Treatment Guidelines for COVID-19
(Version 5.0, dated 4 January 2021)

ABSTRACT

Background

In December 2019, pneumonia cases caused by a novel coronavirus occurred in Wuhan, Hubei Province. As of 11th February 2020, the World Health Organisation has officially named the disease “COVID-19”, and the causative agent, “SARS-CoV-2”. The COVID-19 pandemic has led to over 72 million infections and 1.6 million deaths world-wide as of 15 December 2020. This guideline provides updated interim evidence-based recommendations on the therapeutic management of patients with COVID-19 in Singapore, from our initial guidance issued on 2 April 2020.

Methods

Published clinical trials, cohort studies, society and professional guidelines related to the treatment of COVID-19 were analysed, and where appropriate, selected pre-print data. Each recommendation was discussed by an expert committee and screened for conflicts of interest.

Recommendations

Based on available data, dexamethasone (or equivalent doses of steroids) is recommended for patients with severe COVID-19 (receipt of supplemental oxygen or mechanical ventilation). Remdesivir, is recommended for hospitalised patients who have severe COVID-19 (i.e. SpO2 <94% on room air, requiring supplemental oxygen), and may be used in combination with steroids, although further prospective data for combination therapy with remdesivir is pending. Baricitinib may be considered as an alternative to steroids, and be used in conjunction with remdesivir in patients with severe COVID-19. Hydroxychloroquine and lopinavir/ritonavir are not recommended as clinical trials have failed to show clear clinical benefit. No overt safety concerns have been reported from convalescent plasma therapy although randomised controlled trials have not shown a clear benefit to date. Further definitive data are awaited for Interferons, tocilizumab, and other non-steroid immunomodulator therapies.
Given the propensity for thromboembolic disease with COVID-19, pharmacologic prophylaxis should be considered in patients with severe or critical disease, or those who are elevated risk of thromboembolic disease (e.g. as stratified by a risk score such as the PADUA score), who do not have contraindications.

**Conclusions**

Dexamethasone (or equivalent steroid) should be considered patients with severe COVID-19 (receipt of supplemental oxygen or mechanical ventilation). Remdesivir may be considered for hospitalised patients with severe COVID-19 (i.e. SpO2 <94% on room air, requiring supplemental oxygen), and may be used in combination with steroids or baricitinib. Pharmacologic thromboprophylaxis should be considered in patients with severe or critical disease who do not have contraindications.
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1. Overview

Early supportive care and monitoring—including oxygen supplementation, organ support and prevention of complications, especially acute respiratory distress syndrome, organ failure and secondary nosocomial infections—remain the cornerstone and most important management strategy for clinical management of COVID-19.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus. Similar to SARS-CoV and MERS-CoV, the SARS-CoV-2 encodes non-structural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural proteins (such as spike glycoprotein) and accessory proteins. The four non-structural proteins are key enzymes in the viral life cycle, and the spike glycoprotein is indispensable for virus-cell receptor interactions during viral entry. Initial analyses of genomic sequences from SARS-CoV-2 indicate that the catalytic sites of the four SARS-CoV-2 enzymes that could represent key antiviral targets are highly conserved, and share a high level of sequence similarity with the corresponding SARS-CoV and MERS-CoV enzymes.

Most patients with COVID-19 do not require specific antiviral treatment, beyond supportive care. However, a subset of approximately 20% may progress to severe pneumonia and about 5%-10% may require critical care. This subset of patients who progress to more severe disease may benefit from treatment with medications with antiviral and/or immunomodulatory activity.

Following our previous interim guidance, further data on corticosteroids for treatment of COVID-19 have been published, including a meta-analysis. Final results for remdesivir in the ACTT-1 and ACTT-2 trial have been published. Remdesivir is available for prescribing locally and is conditionally approved by the Health Sciences Authority (HSA), for use in hospitalised patients with COVID-19 with hypoxia. Several other important studies for treatments for COVID-19 (tocilizumab and convalescent plasma) have been published or preliminarily reported since the last review. Key studies informing our recommendations are detailed in Box 1. Key changes from our last update are enumerated in Box 2.
**Box 1. Key studies informing these therapeutic guidelines**

<table>
<thead>
<tr>
<th>Therapeutic Group</th>
<th>Study Title</th>
<th>Authors</th>
<th>Journal / Publication Details</th>
</tr>
</thead>
</table>
**Tocilizumab**


**Lopinавir/ритонавир**


**Hydroxychlorоquine**


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**Box 2. Key changes since last interim guidance version 4.0 dated 31 Aug 2020**

- Updates of the severity classification for COVID-19
- Revision of CRP cut-off to 20 mg/L as a marker of severity
- Removal of the statement on off-label use(s) and WHO criterion for such usage
- Updates on use and dosing of corticosteroids in COVID-19
- Updates on use of remdesivir in COVID-19, including in combination with steroids and baracitinib, Infectious Diseases consultation for patients at high risk of deterioration but who have not met criterion.
- Updates on use of convalescent plasma only in the context of contraindications of other approved medications, and as salvage therapy
- Updates on use of interferon preparations as part of clinical trials
- Statement on use of neutralising antibodies
- Expansion of further recommendations for prophylactic anticoagulation and risk stratification for thromboprophylaxis and bleeding
- Addition on recommendations for paediatric and pregnant patients
2. Classification for persons at low versus high risk of disease progression for COVID-19

<table>
<thead>
<tr>
<th>Low Risk (fulfilling all criterion below)</th>
<th>High Risk (fulfilling any of the criterion below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;30</td>
<td>Age&gt;30, particularly &gt;50</td>
</tr>
<tr>
<td>No chronic comorbidities</td>
<td>Chronic comorbidities (chronic lung, heart or kidney disease, diabetes mellitus, immunosuppression, body mass index &gt;25 if age &lt;60)</td>
</tr>
<tr>
<td>Reassuring clinical features</td>
<td>Worrisome clinical features</td>
</tr>
<tr>
<td>• No dyspnoea</td>
<td>• Dyspnoea</td>
</tr>
<tr>
<td>• Respiratory rate &lt; 20 breaths/min</td>
<td>• Respiratory rate &gt;20 breaths/min</td>
</tr>
<tr>
<td>• Normal SpO2</td>
<td>• Abnormal SpO2 (&lt;94%)</td>
</tr>
<tr>
<td>• Not requiring oxygen therapy</td>
<td>• Requiring oxygen therapy</td>
</tr>
<tr>
<td>Normal Chest X-ray</td>
<td>Chest X-ray with pneumonia</td>
</tr>
</tbody>
</table>

Reassuring laboratory results*

- CRP < 20 mg/L
- LDH ≤ 550 U/L
- Lymphocytes > 1 x 10^9/L
- Neutrophils < 3 x 10^9/L

Worrisome laboratory results

- CRP > 20 mg/L
- LDH > 550 U/L
- Lymphocytes < 1 x 10^9/L
- Neutrophils > 3 x 10^9/L

*Certain risk stratification factors may be non-modifiable (e.g. age), whereas others are dynamic (e.g. evolving clinical features, radiology or laboratory results). Repeat laboratory tests are recommended at intervals (e.g. 2-3 days) for patients for whom there is concern for clinical deterioration or when there is worsening of disease. Please note that these cut offs are based on aggregate data from Singapore COVID-19 cases and there may be some variability in normal reference ranges between laboratories.

3. Clinical severity of COVID-19

<table>
<thead>
<tr>
<th>COVID-19 severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or Presymptomatic</td>
<td>Test positive for SARS-CoV-2 with a virologic test but have no symptoms consistent with COVID-19</td>
</tr>
<tr>
<td>Mild</td>
<td>Any signs/symptoms of COVID-19 (e.g. fever, cough, sore throat, malaise, headache, myalgia, nausea, vomiting, diarrhea, loss of taste/smell) but who do not have shortness of breath or clinical signs of pneumonia or abnormal chest imaging</td>
</tr>
<tr>
<td>Moderate</td>
<td>Shows evidence of lower respiratory tract disease during clinical assessment or imaging and who have an SpO2 of &gt; 94% on room air.</td>
</tr>
<tr>
<td>Severe</td>
<td>Individuals who have a SpO2 of &lt;94% on room air, or P/F ratio of &lt;300 mmHg, respiratory rate of &gt;30 breaths/minute or lung infiltrates occupying &gt;50% of lung fields</td>
</tr>
<tr>
<td>Critical</td>
<td>Individuals with respiratory failure, septic shock, and/or multiple organ dysfunction</td>
</tr>
</tbody>
</table>


4. Staging for COVID-19

The staging proposed by Siddiqi et al is a conceptual framework for patients with COVID-19, however bear in mind individual patient’s courses may vary and not all patients enter Stage II or III.

5. Interim Therapeutic Recommendations for COVID-19

I) Level of Recommendations

The level of recommendations are adapted from the Oxford Centre for Evidence-Based Medicine.

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levels of evidence</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Systematic reviews, meta-analyses, well-designed randomized controlled trials (Phase 3)</td>
</tr>
<tr>
<td>II</td>
<td>Two groups, non-randomized studies (e.g. cohort, case-control) or early phase (e.g. Phase 2, or which lack sufficient power) randomized controlled trials</td>
</tr>
<tr>
<td>III</td>
<td>One-group, non-randomized studies (e.g. before and after, pre-test and post-test)</td>
</tr>
<tr>
<td>IV</td>
<td>Descriptive studies that include analysis of outcomes (single-subject design, case series), randomized controlled trials which are not peer reviewed</td>
</tr>
<tr>
<td>V</td>
<td>Case reports and expert opinion that include narrative literature, reviews and consensus statements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grades of evidence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Consistent level I studies</td>
</tr>
<tr>
<td>B</td>
<td>Consistent level II or III studies or extrapolations from level I studies</td>
</tr>
<tr>
<td>C</td>
<td>Level IV studies or extrapolations from level II or III studies</td>
</tr>
<tr>
<td>D</td>
<td>Level V evidence or troublingly inconsistent or inconclusive studies at any level</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength of recommendations*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Evidence from studies at low risk of bias</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence from studies at moderate risk of bias</td>
</tr>
<tr>
<td>Weak</td>
<td>Evidence from studies at high risk of bias</td>
</tr>
</tbody>
</table>

* Recommendations may also be labelled as “conditional”, where the workgroup considers that there are sufficient evidence for desirable effect of adherence to a recommendation probably outweigh the undesirable effects, but is not confident about these trade-off, is awaiting full peer-review of data.

Most patients with COVID-19 DO NOT require specific antiviral treatment, beyond supportive care. Specific therapy, however, may be considered for patients predicted to progress to severe infection, or who have severe infection.

These interim recommendations and a treatment algorithm were formulated with the current available evidence about COVID-19.
II) Treatment Algorithm for COVID-19

III) Recommendations

1. We recommend corticosteroids (dexamethasone 6 mg or equivalent for up to 10 days) for patients with severe or critical COVID-19 (receipt of supplemental oxygen or mechanical ventilation) (Level I, Grade A, Moderate).

Prior to results released by the RECOVERY trial, steroids have not been conclusively shown to have specific benefits in COVID-19 infection, and the evidence has been somewhat conflicting. Studies with reported benefits have been uncontrolled, and confounded by concurrent treatments, and steroids have been known to cause deleterious effects (e.g. bacterial/fungal superinfection) from SARS (2003) data. Steroid bursts (≤ 14 days) have also been found to be associated with a significant increase in incidence of gastrointestinal bleeding, sepsis, and heart failure within the first month after initiation of steroid therapy.

The RECOVERY trial results reported on 2104 patients who were randomised (unblinded) to received dexamethasone and 4321 patients to standard of care. Patients were eligible if they were hospitalised, and had clinically suspected or laboratory confirmed COVID-19. Dexamethasone was given orally or intravenous at a dose of 6mg once daily for up to 10 days (or until hospital discharge if sooner)(median duration 7 days). The trial found that significantly lower mortality in patients allocated to dexamethasone (overall 22.9% vs 25.7%, p<0.001; if on mechanical ventilation 29.3% vs 41.4%, 95% CI 0.51 to 0.81); if receiving oxygen without invasive mechanical ventilation (23.3% vs. 25.7% in the control arm)
There was no statistically significant benefit if patients were not receiving any respiratory support (17.8% vs. 14.0%, 95% CI 0.91 to 1.55). The receipt of dexamethasone was associated with a reduction in 28-day mortality among those with symptoms for more than 7 days but not among those with a more recent symptom onset (12.3 by chi-square test for trend).

An observation study on 1806 hospitalised COVID-19 patients, of which 140 were treated with glucocorticoids within 48 hours of admission, found that early glucocorticoid treatment and an initial C-reactive protein (CRP) ≥20 mg/dL was associated with significantly reduced risk of mortality or mechanical ventilation (adjusted odds ratio [aOR], 0.20; 95% CI: 0.06-0.67). Conversely, glucocorticoid treatment in patients with CRP levels less than 10 mg/dL was associated with a significantly increased risk of mortality or mechanical ventilation (aOR, 3.14; 95% CI: 1.52-6.50).

A prospective meta-analysis of 7 randomised trials (DEXA-COVID 19, CoDEX, RECOVERY, CAPE COVID, COVID STEROID, REMAP-CAP, Steroids-SARI) consisting of 1703 patients had also found that treatment with corticosteroids (dexamethasone, hydrocortisone, methylprednisolone) was associated with a lower 28-day all-cause mortality for critically ill patients with COVID-19, compared with usual care or placebo. There were 222 deaths among 678 patients randomised to corticosteroids, and 425 deaths among 1025 patients randomised to usual care or placebo (summary OR 0.66; 95% CI: 0.53 to 0.82; P<0.001).

Given the above findings, oral or intravenous dexamethasone 6 mg daily (equivalent to oral prednisolone 40 mg daily, intravenous methylprednisolone 10 mg q6 hours or intravenous hydrocortisone 50mg q8 hours) for up to 10 days is recommended in patients with severe COVID-19 requiring supplemental oxygen or mechanical ventilation and who do not have contraindications to such treatment.

2. **We recommend remdesivir for patients who require supplemental oxygen or have a SpO2 of <94% on room air or who have severe illness, if available (Level I, Grade A, Moderate).** Remdesivir may be combined with steroid therapy (Level III, Grade C, Weak) or baricitinib (Level I, Grade B, Moderate) in patients who are eligible.

One large RCT, ACTT-1, on 1063 patients (541 remdesivir, 521 placebo) showed a shortened time to recovery in hospitalised patients with COVID-19 (10 days vs 15 days, P<0.001) based on an eight-point ordinal scale, although no significant mortality difference was noted (6.7% with remdesivir and 11.9% with placebo by day 15, and 11.4% with remdesivir and 15.2% with placebo by day 29; hazard ratio 0.73; 95% CI 0.52 to 1.03; p=0.07). Specifically, the largest difference observed in HR for mortality was 0.30 (95% CI 0.14-0.64) for patients in category 5 (hospitalized, requiring any supplemental oxygen, but not non-invasive or invasive ventilation, or ECMO). In this study, remdesivir seemed more effective when given to patients who were not as severely ill, and in subgroup analyses the time to recovery was significant for the group on supplemental oxygen (but not for those with more severe disease on ECMO, invasive mechanical ventilation or high flow nasal oxygen), or milder disease (not on oxygen). The benefit of remdesivir for reducing time to recovery was most evident in the subgroup of patients who required supplemental oxygen (baseline ordinal score of 5; recovery rate ratio 1.45 (95% CI 1.18 to 1.79)). This is hypothesized to be related to the mechanism of action of remdesivir as an antiviral which is usually best given during the viral replicative phase in early illness in COVID-19, prior to clinical worsening (e.g. need for mechanical ventilation).
Another study did not find a difference in clinical improvement between a 5-day vs 10-day course of remdesivir for hospitalised patients with COVID-19, although this study was limited in terms of not having a control group, and was thus unable to measure the magnitude of benefit. It should be noted that those receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening were excluded, as were those who had signs of multi-organ failure.

A third study with 237 patients in COVID-19 in China did not find a statistically significant difference in time to clinical improvement, although this trial was felt to be underpowered as it was terminated earlier due to improvement in the COVID-19 situation in Hubei, China and inability to recruit further.

A randomised open-label adaptive trial sponsored by the World Health Organisation evaluating remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon-beta versus standard of care (SOLIDARITY trial) consisting of a total of 11,266 patients recently published interim results. There were 2,750 patients allocated to the remdesivir group and 2708 patients to standard of care. Overall in-hospital mortality was similar between remdesivir and standard of care (11% vs 11.2%; rate ratio 0.95; 95% CI 0.81 to 1.11; p=0.50). In-hospital mortality among patients on supplemental oxygen at enrollment was 12.2% in the remdesivir group compared to 13.8% in the standard of care arm (rate ratio 0.86; 95% CI 0.67 to 1.11), while the mortality among patients ventilated at enrollment was 43.0% versus 37.8% (rate ratio 1.2; 95% CI 0.80 to 1.80).

Methodological differences between SOLIDARITY and ACTT-1 should be noted, despite both being RCTs, including study size and different primary end-points, and the former being a pragmatic open label trial (remdesivir versus standard of care) whereas the latter a placebo-controlled double blinded trial. Even so taken together, the data suggest that remdesivir monotherapy with its modest antiviral effect, does not benefit patients with mild COVID-19 (who will recover anyway) or critical COVID-19 (in which immunomodulation with steroids as shown by the RECOVERY trial may be more beneficial).

For individuals at high risk of hyperinflammation who are diagnosed early during illness (≤10 days) and require supplemental oxygen, remdesivir shortens the time to recovery and reduces the risk of progression. The cost-effectiveness of remdesivir monotherapy and impact in the real-world setting however is however limited.

The Health Sciences Authority (HSA) has conditionally approved remdesivir for treatment of COVID-19 in Singapore on 10 June 2020, for adult patients with SpO2 < 94% (room air), or those requiring oxygen supplementation, mechanical ventilation or ECMO, for treatment up to 10 days. Remdesivir is currently available for prescribing in Singapore for patients who are eligible. Infectious Diseases (ID) physician approval is required. Based on the data by Beigel et al, we recommend an initial treatment duration of 5 days. This might be extended for up to 10 days in patients with more severe illness, with ID approval. We do not recommend the routine use of remdesivir in high risk patients for severe COVID-19 (e.g. immunocompromised, CRP > 20 mg/L, pneumonia) but who do not require oxygen therapy or who are not hypoxic. However, on a case-by-case basis, if remdesivir considered, an ID physician should be consulted. In the event that remdesivir supplies are limited, we recommend that remdesivir be prioritised for use in hospitalised patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated or on ECMO.

**Remdesivir plus corticosteroids**
Of note, the safety and efficacy of remdesivir plus corticosteroids has not been studied in prospective clinical trials. One retrospective, multicentre study in pre-print comprising 2486 patients found that adding dexamethasone to remdesivir compared to remdesivir alone showed a trend toward a lower 28-day mortality (5.1% vs 9.2%, aHR 0.14, 95% CI 0.02-1.03). Despite the lack of clinical trial data, taking together data from the RECOVERY and ACTT-1 trials, patients with severe COVID-19 may benefit from anti-inflammatory effects of corticosteroids, preventing or mitigating hyperinflammatory responses which leads to lung injury and multisystem organ dysfunction.

**Remdesivir plus baricitinib**

Baricitinib is an oral JAK inhibitor used in the treatment of rheumatoid arthritis. Its antiviral activity lies in its affinity for adaptor-associated kinase-1 (AAK1) which is a regulator of viral endocytosis, thereby preventing SARS-CoV-2 from entering and infecting pulmonary cells. It also blunts the downstream inflammatory cascade by the inhibition of JAK1/JAK2 kinase and IL-6-induced STAT3 phosphorylation.

On 19 November 2020, the FDA released an Emergency Use Authorisation (EUA) for remdesivir combined with baricitinib. The data supporting this EUA are based on a double-blind, placebo-controlled RCT (ACTT-2) which included 1,033 patients with moderate or severe COVID-19 (515 patients with remdesivir plus baricitinib versus 518 patients with remdesivir plus placebo). The median time to recovery was 7 days for baricitinib plus remdesivir, versus 8 days for remdesivir plus placebo (rate ratio for recovery, 1.16; 95% CI 1.01 to 1.32, p=0.03). Patients who showed the greatest benefit were those with a baseline ordinal score of 6 in the trial (i.e. on non-invasive ventilation or high-flow nasal oxygen). These patients had a time to recovery of 10 days in the baricitinib plus remdesivir group versus 18 days the control group (rate of recovery, 1.51; 95% CI 1.10 to 2.08). The incidence of progression to death or non-invasive ventilation was lower in the combination group that in the control group (22.5% vs 28.4%; rate ratio 0.77, 0.85% CI 0.60-0.98), as was the incidence of progression to death or invasive ventilation (12.2% vs 17.2%; rate ratio 0.69; 95% CI 0.50 to 0.95). The overall 28-day mortality was 5.1% for the remdesivir plus baricitinib group versus 7.8% for the remdesivir plus placebo group (hazard ratio for death 0.65; 95% CI 0.39 to 1.09).

The planned ACTT-4 trial will examine the efficacy of remdesivir plus baricitinib or dexamethasone in preventing progression to intubation or death.

3. **If dexamethasone, remdesivir and/or baricitinib is not suitable or contraindicated or as part of salvage therapy, convalescent plasma may be considered for patients requiring oxygen or who have a SpO2 of <93% on room air, as part of a monitored expanded access programme (Level II, Grade C, Weak).**

It should be noted that convalescent plasma has not been definitively shown to be effective as a treatment for COVID-19 and concerns remain regarding the risk and benefits of such treatment, in the light of available therapies which have proven efficacy in COVID-19. Convalescent plasma is available in Singapore as part of a monitored expanded access programme. One RCT has been published (103 patients), with a primary outcome of time to clinical improvement within 28 days, defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale, but
this trial was terminated early and was likely underpowered. In this study, severe COVID-19 was defined as respiratory distress as indicated by ≥30 breaths/min; in resting state, oxygen saturation ≤ 93% on room air; or arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) of 300 or less. Life-threatening COVID-19 was defined as respiratory failure requiring mechanical ventilation; shock; or other organ failure (apart from lung) requiring intensive care unit (ICU) monitoring. There was no significant difference in the primary outcome in the convalescent plasma group 51.9% (27/52) vs 43.1% (22/51) in the control group (difference 8.8% [95% CI, −10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; P=0.26). In a post-hoc sub-analysis of those with severe disease, the primary outcome occurred in 91.3% (21/23) of the convalescent plasma group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; P=0.03). No difference was found in the group with life-threatening disease, possibly because the trial was underpowered. At 24, 48 and 72 hours, the convalescent plasma group statistically significant a higher rate of viral nucleic acid negative conversion rate.

Another RCT consisting of 228 patients who received convalescent plasma versus 105 patients who received placebo found no significant difference between the groups in the distribution of clinical outcomes according to the ordinal scale at day 30 (odds ratio, 0.83; 95% CI 0.52 to 1.35; p=0.46). Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of -0.46 percentage points (95% CI, -7.8 to 6.8). Similarly, another trial conducted in India (PLACID), which was an open label phase II RCT comprising 464 patients failed to find benefit with convalescent plasma for a composite outcome of progression to severe disease (PaO2/FiO2 <100 mm Hg) or all-cause mortality at 28 days post-enrolment.

Another pre-print report surveyed the 3-month experience of the convalescent plasma expanded access program in the US. In more than 35,000 hospitalised COVID-19 patients with severe acute respiratory syndrome, 52.3% of whom were in the ICU and 27.5% received mechanical ventilation, it was found that earlier use of convalescent plasma (within 3 days of COVID-19 diagnosis) was associated with a survival benefit (7-day mortality) compared to the later use of convalescent plasma (4 or more days after diagnosis) (8.7% mortality vs 11.9% mortality, P <0.001), and 30-day mortality (21.6% vs 26.7%, P <0.0001). It was also observed that there was a gradient of mortality seen in relation to the titres of antibodies in the transfused plasma, with a significant mortality benefit seen in those given plasma units with high titre antibodies. It should be noted that the measurement methodology of antibody titres has not been standardised internationally and the assays used in Singapore is different from that in the US or in other parts of the world.

While caution should be exercised in convalescent plasma treatment due to the theoretical risk of exacerbating lung injury secondary to immune-enhancement, and a large study on key safety metrics after transfusion of ABO-compatible human COVID-19 convalescent plasma in 20,000 hospitalized adults with severe or life-threatening COVID-19 as part of the US FDA Expanded Access Program for COVID-19 convalescent plasma found an incidence of all serious adverse events (SAEs) in the first four hours after transfusion to be <1%, including mortality rate (0.05%). The seven-day mortality rate in this cohort was 13%, which was felt to be comparable to the estimated 15-20% mortality in severe COVID-19 in hospitalised patients.
Inclusion and exclusion criteria for convalescent plasma therapy are listed in Annex A, including the request forms and workflow.

4. **We do not recommend the use of interferon preparations (e.g. interferon beta-1a/1b, interferon alpha-2b) outside of a clinical trial (Level II, Grade C, Weak).**

In a phase 2 RCT in 125 adults in Hong Kong, combination treatment (lopinavir/ritonavir and ribavirin, with interferon beta-1b if within 7 days of onset of illness, was found to have more rapid nasopharyngeal virologic clearance (7 vs. 12 days) [the study’s primary end point], shorter time to symptom alleviation (4 vs. 8 days), and shorter median hospital stay (9 vs. 15 days).\(^\text{18}\) In a subgroup analysis, patients in the combination therapy group who did not receive interferon did not have better outcomes than the control group, suggesting that interferon may be the backbone of this treatment, and further studies are planned. Patients had mild COVID-19 in both combination and control groups in this trial, however, as indicated by a median NEWS score of 2.

One small open-label RCT comprising 81 patients found that early administration of interferon beta-1a subcutaneously at 12 million IU/ml 3 times weekly for 2 consecutive weeks (before 10 days from onset of symptoms) reduced mortality (OR 13.5, 95% CI 1.5-118), and overall 28-day mortality (19% vs 43.6, \(P = 0.015\)).\(^\text{19}\)

The LOTUS trial which was a non-blinded RCT on lopinavir/ritonavir monotherapy with 199 patients with more severe COVID-19 (overall mortality 22%), showed that time to clinical improvement did not differ between the two groups (median, 16 days), and the mortality rate at 28 days was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs 25%, −5.8 percentage points; 95% CI, −17.3 to 5.7) but this did not reach statistical significance.\(^\text{20}\) In a modified intention-to-treat analysis, which excluded three patients with early death, the between-group difference in the median time to clinical improvement (median, 15 days vs. 16 days) was significant, albeit only very modest (hazard ratio, 1.39; 95% CI, 1.00 to 1.91), and this did not clearly correlate with virologic clearance.\(^\text{20}\)

Based on these results, as well as the preliminary results from the RECOVERY and SOLIDARITY trial, we do not recommend lopinavir/ritonavir as monotherapy. Further results on interferon beta-1a and its use in combination with remdesivir compared to remdesivir alone in the ACTT-3 trial are awaited.

5. **We do not recommend the use of hydroxychloroquine or chloroquine for the treatment of COVID-19 (Level II, Grade B, Moderate) outside of a clinical trial.**

A small study of 20 COVID-19 patients treated with hydroxychloroquine +/- azithromycin by a French group generated interest as it showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine (in six of 20 patients) was reported to more effectively clear the virus. However numerous concerns were raised with this trial, in particular
its open-label and non-randomized nature and small number of patients. Following this conflicting data was reported in several small Chinese open label, randomised controlled trials.

Although one large purported registry study has been retracted due to doubts over the veracity of data, several large observational trials have since shown no clear benefit and a potential for cardiac toxicity, in particular when hydroxychloroquine is combined with azithromycin. Additionally, the RECOVERY Trial interim analysis of 1542 patients who were randomised to hydroxychloroquine, compared with 3132 patients randomised to usual care alone found no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% CI 0.98-1.26]; P =0.10), and no evidence of beneficial effects on hospital stay duration. We therefore do not recommend the use of hydroxychloroquine or chloroquine.

6. **We do not recommend the use of favipiravir outside of a clinical trial (Ungraded).**

One prospective, open-label, RCT of favipiravir in Japan comprising 89 patients randomised to get favipiravir early (day 1) or late (day 6) did not find differences in times to defervescence, viral clearance, disease progression or 28-day mortality. An adaptive, multicentre, open label phase II/III RCT of favipiravir vs standard of care in hospitalised patients with moderate COVID-19 pneumonia reported interim results consisting of 60 patients enrolled in the pilot stage. On day 5, the viral clearance was achieved in 25/40 (62.5%) patients on favipiravir and in 6/20 (30.0%) patients on standard of care (p=0.018). By day 10, the viral clearance was achieved in 37/40 (92.5%) patients on favipiravir and in 16/20 (80.0%) patients on standard of care. The median time to body temperature normalization was 2 days (IQR 1–3) in the favipiravir group and 4 days (IQR 1–8) in the standard of care group (P =0.007).

Evidence of significant clinical benefit of favipiravir is still lacking and if used should be as part of a clinical trial.

7. **We do not recommend the use of other non-corticosteroid immunomodulators (IL-1, IL-6, BTK inhibitors) outside of a clinical trial. (Level IV, Grade C, Weak).**

Besides corticosteroids and baricitinib, the role of non-steroid immunomodulators in the treatment of COVID-19 is still unclear, e.g. IL-1, IL-6 and other immunomodulators e.g. BTK inhibitors are unclear at this point. Further RCT data is awaited.

Data with regards to the role of IL-6 inhibitors such as tocilizumab are still somewhat conflicting. Preliminary results from COVACTA trial in hospitalised adults with severe COVID-19 pneumonia found that treatment with tocilizumab compared to placebo did not meet primary endpoint of improved clinical status using a 7-category ordinal scale (p=0.36; odds ratio, 1.19; 95% CI: 0.81-1.76). There was also no difference between tocilizumab and placebo in the percentage of patients with 28-day mortality (tocilizumab = 19.7% and placebo 19.4% [95% CI: -7.6% to 8.2%, p=0.94]), albeit a positive trend in time to hospital discharge in patients treated with tocilizumab. The EMPACTA trial comprising 389 patients (randomised 2:1, tocilizumab to placebo) found that the patients receiving tocilizumab were less likely to progress to a composite outcome of mechanical ventilation or death,
but did not improve 28-day survival\textsuperscript{35}. Another study from the Boston Area COVID-19 Consortium (BACC), however, did not find benefit with tocilizumab in preventing intubation or death in 243 moderately ill patients hospitalised for COVID-19, although baseline differences (more in category 2 or 3 of a 7-category ordinal scale compared to the EMPACTA trial) may account at least in part for these differences \textsuperscript{36}. The early findings from another trial, REMAP-CAP trial, found that critically ill patients receiving tocilizumab were more likely to improve than patients who received no immunomodulators (odds ratio 1.87). The full results are anticipated\textsuperscript{37}.

Separately, sarilumab, another IL-6 receptor agonist reported lower mortality in patients with critical illness (mortality 28\% in sarilumab 400 mg group, 46\% in sarilumab 200 mg group and 55\% in placebo group), but cited “negative trends” for most outcomes in patients with severe illness.\textsuperscript{38} Further data are required to define the benefit specific subgroups of patients with COVID-19 who may benefit from IL-6 inhibition.

8. \textbf{We do not recommend the routine use of neutralising monoclonal antibodies outside of a clinical trial or monitored programme. (Level IV, Grade C, Weak).}

Virus-neutralising monoclonal antibodies are predicted to reduce viral load, ameliorate symptoms, and prevent hospitalisation. The US FDA has issued an Emergency Use Authorisation for bamlanivimab (LY-CoV555) and casirivimab (previously REGN10933) and imdevimab (previously REGN10987) for the treatment of mild to moderate COVID-19 in adults and paediatric patients who are 12 years of age and older, weighing at least 40kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalisation.

This recommendation for bamlanivimab was based on the interim results of a phase 2 RCT (BLAZE-1) evaluating LY-CoV555 in 452 outpatients with mild to moderate COVID-19 illness (309 in the LY-CoV555 group and 143 in the placebo group).\textsuperscript{39} LY-CoV555 was administered to these patients in doses of 700 mg (101 patients), 2800 mg (107 patients), or 7000 mg (101 patients). The observed mean decrease from baseline in the log viral load for the entire population was −3.81, for an elimination of more than 99.97\% of viral RNA. For patients who received the 2800-mg dose of LYCoV555, the difference from placebo in the decrease from baseline was −0.53 (95\% confidence interval [CI], −0.98 to −0.08; \( P=0.02 \)), for a viral load that was lower by a factor of 3.4.\textsuperscript{39} Smaller differences from placebo in the change from baseline were observed among the patients who received the 700-mg dose (−0.20; 95\% CI, −0.66 to 0.25; \( P=0.38 \)) or the 7000-mg dose (0.09; 95\% CI, −0.37 to 0.55; \( P=0.70 \)).\textsuperscript{39} Of note, the benefit of treatment with bamlanivimab has not been observed in COVID-19 patients who are hospitalised.\textsuperscript{40}

The R10933-10987-2067 study for casirivimab plus imdevimab comprising 799 participants found a potential clinical benefit of for outpatients with mild to moderate COVID-19 (greater time-weighted average change in nasopharyngeal SARS-CoV-2 levels compared to placebo, and lowered COVID-19 related medical visits by 57\% (till Day 29) and no significant difference between in clinical or virologic efficacy between the high dose (8 grams) and low dose (2.4 grams) regimens.\textsuperscript{41}
However, the relatively small number of participants in these early phase trials and the low number of hospitalizations or emergency department visits make it difficult to draw definitive conclusions about the clinical benefit of these monoclonal antibodies. These monoclonal antibodies are also not currently available routinely in Singapore.

9. **We do not recommend** the use of other therapies such as mesenchymal stem cell infusion or donor lymphocyte infusions due to the lack of robust data on efficacy in COVID-19 (Ungraded).

10. **We do not recommend** post-exposure chemoprophylaxis for COVID-19 with hydroxychloroquine (Level 1, Grade A, Strong). We do not recommend pre-exposure chemoprophylaxis with hydroxychloroquine for COVID-19 outside of a clinical trial (Ungraded).

One RCT involving 821 subjects found no benefit with post-exposure prophylaxis,\(^4^2\) although this study had some limitations (only just over 10% of COVID-19 cases confirmed by PCR, and a delay of 3 or more days between exposure and starting preventive treatment. Pre-exposure trials are underway (e.g. Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine [HERO-HCQ] trial, involving 15,000 health care workers; ClinicalTrials.gov number, NCT04334148).

11. **We recommend** the use of pharmacological venous thromboembolism (VTE) prophylaxis for patients with critical or severe COVID-19. We recommend patient risk stratification with the PADUA risk score for patients with mild/moderate COVID-19, in determining whether pharmacological thromboprophylaxis is warranted. If pharmacological prophylaxis is contra-indicated, mechanical prophylaxis is recommended (Level 1, Grade A, Strong).

This recommendation represents good clinical practice in the intensive care setting, and is in keeping with international guidelines\(^4^3,4^4\) based on RCTs which in absolute and relative terms, have demonstrated that pharmacological prophylaxis reduces mortality, pulmonary embolism, and deep vein thrombosis. COVID-19 is associated with thromboembolic disease as a result of various factors, including endothelitis associated with COVID-19, an increase in circulating prothrombotic factors, and immobility in critical illness.\(^4^5,4^6\) PT/PTT, Fibrinogen and D-dimer may be assessed prior to commencement of pharmacologic prophylaxis. Higher rates of thrombosis are seen in ICU COVID-19 patients, in studies that systematically evaluate for them.\(^4^7-5^0\) The International Society on Thrombosis and Haemostasis (ISTH) Interim Guidance (21 Mar 2020) recommends that prophylactic low molecular weight heparin (LMWH) should be considered in all (including non-critically ill) patients if they require hospital admission for COVID-19.\(^5^1\)

All COVID-19 patients should have thrombotic and bleeding risk assessments such as PADUA score (https://www.mdcalc.com/padua-prediction-score-risk-vte) and VTE bleed score (https://practical-haemostasis.com/Clinical%20Prediction%20Scores/Formulae%20code%20and%20formulae/Formul ae/VTED bleedng/vte bleed_score.html) upon diagnosis. In patients with severe COVID-19 infection, we recommend pharmacological thromboprophylaxis unless contraindicated as they are at higher risk of thrombotic events.\(^5^2\) In patients with mild/moderate COVID-19 infection, we recommend risk
stratification of patients using the PADUA risk score in determining whether pharmacological thromboprophylaxis is warranted. We recommend that PADUA assessment be done as part of the admission process for COVID-19 patients in both acute hospitals and also at out-of-hospital isolation facilities (e.g. Community Care Facilities). Persons at high risk of VTE (venous thromboembolism) by PADUA assessment should be assessed for the appropriate thromboprophylaxis agent and its corresponding duration. As an general guidance, persons with high risk of VTE (PADUA score ≥4 points) be administered thromboprophylaxis with SC enoxaparin 40mg once daily (or renal adjusted dose of 20mg once daily) or other low molecular weight heparin (LMWH), until discharge (i.e. from acute hospital or the out-of-hospital facility if transferred from an acute hospital, whichever is later). If patients are discharged to an out-of-hospital facility, where they have to self-administer LMWH, they should receive the appropriate training and education prior to transfer.

Patients should be educated on general measures to prevent thromboembolism or seek urgent consultation for symptoms of thromboembolism. Patients should be informed of risk of thromboembolism especially if travelling on long-haul flights of prolonged duration after a recent diagnosis of COVID-19 and physicians should consider and discuss the role of prophylaxis (e.g. 1 dose of LMWH (e.g. enoxaparin 40 mg once if normal renal function, 2-4 hours prior to travel). Patients should be encouraged to maintain hydration and to avoid immobility, so as to reduce the risk of thromboembolism.

Routine antiplatelet prophylaxis for all COVID-19 recovered patients are not recommended at this point, and further data are awaited. Therapeutic anticoagulation doses, or doses higher than for prophylaxis, should not be used without confirmation of thrombosis.

12. Special populations: Paediatric patients and pregnant women

**Paediatric patients**

Remdesivir: Remdesivir is FDA approved for children with COVID-19 who are aged ≥12 years and weigh ≥40 kg, and its use may be considered in this group if criterion in recommendation 2 are met (require supplemental oxygen or have a SpO₂ of <94% on room air or who have severe or critical illness). There is currently a lack of data for younger children and its use not routinely recommended. There is currently insufficient data for any specific therapeutic approach, including antivirals, for COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) (Ungraded).

Dexamethasone: Children with clinically significant or worsening COVID-19 pulmonary or systemic disease should be given oxygen and/or supportive treatment and dexamethasone (or equivalent steroid) can be considered in children who require oxygen, although it may not be routinely indicated in otherwise well children with minimal oxygen support needed.

**Pregnant women**

Remdesivir: Remdesivir was not studied specifically in the trials that led to its approval, however data from 86 pregnant and postpartum hospitalized patients with severe COVID-19 treated with remdesivir on a compassionate use programme found that it was well tolerated with minimal serious adverse
Steroids: Dexamethasone has a history of use to decrease neonatal complications in premature delivery and used for foetal lung maturity have not been associated with ill-effects. There is however some concern of potential adverse foetal effects (e.g. small head circumference, growth restriction, neonatal hypoglycemia) with repeated doses of antenatal glucocorticoids. Further there is less data of corticosteroids for pregnant women with COVID-19 (e.g. only 6 pregnant women were enrolled in the RECOVERY trial). However, given the benefits, we recommend the use of steroids for pregnant women with severe or critical COVID-19.

Prednisolone, methylprednisolone and hydrocortisone are metabolised by the placenta and have limited foetal transfer. Dexamethasone (and betamethasone) cross the placenta and have substantial foetal transfer. Methylprednisolone and dexamethasone have the most data for benefit in acute lung injury.

As such, we recommend the algorithm suggested by Saad et al,54 with the choice and duration of steroids in a pregnant patient with COVID-19 will depending on whether glucocorticoids are indicated for foetal lung maturity.

Pregnant patient with severe or critical COVID-19, requiring oxygen therapy and/or mechanical ventilation:

<table>
<thead>
<tr>
<th>Glucocorticoids indicated for foetal lung maturity?</th>
<th>Steroid regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (24 weeks to 33 weeks of gestation)</td>
<td>Dexamethasone 6 mg IM q12hourly for 4 doses, then switch to methylprednisolone 10 mg q6hours (oral or IV) to complete a total of 10 days or until recovery/discharge ( whichever comes first)</td>
</tr>
<tr>
<td>No (outside 24 to 33 weeks of gestation, or post-partum and breastfeeding)</td>
<td>Methylprednisolone 10 mg q 6 hours (oral or IV) to complete a total of 10 days or until recovery/discharge (whichever comes first)</td>
</tr>
</tbody>
</table>

Please note that the recommendations above are based on current data, and that updates will be made to this guidance as more evidence becomes available. Attempts should be made to conduct randomised clinical trials to validate treatment protocols. Off-label usage of the above drugs outside of a trial should be monitored so as to accrue real time data that could facilitate analysis of treatment outcomes and any adverse events. Clinical evidence summaries for various therapeutics for COVID-19 are also available from the Ministry of Health-Agency for Care Effectiveness at https://www.moh.gov.sg/covid-19/clinical-evidence-summaries and US-NIH https://www.covid19treatmentguidelines.nih.gov/.
References


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Treatment Guidelines for COVID-19 (Version 5.0, dated 4 Jan 2021)


52. CW Tan, JY Tan, WH Wong et al. A comparison of clinical and laboratory manifestations of thrombotic events in patients with COVID-19 and other respiratory viral infections. doi: 10.21203/rs.3.rs-82066/v1. (not peer-reviewed)
5. **Key Drug Summary Table** *(Note: Therapy should be guided by an Infectious Diseases Physician)*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult Dose</th>
<th>Notes (Please see full product information leaflet/drug use guide)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>6 mg PO or IV for up to 10 days</td>
<td>If dexamethasone is unavailable, may consider substitution with equivalent daily doses of another corticosteroid (e.g. oral prednisolone 40 mg daily, IV methylprednisolone 10 mg q6 hours or IV hydrocortisone 50mg q8 hours) Dexamethasone is not recommended for patients without hypoxemia, or not requiring oxygen. Caution in patients with concurrent infections. Monitor for hyperglycaemia, psychiatric effects, gastrointestinal bleeding, sepsis and heart failure. Please see also <strong>Special populations: Paediatric patients and pregnant women</strong> for recommendations in paediatric and pregnancy.</td>
</tr>
<tr>
<td><strong>Remdesivir</strong></td>
<td>200 mg IV loading dose, followed by 100 mg IV daily for 5 to 10 days</td>
<td>Timing of antiviral initiation may be important, as administration with high viral loads seen after peak viral titre has been found to fail in reducing lung damage despite reducing viral loads. Early therapy may be more beneficial compared to later therapy. May cause LFT abnormalities/hepatitis. Monitor LFTs prior to initiation and regularly while on remdesivir.</td>
</tr>
<tr>
<td><strong>Baracitinib</strong></td>
<td>4mg PO once daily, for up to 14 days</td>
<td>Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed. Prophylaxis for VTE is recommended unless contraindicated. Monitor LFTs and FBC prior to initiation and regularly while on baracitinib. Not recommended for patients with known active tuberculosis infections, who are on dialysis, have end-stage renal disease, or have acute kidney injury.</td>
</tr>
</tbody>
</table>

**Drugs used optimally in the context of a clinical trial (if off-label use, per institutional policy and with careful discussion and monitoring)**

| Convalescent plasma | Request via ID physician-on-call (NCID/TTSH). The standard dose of CP for adults to be administered is 500 mls as a single dose over 1-2 hours. The dose of CP for children is 4-5 ml/kg as a single dose over 1-2 hours. |
Annex A: Indications and Contraindications to Convalescent Plasma therapy

The indications for CP administration are as follows (adapted from WHO severe disease criterion and Arabi et al)¹:

Laboratory-confirmed COVID-19 Infection AND 1) or 2)

1) Severe or Critical illness as defined by:
   WHO Criterion
   a. Dyspnea
   b. RR>30/min
   c. SaO2 ≤93%
   d. \( P/F \) ratio <300
   e. Lung infiltrates >50% of lung fields within 24-48 hours
   Other criterion
   a. Admission to an ICU
   b. Current receipt of mechanical invasive or non-invasive ventilation
   c. Current receipt of intravenous vasoactive medications to maintain mean arterial pressure >65 mmHg
   d. Myocarditis/ myocardial dysfunction secondary to SARS-CoV-2

OR

2) Predicted progression to severe illness as defined by:
   Need for supplemental oxygen /dyspnoea / respiratory rate >20/min AND one of the following:
   a. Marked lymphopenia (<1.0 x 10⁹/L)
   b. Neutrophilia (>3.0x10⁹/L)
   c. Markedly raised and increasing levels of CRP (>20 mg/L)
   d. LDH (> 550 U/L)
   e. Rising Ferritin
   f. D-dimer >1 mcg/ml
   g. Elevated troponin
   h. Progressive lung infiltrates, or a validated predictive model (Reference 6, 7).

Exclusion criteria:
   b. History of allergic reaction to blood or plasma products
   c. Known IgA deficiency (IgA levels should be checked prior to transfusion; levels should not be below reference interval).
   d. Medical conditions in which receipt of 500 mL intravascular volume may be detrimental to the patient (e.g., actively decompensated congestive heart failure).

Requests for convalescent plasma should be made via the Infectious Diseases Physician on call, NCID/TTSH through the TTSH Operator at 63571000.

Request Form for Novel Treatment with Convalescent Plasma Transfusion for COVID-19 Infection

Patient Clinical Information (Please tick and circle accordingly)

Date of COVID-19 (novel coronavirus) confirmation: (i.e. Positive swab)
Date of Onset Illness:
Date of ICU admission: (if applicable)

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Dyspnoea</td>
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<tr>
<td>Respiratory rate &gt;30</td>
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<tr>
<td>Arterial oxygen saturation (SaO2) &lt;93%</td>
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<tr>
<td>PaO2/FiO2 (P/F ratio) &lt;300</td>
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<tr>
<td>Lung infiltrates &gt;50% within 24-48 hours</td>
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<td>Intensive care unit (ICU) patient</td>
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<tr>
<td>Mechanical ventilation</td>
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<tr>
<td>On vasopressors</td>
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<tr>
<td>Marked lymphopenia (&lt;1.0 x10^4/L)</td>
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<tr>
<td>Neutrophilia (&gt;3.0 x10^4/L)</td>
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<tr>
<td>Serum Lactate Dehydrogenase (LDH) &gt; 550 U/L</td>
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<tr>
<td>D-dimer &gt; 1 mcg/ml</td>
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<tr>
<td>Elevated troponin</td>
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<tr>
<td>Suspect or confirmed myocarditis/myocardial dysfunction</td>
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Other Comments on Current Clinical Status:

Blood Group: A / B / O / AB Rhesus Positive / Negative

Serum Immunoglobulin A (IgA) levels: (please include units)

History of Allergic Reactions to Blood Products: (If Yes, please elaborate)
**Clinical Trials Enrolled in (if any), please include intervention(s) if known (e.g. Open label):**

**Other COVID-19 Related Therapy (if any):** ____________________

Patient / Next-of-kin Agreeable in-Principle: Yes / No

### Requestor Details

<table>
<thead>
<tr>
<th>Name of Hospital / Organisation:</th>
<th>Name and MCR No. of Requesting Physician:</th>
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<tr>
<th>Date of Request:</th>
<th>Signature:</th>
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- Refer to Annex 4 Procedure Information Sheet for Novel Treatment with Convalescent Plasma Transfusion for COVID-19 Infection
- Email this form to: Clinical Director NCID (shawn_vasoo@ncid.sg) and cc to HOD TTSH Haematology (kiet_hoe_ong@ttsh.com.sg); and please TigerText information simultaneously. If no response within 24 hours please contact ID consultant on call 63571000 via TTSH operator. If urgent please indicate in email or TigerText, and if no response within 2 hours, please call ID consultant on call.
Version 5.0 Initial Draft prepared by: Ms Grace Hoo, Ms Law Hwa Lin and Dr Shawn Vasoo

Reviewed by: COVID-19 Therapeutic Workgroup

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