Summary of the WHO publications Therapeutics and Covid-19, 6 July 2021 and Drugs to prevent Covid-19, 2 March 2021

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This summary will provide you with the basic recommendations of WHO on the treatment of patients with Covid-19 in different stages of the disease.

General recommendation

- **Systemic corticoids (strong recommendation for use)**
- **IL-6 receptor blockers (strong recommendation for use)**

No general recommendation

- **Remdesivir (conditional recommendation against use)**
- **Ivermectin (recommendation against use except in clinical trials)**

NOT recommended

- **Hydroxychloroquine (strong recommendation against use)**
- **Lopinavir/ritornavir (strong recommendation against use)**

Details on medications that received a general recommendation for use

Systemic corticosteroids

For patients with severe or critical COVID-19 we recommend systemic corticosteroids rather than no corticosteroids.

For patients with non-severe COVID-19 infection (absence of criteria for severe or critical infection) we suggest not to use corticosteroids.

Route: Systemic corticosteroids may be administered both, orally and intravenously. Of note: While the bioavailability of dexamethasone is very high (that is, similar concentrations are achieved in plasma after oral and intravenous intake), critically ill patients may be unable to absorb any nutrients or medications due to intestinal dysfunction. Clinicians therefore may consider administering systemic corticosteroids intravenously rather than orally if intestinal dysfunction is suspected.

Duration: While more patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total duration of regimens evaluated in the seven trials varied between 5 and 14 days, and treatment was generally discontinued at hospital discharge (that is, the duration of treatment could be less than the duration stipulated in the protocols).

Dose: The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (that is, 50 mg every 8 hours), 40 mg of prednisone, or 32 mg of methylprednisolone (8 mg every 6 hours or 16 mg every 12 hours).

Monitoring: It would be prudent to monitor glucose levels in patients with severe and critical COVID-19, regardless of whether the patient is known to have diabetes.

Timing: The timing of therapy from the onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy 7 days or more after symptom onset may be more beneficial than treatment initiated within 7 days of symptom onset. A post hoc subgroup analysis within the PMA did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity often appear late (that is, denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).

Benefit and harm: Corticosteroids are not associated with an increased risk of adverse events, beyond likely increasing the incidence of hyperglycaemia (moderate certainty evidence; absolute effect estimate 46 more per 1000 patients, 95% CI: 23 more to 72 more) and hypernatremia (moderate certainty evidence; 26 more per 1000 patients, 95% CI: 13 more to 41 more). Panel members also noted that, given the expected effect of systemic corticosteroids on mortality, most patients would not refuse this intervention to avoid adverse events believed to be markedly less important to most patients than death. Notwithstanding, clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise.

Ultimately, the panel made its recommendation based on the moderate certainty evidence of a 28-day mortality reduction of 8.7% in the crucially ill and 6.7% in patients with severe COVID-19 who were not critically ill, respectively.

IL-6 receptor blockers

We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection.

Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19 (4), and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.

Route: IL-6 receptor blockers are administered intravenously for the treatment of patients with severe or critical COVID-19. IL-6 receptor blocker therapy should be administered in combination with systemic corticosteroids, which may be administered both orally and intravenously, with due consideration to their high bioavailability but possible malabsorption in the case of intestinal dysfunction with critical illness.

Duration: Tocilizumab and sarilumab are administered as single intravenous doses, typically over 1 hour. A second dose may be administered 12 to 48 hours after the first dose; this was offered variably in major clinical trials at the discretion of treating clinicians if a clinical response was felt to be inadequate. Duration of concurrent systemic corticosteroids is typically up to 10 days, though may vary between 5 and 14 days.

Dose: Tocilizumab is dosed at 8 mg per kilogram of actual body weight, up to a maximum of 800 mg. Sarilumab is most commonly dosed at 400 mg, consistent with what was used in REMAP-CAP (3). Renal dose adjustment is not currently warranted for either drug.

Monitoring: Routine bloodwork including neutrophil count, platelets, transaminases, and total bilirubin should be checked prior to initiation of therapy. All patients should be monitored for signs and symptoms of infection, given the increased risk with immunosuppression in addition to systemic corticosteroids. Patients on longer-term IL-6 receptor blocker therapy are at risk of active tuberculosis, invasive fungal infections and opportunistic pathogens. Risks and benefits of therapy should be considered carefully in patients with any active, severe infection other than COVID-19; caution is advised when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions, which may predispose them to infections.

Timing: IL-6 receptor blockers should be initiated with systemic corticosteroids; specific timing during hospitalization or the course of illness is not specified. That being said, IL-6 receptor blockers have been administered early in the course of hospitalization in the included trials and clinicians may consider this approach if possible. See section on resource implications, equity and human rights.

Benefits and Harms: IL-6 receptor blockers reduce mortality and need for mechanical ventilation based on high certainty evidence. Low certainty evidence suggests they may also reduce duration of mechanical ventilation and hospitalization (8) (9). The evidence regarding the risk of SAEs is uncertain. Low certainty evidence suggested that the risk of bacterial infections in the context of immunosuppression treatment with IL-6 receptor blockers might be similar to usual care (8). However, the GDG had some concerns that, given the short-term follow-up of most trials and the challenges associated with accurately capturing adverse events such as bacterial or fungal infection, the evidence summary may under-represent the risks of treatment with IL-6 receptor blockers.

Details on medications that did not receive a general recommendation for use

Remdesivir (published 20 November 2020)

We suggest against administering remdesivir in addition to usual care.

The GDG made a conditional recommendation against using remdesivir for treatment of hospitalized patients with COVID-19. If administration of remdesivir is considered, it should be noted that its use is contraindicated in those with liver (ALT > 5 times normal at baseline) or renal (eGFR < 30 mL/minute) dysfunction. To date, it can only be administered intravenously, and it has relatively limited availability.

Ivermectin (published 31 March 2021)

We recommend not using ivermectin in patients with COVID-19 except in the context of a clinical trial.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms. A recommendation to only use a drug in the setting of clinical trials is appropriate when there is very low certainty evidence and future research has a large potential for reducing uncertainty about the effects of the intervention and for doing so at reasonable cost.

Details on medications that received a general recommendation AGAINST use

Hydroxychloroquine treatment (published 17 December 2020)

We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19 (strong recommendation, high certainty evidence).

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

The GDG made a strong recommendation against using hydroxychloroquine or chloroquine for treatment of patients with COVID-19. The use of hydroxychloroquine may preclude the use of other important drugs that also prolong the QT interval, such as azithromycin and fluoroquinolones. Concomitant use of drugs that prolong the QT interval should be done with extreme caution.

Benefit and Harm: Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation and may not reduce duration of hospitalization. The evidence does not exclude the potential for a small increased risk of death and mechanical ventilation with hydroxychloroquine. The effect on other less important outcomes, including time to symptom resolution, admission to hospital, and duration of mechanical ventilation, remains uncertain.

Hydroxychloroquine may increase the risk of diarrhoea and nausea/vomiting; a finding consistent with evidence from its use in other conditions. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. Whether or not and to what degree hydroxychloroquine increases the risk of cardiac toxicity, including life-threatening arrhythmias, is uncertain.

Subgroup analyses indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years vs those > 70 years old). Further, the cumulative dose and predicted serum through concentrations did not modify the effect for any outcome. Therefore, we assumed similar effects in all subgroups.

We also reviewed evidence comparing the use of hydroxychloroquine plus azithromycin vs hydroxychloroquine alone. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome (very low certainty).

Hydroxychloroquine prevention (published 2 March 2021)

We recommend against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19 (strong recommendation, high certainty evidence).

Remark: This recommendation applies to individuals with any baseline risk of developing COVID-19 and any hydroxychloroquine dosing regimen.

Used prophylactically, hydroxychloroquine has a small or no effect on death and hospital admission (high certainty), and probably has a small or no effect on laboratory-confirmed COVID-19 (moderate certainty). It probably increases the risk of adverse effects leading to discontinuation of the drug

(moderate certainty). There was no subgroup effect according to known exposure to a person with SARS-CoV-2 infection or hydroxychloroquine dose regimen (extremely low event rates precluded investigation of subgroup effects for mortality). The panel therefore assumed similar relative effects across subgroups.

Lopinavir/ritonavir (published 17 December 2020)

We recommend against administering lopinavir/ritonavir for treatment of COVID-19.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

Benefit and Harms: The GDG panel found a lack of evidence that lopinavir/ritonavir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. For mortality and need for mechanical ventilation this was based on moderate certainty evidence, for the other outcomes low or very low certainty evidence.

There was low certainty evidence that lopinavir/ritonavir may increase the risk of diarrhoea and nausea and vomiting, a finding consistent with the indirect evidence evaluating its use in patients with HIV. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited.

There was an uncertain effect on viral clearance and acute kidney injury. This indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years versus those 70 years and older).