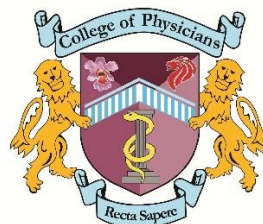




National Centre for
Infectious Diseases



CHAPTER OF INFECTIOUS DISEASE PHYSICIANS
COLLEGE OF PHYSICIANS, SINGAPORE

Treatment Guidelines for COVID-19

(Version 7.0, dated 28 July 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 176 million infections and 3.8 million deaths world-wide as of 14 June 2021. This guideline provides updated interim evidence-based recommendations for 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 published till 1 June 2021 were reviewed, and where appropriate, selected pre-print data. Each recommendation was discussed and arrived at via consensus by the guideline committee, with the evidence behind each recommendation reviewed, 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 may be considered for hospitalised patients who have severe COVID-19 (i.e. SpO₂ <94% on room air, requiring supplemental oxygen) in combination with steroids. Baricitinib may be considered as an alternative to steroids, and used in conjunction with remdesivir in patients with severe COVID-19. Tocilizumab may be considered in patients who are already maximised on standard-of-care (e.g. steroids), who require high-flow or more intensive respiratory support and have features of hyperinflammation due to COVID-19. Monoclonal antibodies (e.g. casirivimab and imdevimab) may be considered for patients with mild to moderate COVID-19 who at high risk for severe disease, within 10 days of symptoms onset. Although no overt safety concerns have been reported from convalescent plasma therapy, randomised controlled

trials have not shown a clear benefit to date. Given the emerging variants of concern (VOCs), as with monoclonal antibody therapies, efficacy of humoral therapies towards specific VOCs should be monitored. We do not recommend as treatment or prophylaxis hydroxychloroquine, lopinavir/ritonavir, ivermectin, favipiravir, interferon preparations, mesenchymal stem cell infusion or donor lymphocyte infusions and other non-steroid immunomodulator therapies at this time due to the lack of robust supporting data. 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 used in combination with steroids or baricitinib. Tocilizumab may be considered in patients with hyperinflammation, at high risk of progression, or, progressing to more intensive respiratory support despite steroid therapy. Pharmacologic thromboprophylaxis should be considered in patients with severe or critical disease who do not have contraindications.

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Versions

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4.0 issued 31 Aug 2020
3.0 issued 6 July 2020
2.0 issued 15 June 2020
1.0 issued 2 April 2020

1. Overview

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus which causes COVID-19. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 infection may lead to severe respiratory disease.

Most patients with COVID-19 do not require specific antiviral treatment, and can be adequately managed with supportive care even in the presence of pneumonia. Approximately 20% of patients with COVID-19 may progress to severe pneumonia and about 2-5% may require critical care. For this group of patients who progress to more severe disease, SARS-CoV-2 antivirals and/or immunomodulatory agents can be beneficial. For select individuals SARS-CoV-2 monoclonal antibodies have also recently been shown to reduce the risk of progression.

Despite these advances, 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 of clinical management of COVID-19.

The COVID-19 treatment guidelines outlines pharmacologic treatment guidance for patients with COVID-19 in Singapore, and has undergone multiple updates with the accumulation of new evidence. Following our previous interim guidance, further data on tocilizumab and monoclonal antibodies 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

Dexamethasone and other steroids

RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with COVID-19. *N Engl J Med* 2021 Feb 25;384(8):693-704.

WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*. 2020 Oct 6;324(13):1330-1341. doi: 10.1001/jama.2020.17023. PMID: 32876694; PMCID: PMC7489434.

Remdesivir

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020 Nov 5;383(19):1813-1826. doi: 10.1056/NEJMoa2007764. Epub 2020 Oct 8. PMID: 32445440; PMCID: PMC7262788.

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med*. 2020 Nov 5;383(19):1827-1837.

Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; 395:1569-1578.

WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021 Feb 11;384(6):497-511.

Spinner CD, Gottlieb RL, Criner GJ, et al; GS-US-540-5774 Investigators. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020 Sep 15;324(11):1048-1057. doi: 10.1001/jama.2020.16349. PMID: 32821939; PMCID: PMC7442954.

Baricitinib and Remdesivir

Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med* 2021 Mar 4;384(9):795-807.

Tofacitinib

Guimarães PO, Quirk D, Furtado RH, et al; STOP-COVID Trial Investigators. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med*. 2021 Jun 16. doi: 10.1056/NEJMoa2101643. PMID: 34133856.

Tocilizumab

Ghosh L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. *Cochrane Database Syst Rev*. 2021 Mar 18;3:CD013881. doi: 10.1002/14651858.CD013881. PMID: 33734435.

RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0. PMID: 33933206; PMCID: PMC8084355

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 Apr 22;384(16):1491-1502.

Stone JH, Frigault MJ, Serling-Boyd NJ, et al; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med*. 2020 Dec 10;383(24):2333-2344. doi: 10.1056/NEJMoa2028836. Epub 2020 Oct 21. PMID: 33085857; PMCID: PMC7646626.

Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med* 2021; 384(1): 20-30.

Convalescent Plasma

Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. *JAMA* 2020 Aug 4;324(5):460-470. doi: 10.1001/jama.2020.10044. Erratum in: *JAMA* 2020 Aug 4;324(5):519. PMID:32492084; PMCID: PMC7270883.

Simonovich VA, Burgos Prax LD, Scibona P, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. *N Engl J Med* 2021 Feb 18;384(7):619-629. doi: 10.1056/NEJMoa2031304. Epub 2020 Nov 24. PMID: 33232588; PMCID: PMC7722692.

Agarwal A, Mukherjee A, Kumar G, et al; PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ*. 2020 Oct 22;371:m3939. doi: 10.1136/bmj.m3939. Erratum in: *BMJ*. 2020 Nov 3;371:m4232. PMID: 33093056; PMCID: PMC7578662.

Libster R, Pérez Marc G, Wappner D et al; Fundación INFANT–COVID-19 Group. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. *N Engl J Med*. 2021 Feb 18;384(7):610-618. doi: 10.1056/NEJMoa2033700. Epub 2021 Jan 6. PMID: 33406353; PMCID: PMC7793608.

Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. *N Engl J Med*. 2021 Mar 18;384(11):1015-1027. doi: 10.1056/NEJMoa2031893. Epub 2021 Jan 13. PMID: 33523609; PMCID: PMC7821984.

Joyner MJ, Bruno KA, Klassen SA, et al. Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. *Mayo Clin Proc*. 2020 Sep;95(9):1888-1897. doi: 10.1016/j.mayocp.2020.06.028. Epub 2020 Jul 19. PMID: 32861333; PMCID: PMC7368917.

Interferons

Hung IF, Lung KC, Tso E, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020 May 30;395(10238):1695-1704.

Davoudi-Monfared E, Rahmani H, Khalili H, et al. A Randomized Clinical Trial of the Efficacy and Safety of Interferon β -1a in Treatment of Severe COVID-19. *Antimicrob Agents Chemother*. 2020 Aug 20;64(9):e01061-20. doi: 10.1128/AAC.01061-20. PMID: 32661006; PMCID: PMC7449227.

WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021 Feb 11;384(6):497-511.

Lopinavir/ritonavir

Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir/ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020;382(19):1787-1799. doi:10.1056/NEJMoa2001282.

WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021 Feb 11;384(6):497-511.

Ivermectin

López-Medina E, López P, Hurtado IC, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. *JAMA*. 2021 Apr 13;325(14):1426-1435. doi: 10.1001/jama.2021.3071. PMID: 33662102; PMCID: PMC7934083.

Hydroxychloroquine

RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020 Nov 19;383(21):2030-2040. doi: 10.1056/NEJMoa2022926. Epub 2020 Oct 8. PMID: 33031652; PMCID: PMC7556338.

WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021 Feb 11;384(6):497-511.

- Updated methylprednisolone equivalent dose (32 mg daily), compared with dexamethasone (6mg daily)
- Elaboration on the use of remdesivir in non-severe COVID-19 (e.g. moderate) in patients with high risk of progression guided by Infectious Diseases consultation.
- Update on preliminary findings of ACTT-4 (remdesivir + dexamethasone vs remdesivir + baricitinib).
- Added statement on use of tofacitinib
- Updates on the use of tocilizumab in select patients optimized on steroid therapy, with increased/increasing oxygen needs, and hyperinflammation.
- Updates on the dosing and use of neutralising antibodies (casirivimab and imdevimab, and sotrovimab). Statement on variants of concern and impact of efficacy of humoral therapies, addition of examples of request and monitoring forms for monoclonal antibodies. Update on the indications for casirivimab and imdevimab with RECOVERY trial data.
- Updates of references for convalescent plasma therapy and hydroxychloroquine
- Inclusion of references for ivermectin.

2. Classification for persons at low versus high risk of disease progression for COVID-19

Low Risk (fulfilling all criterion below)	High Risk (fulfilling any of the criterion below)
Age <30	Age \geq 30, particularly >50
No chronic comorbidities	Chronic comorbidities (chronic lung, heart or kidney disease, diabetes mellitus, immunosuppression, body mass index >25 if age <60)
Reassuring clinical features <ul style="list-style-type: none"> • No dyspnoea • Respiratory rate \leq 20 breaths/min • Normal SpO₂ • Not requiring oxygen therapy 	Worrisome clinical features <ul style="list-style-type: none"> • Dyspnoea • Respiratory rate >20 breaths/min • Abnormal SpO₂ (\leq94%) • Requiring oxygen therapy
Normal Chest X-ray	Chest X-ray with pneumonia
Reassuring laboratory results* <ul style="list-style-type: none"> • CRP \leq 20 mg/L • LDH \leq 550 U/L • Lymphocytes \geq 1 x 10⁹/L • Neutrophils \leq 3 x 10⁹/L 	Worrisome laboratory results <ul style="list-style-type: none"> • CRP > 20 mg/L • LDH > 550 U/L • Lymphocytes < 1 x 10⁹/L • Neutrophils > 3 x 10⁹/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.

Young et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020; Fan et al. Hematologic parameters in patients with COVID-19 infection. American J of Haematology. Published 4 March 2020; Young and Puah SH et al (unpublished).

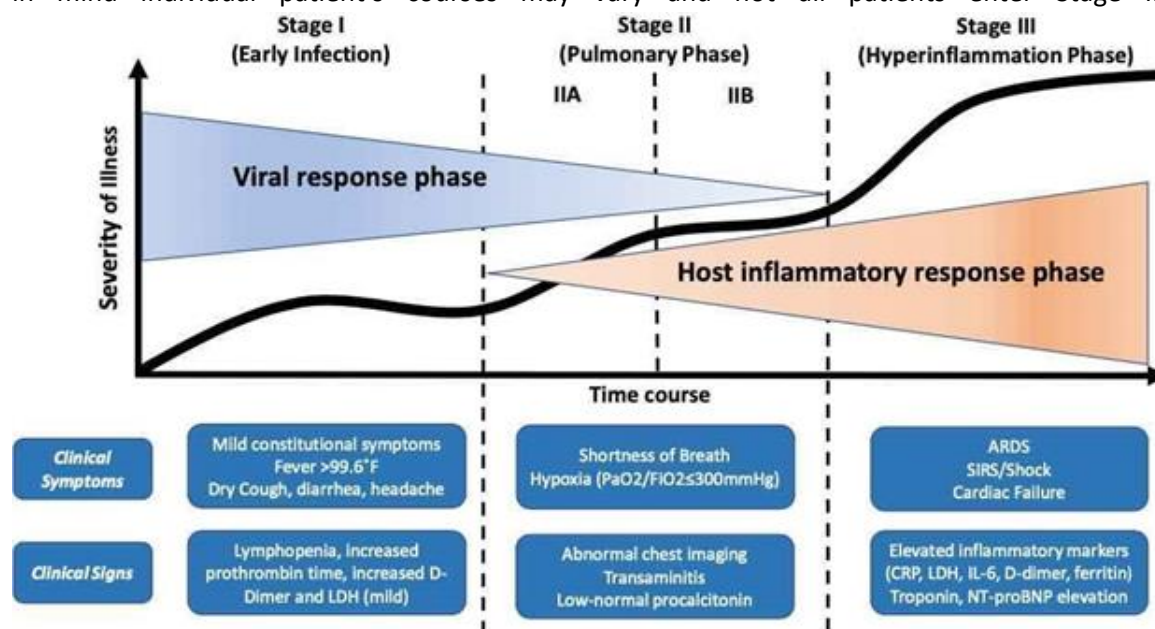
3. Clinical severity of COVID-19

COVID-19 severity	
Asymptomatic or Presymptomatic	Test positive for SARS-CoV-2 with a virologic test but have no symptoms consistent with COVID-19
Mild	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
Moderate	Shows evidence of lower respiratory tract disease during clinical assessment or imaging and who have a SpO ₂ of $\geq 94\%$ on room air.
Severe	Individuals who have a SpO ₂ of $<94\%$ on room air, or P/F ratio of <300 mmHg, respiratory rate of >30 breaths/minute or lung infiltrates occupying $>50\%$ of lung fields
Critical	Individuals with respiratory failure, septic shock, and/or multiple organ dysfunction

*COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19treatmentguidelines.nih.gov/>. Accessed [15 Dec 2020].

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.



Framework proposed by Siddiqi et al, "COVID-19 Illness in Native and Immunosuppressed States", J Heart and Lung Transplantation, 2020.

5. Therapeutic Recommendations for COVID-19

I) Level of Recommendations

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

Category	Definition
Levels of evidence	
I	Systematic reviews, meta-analyses, well-designed randomized controlled trials (Phase 3)
II	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
III	One-group, non-randomized studies (e.g. before and after, pre-test and post-test)
IV	Descriptive studies that include analysis of outcomes (single-subject design, case series), randomized controlled trials which are not peer reviewed
V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
Grades of evidence	
A	Consistent level I studies
B	Consistent level II or III studies or extrapolations from level I studies
C	Level IV studies or extrapolations from level II or III studies
D	Level V evidence or troublingly inconsistent or inconclusive studies at any level
Strength of recommendations*	
Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

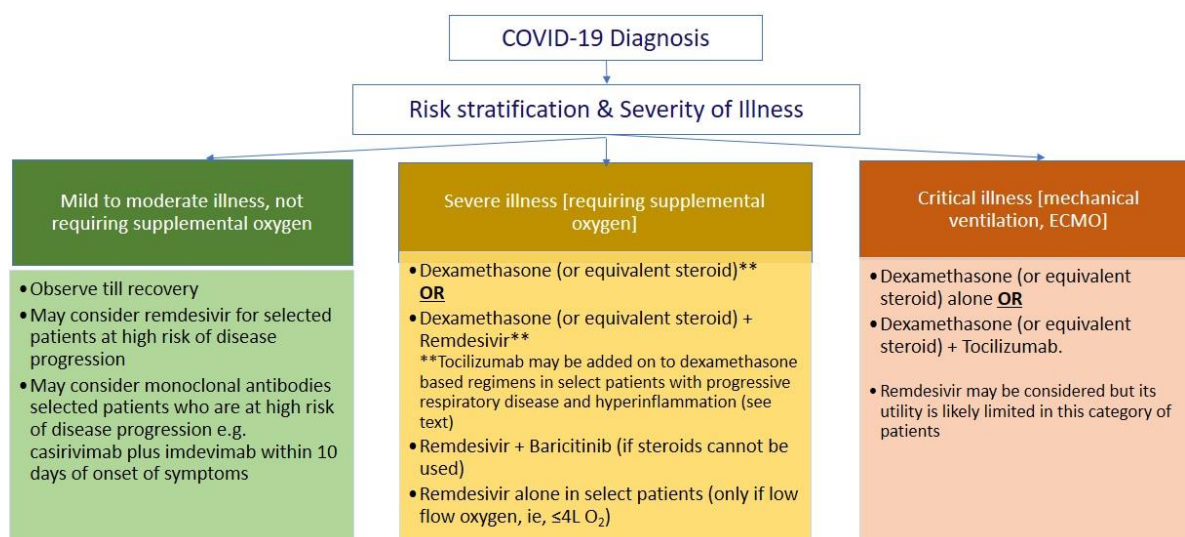
* Recommendations may also be labelled as “conditional”, where the workgroup considers that there are sufficient evidence for desirable effect of adherence to a recommendation probably outweigh the undesirable effects, but is not confident about these trade-off, is awaiting full peer-review of data.

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



All patients: Risk stratify risk for venous thromboembolism with the PADUA score and risk for bleeding VTE bleeding risk score. Patients with severe COVID-19 or a PADUA score ≥ 4 , and without contraindications should be started on pharmacologic thromboprophylaxis, till discharge from acute or community care facility. If there are contraindications to pharmacologic thromboprophylaxis, mechanical thromboprophylaxis should be considered (e.g. pneumatic calf pumps)

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 were not conclusively shown to have specific benefits in COVID-19 infection, and the evidence had been somewhat conflicting.¹ 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.²

The RECOVERY trial results reported on 2104 patients who were randomised (unblinded) to received dexamethasone and 4321 patients to standard of care.³ It should be noted that $<0.1\%$ of patients in the RECOVERY trial received concomitant remdesivir. 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. 26.2%; 95% CI

0.72 to 0.94). 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).³

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).⁴ 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).⁴

A randomised controlled trial (RCT) in Iran (n=86 hospitalised patients) which compared methylprednisolone (2 mg/kg/day; intervention group) versus dexamethasone (6 mg/kg/day; control group) found that methylprednisolone demonstrated significantly better clinical status compared to the control group at day 5 (4.02 vs. 5.21, $p = 0.002$) and day 10 (2.90 vs. 4.71, $p = 0.001$) of admission, a significant difference in the overall mean score (3.909 vs. 4.873, $p = 0.004$), a shorter mean length of hospital stay (7.43 ± 3.64 vs. 10.52 ± 5.47 days, $p = 0.015$), and a lower need for a ventilator (18.2% vs 38.1%, $p = 0.040$).⁵ Further studies are needed to assess the comparative performance and optimal dosing of various steroid preparations.

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; $P < 0.001$).⁶

Given the above findings, oral or intravenous dexamethasone 6 mg daily (equivalent to oral prednisolone 40 mg daily, intravenous methylprednisolone 32 mg daily 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 $\leq 94\%$ 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 1062 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; $p = 0.07$).⁷ 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 was 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).⁷ 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).⁷ 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). ACTT-1 also showed that remdesivir reduced progression to high flow oxygen or non-invasive ventilation, or progression to 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-19,⁸ 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 different 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.⁹

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 the subgroup analysis, 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).¹⁰

Methodological differences between SOLIDARITY and ACTT-1 should be noted,¹¹ 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) conditionally approved remdesivir for treatment of COVID-19 in Singapore on 10 June 2020, for adult patients with $\text{SpO}_2 \leq 94\%$ (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,⁷ 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. In selected patients, and as guided by ID consultation, remdesivir may be considered for

those with COVID-19 at high risk for progression to more severe disease (e.g. age ≥ 70 , immunocompromised patients, pneumonia, rising CRP levels due to COVID-19). One open-label randomised controlled trial in patients with moderate COVID-19 (i.e. not on oxygen at enrolment) found a better clinical status distribution in persons randomised to a 5 day course of remdesivir than those who received standard of care. Although the trial suggests a modest clinical benefit, its open label nature, a median of 9 days of symptoms prior to patient enrolment, lack of a clear benefit in those who received a 10 day course (as compared with standard of care, although these had a median actual duration of treatment of only 6 days with remdesivir) preclude a clear assessment of the importance of their findings.¹² Any benefit of remdesivir is most likely to be gained when administered in early illness (in the first week of disease). Remdesivir alone, with close observation, is a reasonable option for patients who are on low flow oxygen (i.e., $\leq 4\text{L/min}$). Remdesivir may also be considered for patients who are not on oxygen but are at high risk for mortality. Clinicians may consider using tools such as the 4C Mortality Score for COVID-19 (<https://www.mdcalc.com/4c-mortality-score-covid-19>) to determine mortality risks.¹³ Further trials are ongoing with the early administration of remdesivir in the outpatient setting (NCT04501952) and remdesivir by inhalation (NCT04539262).

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, further data is pending regarding the safety and efficacy of remdesivir plus corticosteroids combination in prospective clinical trials. One retrospective, multicentre study in pre-print comprising 2485 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).¹⁴ Despite the lack of clinical trial data, the theoretical rationale is the treatment of the viral infection with an antiviral agent and preventing or mitigating hyperinflammatory responses which lead to lung injury and multisystem organ dysfunction that is a possible consequence of the infection. If remdesivir is considered in patients with severe COVID-19, combination therapy should be strongly considered unless there is a contraindication to steroid use. For patients who are receiving remdesivir monotherapy but progress to require oxygen through a high-flow device, non-invasive ventilation, invasive mechanical ventilation, or ECMO, we recommend adding on dexamethasone (or equivalent steroid).

Remdesivir plus baricitinib, and other JAK inhibitors

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).¹⁵ 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 (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), and were most likely to have clinical improvement at day 15 (odds ratio 2.2; 95% CI 1.4 to 3.6). The incidence of progression to death or non-invasive ventilation was lower in the combination group than in the control group (22.5% vs 28.4%; rate ratio 0.77, 95% 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).

COV-BARRIER (in pre-print) is a phase 3 RCT evaluating baricitinib 4 mg once daily for up to 14 days plus standard of care ($n=764$) (SoC)(which included 79% receiving corticosteroids and 19% receiving remdesivir, with some receiving both) versus placebo plus SoC ($n=761$).¹⁶ The trial did not meet statistical significance on the primary endpoint, which was defined as a difference in the proportion of participants progressing to the first occurrence of non-invasive ventilation including high flow oxygen or invasive mechanical ventilation including extracorporeal membrane oxygenation (ECMO) or death by Day 28. However, the 28-day all-cause mortality was 8.1% for baricitinib and 13.1% for placebo, corresponding to a 38.25% reduction in mortality (hazard ratio 0.57, 95% CI 0.41 to 0.78; nominal $p=0.002$). A numerical reduction in mortality was observed for all baseline severity subgroups of baricitinib-treated patients and was most pronounced for patients receiving non-invasive mechanical ventilation at baseline (17.5% versus 29.4% for baricitinib plus SoC versus SoC; hazard ratio [HR]: 0.52; 95% CI: 0.33, 0.80; nominal p -value=0.0065). A reduction in mortality was also seen for the pre-specified subgroups of patients being treated with or without corticosteroids at baseline. Full data are awaited. Pending these data, and based on the ACTT-2 results, baricitinib when used should be in combination with remdesivir wherever possible for the treatment of COVID-19.

The ACTT-4 trial examined the efficacy of remdesivir plus baricitinib or dexamethasone in preventing progression to intubation or death in patients with severe COVID-19. Enrolment closed in April 2021 as an independent data and safety monitoring board found that was ‘unlikely’ that a significant difference between both arms would be found, in an NIH statement released (<https://www.nih.gov/news-events/news-releases/nih-closes-enrollment-trial-comparing-covid-19-treatment-regimens>).

An RCT (STOP-COVID) comprising 289 patients in Brazil found the decreased cumulative incidence of death or respiratory failure through day 28 with tofacitinib vs placebo (18.1% vs 29%, risk ratio 0.63, 95% CI 0.41-0.97, $p = 0.04$)¹⁷. The trial included patients 18 years or older with laboratory confirmed COVID-19 infection with pneumonia, who had been hospitalised for <72 hours. Tofacitinib was dosed at 10 mg BD up to 14 days and dose adjusted with renal and hepatic function on those on concurrent medications which were CYP3A4/CYP2C19 inhibitors. Patients on noninvasive or invasive mechanical ventilation and ECMO, and a history of thrombosis or current thrombosis, known immunosuppression, and active cancer on treatment were excluded. In this trial tofacitinib was dosed for a median of 5

days in the intervention group and 89.3% of patients overall received glucocorticoids, and non received remdesivir. Based on these results, and further ongoing trials with tofacitinib, JAK inhibitors may be considered in patients with severe COVID-19, but who are not yet mechanically ventilated. While awaiting further trial data, we recommend that JAK inhibitors be used with remdesivir wherever possible, and that tofacitinib may be an alternative if baricitinib is not available.

3. We recommend considering tocilizumab in addition to dexamethasone (or equivalent steroid) for patients who are at high risk of or who are exhibiting rapid respiratory decompensation due to COVID-19 associated systemic inflammation (e.g. as evidenced by significantly elevated inflammatory markers such a CRP level of ≥ 75 mg/L and rising), optimally within 24-48 hours after admission into a critical care unit if the patient requires such care (Level I, Grade B, Moderate).

A meta-analysis of overall cumulated evidence from multiple trials suggest a mortality benefit with tocilizumab (all-cause mortality at Day 28, RR 0.89, 95 CI 0.82-0.97).¹⁸

Two of the largest trials which support the use of tocilizumab include the RECOVERY¹⁹ and the REMAP-CAP²⁰ trials:

- RECOVERY trial (over 4000 patients), an open-label randomised trial, where patients with oxygen saturation $< 92\%$ on room air, or oxygen supplementation, and a CRP ≥ 75 mg/L were treated with one or two weight adjusted doses of tocilizumab along with standard of care, e.g. steroids (82% receipt). The median CRP at randomisation was 143 (107-203) mg/L.

The RECOVERY trial found a mortality benefit for tocilizumab plus systemic steroids. Allocation to tocilizumab was associated with a significant reduction in the primary outcome of 28-day mortality compared with usual care alone. Overall, 621 (31%) of the 2022 patients allocated tocilizumab and 729 (35%) of the 2094 patients allocated to usual care died within 28 days (rate ratio 0.85; 95% CI 0.76–0.94; $p=0.0028$). Consistent results were seen in all pre-specified subgroups of patients, including those receiving systemic corticosteroids. Patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days (57% vs 50%; rate ratio 1.22; 1.12–1.33; $p<0.0001$). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% vs 42%; risk ratio 0.84; 95% CI 0.77–0.92; $p<0.0001$).

- In the REMAP-CAP trial (over 700 patients), critically ill adult patients with COVID-19, within 24 hours after starting organ support in the intensive care unit, were randomized to receive open-label tocilizumab or usual care alone. Respiratory organ support was defined as invasive or non-invasive mechanical ventilation, including through high-flow nasal cannulae if the flow rate was >30 L/min and the fraction of inspired oxygen was more than 0.4.). In this trial, $>80\%$ also received concomitant steroids and 33%, remdesivir. The median (IQR) CRP for patients enrolled in the tocilizumab arm was 150 (85-221) mg/L. Compared to usual care, the use of tocilizumab

reduced in-hospital mortality (28% vs. 36%) and increased the number of days free of respiratory and cardiovascular organ support (10 days vs. 0 days; OR 1.64; 95% CI, 1.25–2.14)

Other trials have not shown a clear effect of mortality (CORIMUNO-TOCI²¹, COVACTA²², EMPACTA²³, NCT04346455²⁴, BACC Bay Tocilizumab Trial²⁵, TOCIBRAS²⁶, but there were overall smaller in terms of trial and thus effect size. The COVACTA trial although not showing a 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) showed a positive trend in time to hospital discharge in patients treated with tocilizumab. The EMPACTA trial found a reduced likelihood of progression to the composite outcome of mechanical ventilation or death, but did not find a survival benefit at 28-days.

Based on the REMAP-CAP and RECOVERY studies, and a meta-analyses of the trials above which indicate an overall 28-day mortality benefit with tocilizumab, we recommend the consideration of tocilizumab added to dexamethasone (or equivalent steroid) for patients with hyperinflammation (e.g. as evidenced by significantly elevated inflammatory markers such as a CRP \geq 75 mg/L and rising) who are at high risk or are exhibiting rapid respiratory decompensation due to COVID-19, if there are no contraindications to its use. Treating physicians should discuss the risks and benefits of tocilizumab use, including the risk of infection(s) and lower intestinal perforation, in particular in patients receiving concomitant steroids and with underlying gastrointestinal disease. Use of IL-6 inhibitors should be guided by Infectious Diseases, additional consultation with rheumatologists-allergist-immunologists (RAI) or intensivists may be needed for complex cases. Currently, we do not recommend the use of tocilizumab in patients who are receiving JAK inhibitors (e.g. baricitinib) due to the lack of efficacy and safety data.

- 4. Monoclonal antibodies such as casirivimab plus imdevimab, or sotrovimab may be considered for carefully selected patients with mild to moderate illness who are not on oxygen, but are at high risk of disease progression. Casirivimab plus imdevimab may be considered for patients with severe COVID-19, who are seronegative. These monoclonal antibodies should be administered as part of a monitored programme (Level IV, Grade C, Weak).**

Virus-neutralising monoclonal antibodies are predicted to reduce viral load, ameliorate symptoms, and prevent hospitalisation. Two combination anti-SARS-CoV-2 monoclonal antibody products—bamlanivimab plus etesevimab, and casirivimab plus imdevimab have received the U.S. FDA Emergency Use Authorisation (EUA) for the treatment of outpatient 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. Treatment should be started as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset. There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab. There are SARS-CoV-2 variants, particularly those that contain the mutation E484K, that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro;²⁷ however, the clinical impact of these mutations is not known. It is worth noting that studies for these monoclonal antibodies were conducted before the widespread circulation of the variants of concern.

The data supporting the EUA for casirivimab and imdevimab (REGEN-COV) are based on the analysis of Phase 1/2 data of the ongoing trial R10933-10987-COV-2067 (Phase 3 results are available in press release but have not been peer-reviewed)²⁸. Ambulatory adults with mild-to-moderate COVID-19 symptoms who had a sample collected for the first positive SARS-CoV-2 viral infection determination within 3 days received either casirivimab plus imdevimab or placebo. The pre-specified primary endpoint was the time weighted average (TWA) change from baseline in viral load (\log_{10} copies/mL), as measured by RT-qPCR in nasopharyngeal swab samples, in subjects with a positive baseline RT-qPCR value, i.e., the modified full analysis set (mFAS). In the mFAS for the Phase 1/2 analysis, the difference in TWA from Day 1 through Day 7 for the pooled doses of REGEN-COV compared with placebo (n=665) was $-0.36 \log_{10}$ copies/mL ($p<0.0001$). The predefined secondary endpoint was medically attended visits (MAV) related to COVID-19. A lower proportion of subjects treated with REGEN-COV had COVID-19 related MAVs (2.8% for combined treatment arms vs 6.5% placebo). In post-hoc analyses, a lower proportion of subjects treated with REGEN-COV had COVID-19-related hospitalizations or emergency room visits compared to placebo. The absolute risk reduction for REGEN-COV compared to placebo was greater in subjects at high risk for progression to severe COVID-19 and/or hospitalization. The Phase 3 outcomes trial in high-risk non-hospitalized COVID-19 patients ("outpatients") met its primary endpoint, showing the investigational REGEN-COV significantly reduced the risk of hospitalization or death by 70% (1,200 mg intravenous [IV], ($p=0.0024$)) and 71% (2,400 mg IV, ($p<0.0001$)) compared to placebo.

Casirivimab and imdevimab (REGEN-COV) may be considered in:

- high risk patients with laboratory confirmed COVID-19 AND
- Who are within 10 days of symptom onset (**Priority should be given to those who are unvaccinated for COVID-19, or are seronegative for SARS-CoV-2**)

High risk patients being considered for Casirivimab and imdevimab (REGEN-COV) are defined as patients who meet at least one of the following criteria:

- Are ≥ 65 years of age
- Are ≥ 55 years of age AND have
 - cardiovascular disease, OR
 - hypertension, OR
 - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 18-65 years of age AND have
 - Diabetes
 - Have a body mass index (BMI) ≥ 35
 - Chronic kidney disease
 - An immunosuppressive disease, or are currently receiving immunosuppressive treatment
- Are 12 – 17 years of age AND have
 - BMI ≥ 85 th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
 - Chronic kidney disease
 - Diabetes
 - Immunosuppressive disease or treatment

- sickle cell disease, OR
- congenital or acquired heart disease, OR
- neurodevelopmental disorders, for example, cerebral palsy, OR
- a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
- asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

On 30th June 2021, the Health Sciences Authority (HSA) has issued an interim authorisation of sotrovimab (also known as VIR-7831 and GSK4182136) for the treatment of adult patients aged ≥18 years with COVID-19 who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19. The interim analysis of phase 3 COMET-ICE trial, which was a randomised, double-blind, placebo-controlled study that evaluated sotrovimab as monotherapy for the early treatment of COVID-19 in adults at high risk of hospitalisation.²⁹ Patients included and who may be considered for sotrovimab include:

- High risk patients with laboratory confirmed COVID-19 AND
- Who are within 5 days of symptom onset **(Priority should be given to those who are unvaccinated for COVID-19, or are seronegative for SARS-CoV-2) AND**
- Who have an oxygen saturation on room air ≥94%

High risk patients who may be considered for sotrovimab are defined as those:

- Age 18 years and older with at least 1 of the following comorbidities:
 - diabetes,
 - obesity (BMI>30 kg/m²),
 - chronic kidney disease,
 - congestive heart failure,
 - chronic obstructive pulmonary disease, or moderate to severe asthma, or
 - aged 55 years and older.

The study endpoint was assessed on day 29 post-treatment. Based on the interim analysis from 583 patients, there was an 85% reduction in the relative risk for progression to hospitalisation for acute treatment (of > 24 hours) or death compared to placebo, with a relative risk ratio (RRR) of 0.15 (p = 0.002). The final analysis when all 1,057 subjects were included, demonstrated a 79% relative risk reduction, RRR = 0.21 (p < 0.001). There were 6% (30 / 529) of subjects in the placebo group and 1% (6 / 528) in the sotrovimab group who had progressed. There were lower proportions of subjects in the sotrovimab group (1%) compared to the placebo group (5%) who progressed to severe or critical respiratory disease requiring oxygen supplementation. The mortality rates due to COVID-19 were very low, with no death reported in the sotrovimab group and 2 deaths (<1%) in the placebo group.

Local variant epidemiology and susceptibility should be considered in the choice of the most appropriate neutralizing antibody therapy. Real-world data is still awaited for the efficacy of such therapy against emerging variants of concern (VOCs) such as B.1.617. Casirivimab and imdevimab individually and together retained neutralization activity against pseudovirus expressing all spike protein substitutions found in the B.1.1.7 lineage (UK origin) and against pseudovirus expressing only N501Y found in B.1.1.7 and other circulating lineages. Casirivimab and imdevimab together retained

neutralization activity against pseudovirus expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.1351 lineage (South Africa origin), and against K417T+E484K, found in the P.1 lineage (Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudovirus expressing K417N or E484K, as indicated above. The E484K substitution is also found in the B.1.526 lineage (New York origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (California origin). Pseudotyped virus-like particle *in vitro* assessments indicate that sotrovimab retains activity against the UK (B.1.1.7; 2.30-fold change in EC50 value); South Africa (B.1.351; 0.60-fold change in EC50 value); Brazil (P.1; 0.35-fold change in EC50 value); and California (B.1.427/B.1.429; 0.70-fold change in EC50 value) variant spike proteins. Microneutralization data from authentic SARS-CoV-2 variant virus also indicate that sotrovimab retains activity against the UK (3-fold change in EC50 value), South Africa (1.2-fold change in EC50 value) and Brazil (1.4-fold change in EC50 value) variants.²⁹

It is, however, not known how pseudovirus data correlate with clinical outcomes. Genotypic and phenotypic testing for variants and their correlation with patient important outcomes is being studied in clinical trials evaluating neutralizing antibodies and results are awaited.

It should be noted that monoclonal antibodies *may* be associated with worse clinical outcomes when administered to hospitalised patients with COVID-19 requiring high flow oxygen or mechanical ventilation, although this may be due to progression of disease. In patients hospitalised with COVID-19, however, who were seronegative (n=3153 who were negative anti-spike IgG to SARS-CoV-2), the RECOVERY trial (results in pre-print) found that casirivimab and imdevimab (REGEN-COV) reduced 28-day mortality (24% vs 30%, rate ratio 0.80, 95% CI 0.70-0.91, p=0.001)³⁰. The dose of casirivimab and imdevimab (REGEN-COV) used in this trial, however, was higher at 8g (4g casirivimab and 4 g imdevimab). Most of the seronegative patients in this trial (99%) randomised to receive casirivimab and imdevimab (REGEN-COV) or usual care also required oxygen, and 91.3% received corticosteroids.

Based on the above information, FDA and EMA approved dosing, and availability locally, casirivimab and imdevimab (REGEN-COV) [1.2g] or sotrovimab [500 mg] may be considered for the treatment of mild-to-moderate COVID-19 disease in those who are at high risk for progressing to severe COVID-19 as part of a monitored programme. Based on data from the RECOVERY trial³⁰, on a case-by-case basis, higher-dose casirivimab and imdevimab (REGEN-COV) [8g] may be considered in seronegative (anti-spike IgG negative or neutralizing antibody, e.g. Cpass negative) patients with severe COVID-19. Therapy with monoclonal antibodies should be guided by Infectious Diseases physicians.

The role of monoclonal antibodies in the prevention of COVID-19 are yet to be clearly defined. The BLAZE-2 COVID-19 prevention trial (NCT04497987) found that, at 8-weeks follow-up, bamlanivimab lowered the frequency of symptomatic COVID-19 in a study which enrolled 965 participants (299 residents and 666 staff at skilled nursing and assisted living facilities) (OR 0.43, p=0.00021).³¹ However the full data has not been published and the use of monoclonal antibodies for the prevention of COVID-19 would be considered 'off-label' currently, and any potential use-cases should be referred to Infectious Diseases.

Hospitals should track the use and outcomes for SARS-CoV-2 monoclonal antibodies as part of a hospital-based monitoring programme given the novel use of these medications. Please refer to

Annex B for an example of the information that such monitoring programme for casirivimab and imdevimab (REGEN-COV) or sotrovimab that hospitals may track.

5. We do not recommend the routine use of convalescent plasma for the treatment of COVID-19. (Level II, Grade C, Weak).

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. Efficacy is also uncertain, for example, of units collected prior to the emergence of VOCs, for treatment of disease caused by VOCs. Hence convalescent plasma, if considered, should only be used as part of salvage therapy 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.³² In this study, severe COVID-19 was defined as respiratory distress as indicated by ≥ 30 breaths/min; in resting state, oxygen saturation $\leq 93\%$ 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.³²

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).³³ 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.³⁴

A retrospective US national registry based study comprising 3082 patients found a 30-day mortality rate after plasma transfusion in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group, with a subanalysis showing no mortality benefit in those on mechanical ventilation.³⁵

One randomized, double-blind, placebo-controlled trial (n=160) of convalescent plasma with high IgG titers against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older adult patients within 72 hours after the onset of mild Covid-19 symptoms found a reduction in the progression of Covid-19 (severe respiratory disease) (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P = 0.03), with a relative risk reduction of 48%.³⁶

While caution should be exercised in convalescent plasma treatment due to the theoretical risk of exacerbating lung injury secondary to immune-enhancement, a large study on key safety metrics after transfusion of ABO-compatible human COVID-19 convalescent plasma in 20,000 hospitalised adults with severe or life-threatening COVID-19 as part of the US FDA Expanded Access Program for COVID-19 convalescent plasma found the incidence of all serious adverse events (SAEs) in the first four hours after transfusion to be <1%.³⁷

Given the availability of other effective treatments, we do not recommend the routine use of convalescent plasma for the treatment of COVID-19. The convalescent plasma programme in Singapore has ceased prospective collection of units and is anticipated to be suspended in September 2021, and remaining units may only be considered for use as salvage therapy in exceptional circumstances. Inclusion and exclusion criteria for the convalescent plasma therapy monitored programme are listed in Annex A, including the request forms and workflow.

6. 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).³⁸ 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).³⁹ However, the WHO-sponsored SOLIDARITY trial, comprising 11,330 adults (and 2063 to interferon beta-1a) also failed to show a mortality benefit, or reduction in ventilation or hospitalization duration in patients receiving interferon beta-1a.¹⁰

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.⁴⁰ 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.⁴⁰

Based on these results, as well as the results from the RECOVERY and SOLIDARITY trials, we do not recommend lopinavir/ritonavir as therapy. We also do not recommend interferon beta-1a as therapy at this point. Further results on interferon beta-1a and its use in combination with remdesivir compared to remdesivir alone in the ACTT-3 trial (NCT04492475) are awaited.

7. We do not recommend the use of hydroxychloroquine or chloroquine for the treatment of COVID-19 (Level I, Grade A, Strong).

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.⁴¹ Following this conflicting data was reported in several small Chinese open label, randomised controlled trials.^{42, 43}

Although one large purported registry study has been retracted due to doubts over the veracity of data,⁴³ several large observational trials have since shown no clear benefit and a potential for cardiac toxicity,⁴⁴⁻⁴⁷ in particular when hydroxychloroquine is combined with azithromycin.⁴⁵ 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.⁴⁸ We therefore do not recommend the use of hydroxychloroquine or chloroquine.

8. 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.⁵⁰

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.⁵¹ 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.

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

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

One potential emerging treatment is lenzilumab, which is a novel Humaneered® anti-human granulocyte macrophage colony-stimulating factor (GM-CSF) monoclonal antibody that directly binds GM-CSF and prevents signaling through its receptor, and downstream activation and trafficking of myeloid cells and elevation of chemokines (e.g. IP-10, MCP-1, IL-8), cytokines (IL-6, IL-1) and other markers of systemic inflammation (CRP, D-dimer, ferritin). The LIVE-AIR trial (in pre-print) was a phase 3 randomized, double-blind, placebo-controlled study in 520 hospitalised subjects with severe COVID-19 pneumonia who were on oxygen but not invasive mechanical ventilation.⁵² Majority of the participants also received steroids (93.7%), remdesivir (72.4%), or both (69.1%). The primary endpoint was the difference between lenzilumab treatment and placebo treatment in survival without ventilation (SWOV) through 28 days following treatment in the modified intent to treat population (mITT) who received at least one dose of investigational treatment under the documented supervision of the study investigators. The study achieved its pre-specified primary endpoint. Lenzilumab improved the likelihood of SWOV by 54% in the mITT population (HR: 1.54; 95%CI: 1.02-2.31, p=0.041). Full publication of these results are pending.

10. 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).

11. We do not recommend the use of ivermectin for the treatment or prophylaxis for COVID-19 due to the lack of robust data (Ungraded).

One RCT of 476 patients with mild COVID-19 did not find any difference in time to symptom resolution with a 5-day course of ivermectin, compared to placebo⁵³. An RCT in Singapore also did not show a protective effect of a single 12 mg dose of oral ivermectin in preventing COVID-19⁵⁴.

12. We do not recommend post- or pre- exposure chemoprophylaxis for COVID-19 with hydroxychloroquine except in a study setting (Level I, Grade B, Moderate).

One RCT involving 821 subjects found no benefit with post-exposure prophylaxis,⁵⁵ although this study had some limitations (only 15% of COVID-19 cases confirmed by PCR, and a delay of 3 or more days between exposure and starting preventive treatment). Another randomised controlled trial conducted in Singapore with 3037 participants in a dormitory setting with a COVID-19 outbreak, looked at hydroxychloroquine, iodine-spray and Vitamin C/Zinc, and found absolute risk reductions of COVID-19 infection with oral hydroxychloroquine (21%, 2–42%) and povidone-iodine throat spray (24%, 7–39%)⁵⁴. This trial was however, open label, and cluster-randomised (not individually

randomised) and infection-pressure might not have been homogenous across groups. A separate meta-analysis (not including the Singaporean study⁵⁴) of over 4000 participants in 4 studies found that hydroxychloroquine might have trivial to no effect on suspected, probable, or laboratory confirmed infection.⁵⁶ The evidence for prophylaxis with hydroxychloroquine is currently at best uncertain and other pre-exposure trial results are awaited (e.g. Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine [HERO-HCQ] trial, involving 15,000 health care workers; ClinicalTrials.gov number, NCT04334148).

13. 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^{57, 58} 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.^{59, 60} D-dimer should not be used as a screening tool for VTE; instead, it should be used as a diagnostic tool of exclusion. Higher rates of thrombosis are seen in ICU COVID-19 patients, in studies that systematically evaluate for them.⁶¹⁻⁶⁴ The American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 recommends that prophylactic low molecular weight heparin (LMWH) should be considered in all (including non-critically ill) patients.⁶⁵

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/Formulae/VTED_bleeding/vte_bleed_score.html), or any Risk Assessment Model that the hospital uses, upon diagnosis and 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). In the absence of a locally validated scoring system, we propose to adopt PADUA risk stratification, acknowledging that it has not been extensively validated in the Asian/Singaporean population. Persons at high risk of VTE (such as PADUA score ≥ 4 points) should be assessed for thromboprophylaxis with an appropriate agent and duration at an acute hospital. In patients with severe COVID-19 infection, we recommend pharmacological thromboprophylaxis unless contraindicated as they are at higher risk of thrombotic events.⁶⁶ In patients with mild/moderate COVID-19 infection, we recommend risk stratification of patients, such as with the PADUA risk score, to determine whether pharmacological thromboprophylaxis is warranted. In patients with contraindications to pharmacological thromboprophylaxis, the use of pneumatic calf pumps is recommended.

As a general guidance, persons with high risk of VTE (such as 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 encouraged to maintain hydration and to avoid immobility, so as to reduce the risk of thromboembolism.

We recommend that treating clinicians have a high index of suspicion and low threshold for imaging in situations where VTEs are suspected, such as when heart rate ≥ 100 beats/min, oxygen saturation $< 94\%$ on room air, or desaturations on exercise). For lower limb DVT or PE provoked by COVID-19, the recommended length of treatment is 3 months.

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.^{67, 68}

14. 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 0.15 mg/kg IV or orally once daily (maximum dose 6 mg) (or equivalent steroid) can be considered in children who require oxygen, with or without mechanical ventilation, although it may not be routinely indicated in otherwise well children needing minimal or no oxygen support.

Pregnant women

Remdesivir: Remdesivir was not studied specifically in the trials that led to its approval, however data from 86 pregnant and postpartum hospitalised patients with severe COVID-19 treated with remdesivir on a compassionate use programme found that it was well tolerated with minimal serious adverse events (16%, mostly grade 1/2 laboratory abnormalities).⁶⁹ At Day 28 of follow-up, among pregnant women (n=67), and among postpartum women (n=19, all immediate postpartum, median duration post-delivery, 1 day), respectively, 93% and 89% of those on mechanical ventilation were extubated, 93% and 89% recovered, and 90% and 84% were discharged.

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, and 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,⁷⁰ 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:

Glucocorticoids indicated for foetal lung maturity?	Steroid regimen
Yes (24 weeks to 33 weeks of gestation)	Dexamethasone 6 mg IM q12hourly for 4 doses, then switch to methylprednisolone 32 mg daily (oral or IV) to complete a total of 10 days or until recovery/discharge (whichever comes first)
No (outside 24 to 33 weeks of gestation, or post-partum and breastfeeding)	Methylprednisolone 32 mg daily (oral or IV) to complete a total of 10 days or until recovery/discharge (whichever comes first)

General comments on the management of pregnant women:

Maternal SpO₂ should be kept at least 95% and above, PaO₂ above 70 mmHg to maintain sufficient oxygen diffusion gradient across the placenta to the foetus. Hypoxia in adults is defined as $\leq 94\%$.

Prone positioning may be difficult in pregnant patient in later trimesters due to aortocaval compression. Left lateral position may be an alternative if proning not feasible for pregnant woman with COVID-19 related ARDS.

VTE prophylaxis in pregnant women with COVID-19 is an individualized decision and should be considered for those with severe COVID-19. Unfractionated heparin may be preferred for those closer to delivery as it is more readily reversed.

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. **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/>.**

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5. Key Drug Summary Table (Note: Therapy should be guided by an Infectious Diseases Physician;
Use as clinically available per institutional policy or as part of a clinical trial)

Medication	Class	Adult Dose with normal renal/hepatic function	Notes (Please see full product information leaflet/drug use guide)
Antivirals			
Remdesivir	RNA-dependent RNA polymerase inhibitor	200 mg IV loading dose, followed by 100 mg IV daily for 5 to 10 days	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.
Immunomodulators			
Dexamethasone	Steroid	6 mg PO or IV for up to 10 days	If dexamethasone is unavailable, may consider substitution with equivalent daily doses of another corticosteroid (e.g. oral prednisolone 40 mg daily, IV methylprednisolone 32 mg daily 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 Special populations: Paediatric patients and pregnant women for recommendations in paediatric and pregnancy.
Baricitinib	JAK inhibitor	4mg PO once daily, for up to 14 days	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 baricitinib. Not recommended for patients with known active tuberculosis infections, who are on dialysis, have end-stage renal disease, or have acute kidney injury.
Tofacitinib	JAK inhibitor	10 mg twice daily for up to 14 days	Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed. Prophylaxis for VTE is recommended unless contraindicated. Dose reduce to 5 mg twice daily in moderate to severe renal or hepatic impairment Patients receiving tofacitinib are at increased risk of serious infections which may result in fatality, Not recommended in patients with other concurrent chronic or recurrent infections, lymphoma and other active malignancies requiring treatment.
Tocilizumab	IL-6 inhibitor	8 mg/kg IV ONCE (up to maximum of 800mg per dose). A repeat dose may be	Consider discussion with Rheumatology-Allergy-Immunology/Intensive Care Physicians for complex cases. Tocilizumab, in particular in combination with corticosteroids, may increase the risk of opportunistic infections or reactivation and lower intestinal perforation.

		given after 12-24 hours.	Some experts recommend prophylactic treatment with ivermectin for patients who are from areas where strongyloidiasis is endemic.
Viral-neutralising, antibody-based therapies			
Casirivimab and imdevimab (REGEN-COV)	Monoclonal antibody to SARS-CoV-2 spike protein	600 mg of casirivimab and 600 mg of imdevimab administered together as a single IV infusion	Administer in health care settings by qualified health care providers who have immediate access to medications to treat severe infusion reactions and to emergency medical services. Patients should be monitored during the infusion and for at least 1 hour after the infusion is completed. Note: A higher dose (8 g comprising 4 g of casirivimab and 4 g of imdevimab) may be considered in seronegative, hospitalised patients with severe COVID-19
Sotrovimab	Monoclonal antibody to SARS-CoV-2 spike protein	500mg IV single dose infusion	Administer as a single IV infusion over 30 minutes; must not be administered as an intravenous push or bolus. Patients should be monitored during and for at least 1 hour after infusion is complete. Anaphylaxis has been reported. If occurs, immediately discontinue administration and initiate appropriate therapy. Infusion-related reactions have been reported. If occurs, consider slowing or stopping the infusion along with appropriate supportive care.
Convalescent plasma (CP)	Neutralising antibodies to SARS-CoV-2	Only for salvage therapy / Not first-line. 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.	

*LFT=Liver function tests, VTE = Venous thromboembolism

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. Dyspnoea
- 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.

¹ Available at: <http://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>;
Arabi YM, Hajeer AH, Luke T, et al. Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. Emerg Infect Dis. 2016;22(9):1554 - 1561. doi:10.3201/eid2209.151164

 Tan Tock Seng HOSPITAL	<i>Affix Patient Label</i>
	Patient Name: _____ Patient NRIC: _____
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>(i.e. Positive swab)</i>																																																					
Date of Onset Illness: _____																																																					
Date of ICU admission: _____ <i>(if applicable)</i>																																																					
<table border="1"> <thead> <tr> <th>Clinical Feature</th> <th>Yes</th> <th>No</th> <th>Clinical Feature</th> <th>Yes</th> <th>No</th> </tr> </thead> <tbody> <tr> <td>Dyspnoea</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>On vasopressors</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Respiratory rate >30</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Marked lymphopenia (<1.0 x10⁹/L)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Arterial oxygen saturation (SaO₂) <93%</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Neutrophilia (>3.0 x10⁹)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>PaO₂/FiO₂ (P/F ratio) <300</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Serum Lactate Dehydrogenase (LDH) > 550 U/L</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Lung infiltrates >50% within 24-48 hours</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>D-dimer > 1 mcg/ml</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Intensive care unit (ICU) patient</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Elevated troponin</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Mechanical ventilation</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Suspect or confirmed myocarditis/myocardial dysfunction</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>						Clinical Feature	Yes	No	Clinical Feature	Yes	No	Dyspnoea	<input type="checkbox"/>	<input type="checkbox"/>	On vasopressors	<input type="checkbox"/>	<input type="checkbox"/>	Respiratory rate >30	<input type="checkbox"/>	<input type="checkbox"/>	Marked lymphopenia (<1.0 x10 ⁹ /L)	<input type="checkbox"/>	<input type="checkbox"/>	Arterial oxygen saturation (SaO ₂) <93%	<input type="checkbox"/>	<input type="checkbox"/>	Neutrophilia (>3.0 x10 ⁹)	<input type="checkbox"/>	<input type="checkbox"/>	PaO ₂ /FiO ₂ (P/F ratio) <300	<input type="checkbox"/>	<input type="checkbox"/>	Serum Lactate Dehydrogenase (LDH) > 550 U/L	<input type="checkbox"/>	<input type="checkbox"/>	Lung infiltrates >50% within 24-48 hours	<input type="checkbox"/>	<input type="checkbox"/>	D-dimer > 1 mcg/ml	<input type="checkbox"/>	<input type="checkbox"/>	Intensive care unit (ICU) patient	<input type="checkbox"/>	<input type="checkbox"/>	Elevated troponin	<input type="checkbox"/>	<input type="checkbox"/>	Mechanical ventilation	<input type="checkbox"/>	<input type="checkbox"/>	Suspect or confirmed myocarditis/myocardial dysfunction	<input type="checkbox"/>	<input type="checkbox"/>
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Other Comments on Current Clinical Status: 																																																					
Blood Group: _____ A / B / O / AB Rhesus Positive / Negative																																																					
Serum Immunoglobulin A (IgA) levels: _____ <i>(please include units)</i>																																																					
History of Allergic Reactions to Blood Products: _____ <i>(If Yes, please elaborate)</i>																																																					

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	
Name of Hospital / Organisation:	Name and MCR No. of Requesting Physician:
Date of Request:	Signature:

- 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 (kiat_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.

Annex B: Examples of Request and monitoring forms for Sotrovimab and Casirivimab/imdevimab for hospitals to adapt

Hospital Logo	<i>Affix Patient Label</i>																														
Request and monitoring form for Sotrovimab for COVID-19 patients	Name: NRIC: DOB:																														
Patient Clinical Information (*Please tick and fill accordingly)																															
Date of 1 st positive COVID-19 PCR test: _____ Date of illness onset: _____ Date of hospitalization: _____ COVID vaccinated? Y / N If yes, date(s) of vaccination: _____ Age of patient: _____ On oxygen or SpO2 <94% on room air Y/ N																															
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 35%;">Risk factors</th> <th style="width: 10%;">Yes</th> <th style="width: 10%;">No</th> <th style="width: 35%;">Risk factors</th> <th style="width: 10%;">Yes</th> <th style="width: 10%;">No</th> </tr> </thead> <tbody> <tr> <td>Age 55 years and above</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Congestive heart failure</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Chronic kidney disease</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Diabetes</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Chronic obstructive pulmonary disease</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td>Obesity (BMI >30 kg/m²)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Moderate to severe asthma</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Risk factors	Yes	No	Risk factors	Yes	No	Age 55 years and above	<input type="checkbox"/>	<input type="checkbox"/>	Congestive heart failure	<input type="checkbox"/>	<input type="checkbox"/>	Chronic kidney disease	<input type="checkbox"/>	<input type="checkbox"/>	Diabetes	<input type="checkbox"/>	<input type="checkbox"/>	Chronic obstructive pulmonary disease	<input type="checkbox"/>	<input type="checkbox"/>	Obesity (BMI >30 kg/m ²)	<input type="checkbox"/>	<input type="checkbox"/>	Moderate to severe asthma	<input type="checkbox"/>	<input type="checkbox"/>				
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<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 70%;">Other risk indicators (most recent results during this admission, at time of request)</th> <th style="width: 10%;">Yes</th> <th style="width: 10%;">No</th> <th style="width: 10%;">Unk</th> </tr> </thead> <tbody> <tr> <td>Pneumonia</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>LDH > 550 U/L</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Lymphocytes < 1 x 10⁹/L</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Neutrophils > 3 x 10⁹/L</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Any positive SARS-CoV-2 serology test (S or neutralizing antibody)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table>	Other risk indicators (most recent results during this admission, at time of request)	Yes	No	Unk	Pneumonia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	LDH > 550 U/L	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Lymphocytes < 1 x 10 ⁹ /L	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Neutrophils > 3 x 10 ⁹ /L	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Any positive SARS-CoV-2 serology test (S or neutralizing antibody)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	(Unk = unknown)						
Other risk indicators (most recent results during this admission, at time of request)	Yes	No	Unk																												
Pneumonia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																												
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Any positive SARS-CoV-2 serology test (S or neutralizing antibody)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																												
Other comments on risk factors and current clinical status:																															

Requestor details	
Name of approving Infectious Disease physician:	
Name and MCR no. of requesting physician:	Signature:
Date of request:	Email address and contact number:
To be filled 14 days after dose: Outcomes (*Please tick and fill accordingly)	
Date of administration: _____	
<p>Healthcare professionals in addition are required to report any suspected SAEs observed with the use of sotrovimab to the Vigilance and Compliance Branch at Tel: 6866 1111, Fax: 64789069, or report online at https://www.hsa.gov.sg/adverse-events.</p>	
Adverse events following Sotrovimab	Yes No
Anaphylaxis	<input type="checkbox"/> <input type="checkbox"/>
Hypersensitivity reactions	<input type="checkbox"/> <input type="checkbox"/>
Infusion-related reactions	<input type="checkbox"/> <input type="checkbox"/>
Clinical worsening of COVID-19	<input type="checkbox"/> <input type="checkbox"/>
Gastrointestinal: Nausea, vomiting	<input type="checkbox"/> <input type="checkbox"/>
Dermatologic: Pruritis, skin rash	<input type="checkbox"/> <input type="checkbox"/>
Others: _____	
Clinical outcomes	Yes No
Nil oxygen required throughout	<input type="checkbox"/> <input type="checkbox"/>
Low-flow oxygen	<input type="checkbox"/> <input type="checkbox"/>
High-flow oxygen	<input type="checkbox"/> <input type="checkbox"/>
Mechanical ventilation	<input type="checkbox"/> <input type="checkbox"/>
Death	<input type="checkbox"/> <input type="checkbox"/>
Others: _____	

Date of discharge or death: _____	

Hospital Logo	Affix Patient Label Name:
Request and monitoring form for Casirivimab and imdevimab (REGEN-COV) for COVID-19 patients	NRIC:
	DOB:
	Race: Sex:

Patient Clinical Information (*Please tick and fill accordingly)					
Date of 1 st positive COVID-19 PCR test: _____					
Date of illness onset: _____					
Date of hospitalization: _____					
COVID vaccinated? Y / N					
If yes, date(s) of vaccination: _____					
Age of patient: _____					
On oxygen or SpO2 <94% on room air Y/ N					
Dose requested (circle) 1.2 g / 8 g					
Risk factors	Yes	No	Risk factors	Yes	No
Age 55 years and above	<input type="checkbox"/>	<input type="checkbox"/>	Congestive heart failure	<input type="checkbox"/>	<input type="checkbox"/>
Chronic kidney disease	<input type="checkbox"/>	<input type="checkbox"/>	Diabetes	<input type="checkbox"/>	<input type="checkbox"/>
Chronic obstructive pulmonary disease	<input type="checkbox"/>	<input type="checkbox"/>	Obesity (BMI >35 kg/m ²)	<input type="checkbox"/>	<input type="checkbox"/>
Moderate to severe asthma	<input type="checkbox"/>	<input type="checkbox"/>	Hypertension	<input type="checkbox"/>	<input type="checkbox"/>
Cardiovascular disease	<input type="checkbox"/>	<input type="checkbox"/>	Immunosuppressive disease or treatment	<input type="checkbox"/>	<input type="checkbox"/>
Other risk indicators (most recent results during this admission, at time of request)			Yes	No	Unk
Pneumonia			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LDH > 550 U/L			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lymphocytes < 1 x 10 ⁹ /L			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Neutrophils > 3 x 10 ⁹ /L			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Any positive SARS-CoV-2 serology test (S or neutralizing antibody)			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			(Unk = unknown)		
Other comments on risk factors or current clinical status:					

Requestor details	
Name of approving Infectious Disease physician	
Name and MCR no. of requesting physician:	Signature:
Date of request:	Email address and contact number:
To be filled 14 days after dose: Outcomes (*Please tick and fill accordingly)	
Date of administration: _____	
Healthcare professionals in addition are required to report any suspected SAEs observed with the use of sotrovimab to the Vigilance and Compliance Branch at Tel: 6866 1111, Fax: 64789069, or report online at https://www.hsa.gov.sg/adverse-events .	
Adverse events following Casirivimab and imdevimab (REGEN-COV)	Yes No
Anaphylaxis	<input type="checkbox"/> <input type="checkbox"/>
Hypersensitivity reactions	<input type="checkbox"/> <input type="checkbox"/>
Infusion-related reactions	<input type="checkbox"/> <input type="checkbox"/>
Clinical worsening of COVID-19	<input type="checkbox"/> <input type="checkbox"/>
Gastrointestinal: Nausea, vomiting	<input type="checkbox"/> <input type="checkbox"/>
Dermatologic: Pruritis, skin rash	<input type="checkbox"/> <input type="checkbox"/>
Others: _____	
Clinical outcomes	Yes No
Nil oxygen required throughout	<input type="checkbox"/> <input type="checkbox"/>
Low-flow oxygen	<input type="checkbox"/> <input type="checkbox"/>
High-flow oxygen	<input type="checkbox"/> <input type="checkbox"/>
Mechanical ventilation	<input type="checkbox"/> <input type="checkbox"/>
Death	<input type="checkbox"/> <input type="checkbox"/>
Others: _____	
Date of discharge or death: _____	

Dr Shawn Vasoo (ID) – NCID – Clinical Director, Chair
A/Prof Tan Thuan Tong (ID) - SGH – Head, ID
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