommend either for or against anticoagulation in younger hospitalized children with COVID-19, although institutional standards for anticoagulation should be followed. There is insufficient evidence for the Panel to recommend either for or against high-intensity anticoagulation for children of any age with COVID-19.

### **Other Therapeutic Agents**

For other therapies that have been studied or are under investigation for the treatment of COVID-19, see [Therapies](#).

## References

1. Schuster JE, Halasa NB, Nakamura M, et al. A description of COVID-19-directed therapy in children admitted to US intensive care units 2020. *J Pediatric Infect Dis Soc.* 2022;11(5):191-198. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35022779>.
2. Goldman DL, Aldrich ML, Hagmann SHF, et al. Compassionate use of remdesivir in children with severe COVID-19. *Pediatrics.* 2021;147(5):e202004780. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33883243>.
3. 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;9(6):701-715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32318706>.
4. Dulek DE, Fuhlbrigge RC, Tribble AC, et al. Multidisciplinary guidance regarding the use of immunomodulatory therapies for acute coronavirus disease 2019 in pediatric patients. *J Pediatric Infect Dis Soc.* 2020;9(6):716-737. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32808988>.
5. Wolf J, Abzug MJ, Anosike BI, et al. Updated guidance on use and prioritization of monoclonal antibody therapy for treatment of COVID-19 in adolescents. *J Pediatric Infect Dis Soc.* 2022;11(5):177-185. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35107571>.
6. Remdesivir (Veklury) [package insert]. Food and Drug Administration. 2022. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/214787Orig1s015lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214787Orig1s015lbl.pdf).
7. Vangeel L, Chiu W, De Jonghe S, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *Antiviral Res.* 2022;198:105252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35085683>.
8. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA.* 2020;324(11):1048-1057. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32821939>.
9. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med.* 2020;383(19):1813-1826. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32445440>.
10. WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet.* 2022;399(10339):1941-1953. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35512728>.
11. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a Phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis.* 2022;22(2):209-221. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34534511>.
12. Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ.* 2022;194(7):E242-E251. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35045989>.
13. Ahmed A, Rojo P, Agwu A, et al. Remdesivir treatment for COVID-19 in hospitalized children: CARAVAN interim results. 2022. Available at: <https://www.croiconference.org/abstract/remdesivir-treatment-for-covid-19-in-hospitalized-children-caravan-interim-results/>. Accessed July 7, 2022.
14. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med.* 2022;386(4):305-315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34937145>.
15. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med.* 2021;384(8):693-704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
16. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics.* 2014;134(5):e1474-e1502. Available at: <https://www.ncbi.nlm.nih.gov/>



[pubmed/25349312](https://pubmed/25349312).

17. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of baricitinib. 2022. Available at: <https://www.fda.gov/media/143823/download>.
18. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33306283>.
19. Wolfe CR, Tomashek KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. *Lancet Respir Med*. 2022; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35617986>.
20. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet*. 2022;400(10349):359-368. Available at: <https://pubmed.ncbi.nlm.nih.gov/35908569/>.
21. Sanchez GAM, Reinhardt A, Ramsey S, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest*. 2018;128(7):3041-3052. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29649002>.
22. Kim H, Dill S, O'Brien M, et al. Janus kinase (JAK) inhibition with baricitinib in refractory juvenile dermatomyositis. *Ann Rheum Dis*. 2021;80(3):406-408. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32843325>.
23. Vanderver A, Adang L, Gavazzi F, et al. Janus kinase inhibition in the Aicardi-Goutieres syndrome. *N Engl J Med*. 2020;383(10):986-989. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32877590>.
24. Kim H, Brooks KM, Tang CC, et al. Pharmacokinetics, pharmacodynamics, and proposed dosing of the oral JAK1 and JAK2 inhibitor baricitinib in pediatric and young adult CANDLE and SAVI patients. *Clin Pharmacol Ther*. 2018;104(2):364-373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29134648>.
25. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34133856>.
26. Ruperto N, Brunner HI, Zuber Z, et al. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a Phase 1, open-label, multicenter study. *Pediatr Rheumatol Online J*. 2017;15(1):86. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29282090>.
27. Ruperto N, Brunner HI, Synoverska O, et al. Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal Phase 3 randomised trial. *Lancet*. 2021;398(10315):1984-1996. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34767764>.
28. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Actemra (tocilizumab). 2021. Available at: <https://www.fda.gov/media/150321/download>.
29. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33933206>.
30. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33631065>.
31. Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a Phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis*. 2015;74(6):1110-1117. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24834925>.
32. Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab for polyarticular-course juvenile idiopathic arthritis in the open-label two-year extension of a Phase III trial. *Arthritis Rheumatol*. 2021;73(3):530-541. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32951358>.
33. De Benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med*. 2012;367(25):2385-2395. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23252525>.

34. DeWitt EM, Kimura Y, Beukelman T, et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(7):1001-1010. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22290637>.
35. Horneff G, Schulz AC, Klotsche J, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. *Arthritis Res Ther*. 2017;19(1):256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29166924>.
36. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. *Expert Rev Clin Immunol*. 2019;15(8):813-822. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31219357>.
37. Derespina KR, Kaushik S, Plichta A, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J Pediatr*. 2020;226:55-63. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32681989>.
38. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr*. 2020;174(9):868-873. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32392288>.
39. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32593339>.
40. Whitworth H, Sartain SE, Kumar R, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. *Blood*. 2021;138(2):190-198. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33895804>.