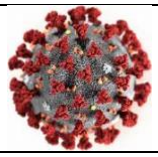
National COVID-19 Science Task Force (NCS-TF)



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Contact person: Oriol Manuel oriol.manuel@chuv.ch and Alexandra Calmy Alexandra.Calmy@hcuge.ch	
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Policy brief on the reduction of Covid-19-associated mortality by drug therapies

Summary of request/problem

Several clinical trials evaluating repurposed or novel drugs for therapy/prevention of Covid-19 have been published since the writing of the first version of this policy brief in August 2020. In some instances, these new publications have changed the routine clinical practice. In this update, we review the current evidence on the best therapeutic approaches to treat patients with Covid-19 in both outpatient and inpatient settings. This document summarizes all significant evidence available, but it is not intended as a practical guideline. These are published and updated by national societies, such as the Swiss Society of Infectious Diseases and the Swiss Society of Intensive Care Medicine, among others.

Executive summary:

Several drugs are emerging for the treatment of Covid-19, but few demonstrated a convincing effect on mortality; dexamethasone showed a significant reduction of Covid-19 caused mortality in patients with moderate or severe disease requiring oxygen; remdesivir demonstrated an improvement in clinical status with no impact on mortality in large international randomized controlled trials. More recently, tocilizumab (an Il-6 inhibitor) has shown a decrease in mortality in patients with moderate and severe Covid-19. Studies are still ongoing in post-exposure prophylaxis or in ambulatory patients with antivirals or monoclonal antibodies; in this setting, colchicine may reduce the need for hospitalization in patients with mild disease.

Main text

Since the beginning of the pandemic, hundreds of clinical trials assessing therapeutic options for Covid-19 have been included in international registers. However, very few have been completed with the appropriate power to detect a significant effect on mortality[1-3].

A consortium, led among others by Cochrane France, Cochrane Ireland, Cochrane South Africa, the French National Institute of Health and Medical Research (Inserm) and the University of Milan, has

established a living mapping and systematic review of Covid-19 studies and has entered the results of 172 randomized controlled clinical trials (139 on treatments, 8 on prevention and 17 on vaccines (covid-nma.com, data extracted on January 21st, 2021).

In addition, several so-called "mega-trials" including thousands of patients are currently ongoing worldwide and have already produced some significant interim results. The most important ones the following:

Recovery trial (https://www.recoverytrial.net/). A UK-based trial initially evaluating several therapeutic arms: lopinavir/ritonavir (LPVr), hydroxychloroquine (HCQ), dexamethasone and azithromycin. Several additional arms were included later. After interim analyses showing the lack of clinical benefit of HCQ[4], LPVr[5], azithromycin[6], convalescent plasma and the efficacy of dexamethasone (see below)[3], the current trial design includes colchicine, casirivimab/imdevimab (REGN-CoV-2), aspirin, and a pediatric arm of dexamethasone. The trial has currently included more than 35,000 patients.

Solidarity trial (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments). A WHO-sponsored trial with initially five arms: remdesivir, HCQ, LPVr and interferon beta +/- LPVr, compared to a standard of care. The trial has enrolled more than 15,000 patients in over 400 participating hospitals in 35 countries. An interim analysis confirmed the lack of reduction in mortality of any of the four intervention arms[1]. A new design of the study including novel arms is currently being planned.

ACTT trial (known as the "Adaptive COVID-19 Treatment Trial" [https://www.niaid.nih.gov/clinical-trials/adaptive-covid-19-treatment-trial-actt]). A United States National Institution of Allergy and Infectious Diseases (NIH)-sponsored trial with also an adaptive design. The ACTT-1 trial compared remdesivir with placebo in more than 1000 patients, showing a shorter time to clinical improvement in the remdesivir arm, but not a reduction in mortality (see below)[7]. The ACTT-2 trial has compared baricitinib (a JAK inhibitor) to a placebo, showing a reduction of one day in time to improvement in the baricitinib arm, a tendency for less progression to severe disease but no difference in mortality[8].

REMAP-CAP (https://www.remapcap.org/) is an international randomized, embedded, multi-factorial, adaptive platform trial for community-acquired pneumonia (including Covid-19), evaluating in parallel several therapeutic interventions in various domains (immunomodulatory, antiviral, antibiotic), mostly in critical care patients. The first results of the steroids and anti-IL6 therapies have been released[2]. The trial has currently enrolled close to 5000 patients with Covid-19.

In this policy brief, we focus on the evidence obtained by published randomized clinical trials for the drugs under investigation.

Drugs studied in randomized clinical trials

1. *Dexamethasone*

Steroids were recommended (with weak evidence) to treat acute respiratory distress outside of Covid-19. The Recovery trial included more than 6000 patients randomized to receive dexamethasone 6 mg daily for 10 days compared with usual care alone[3]. Overall, the use of dexamethasone was associated with a 17% reduction in 28-day mortality (relative risk [RR] 0.83

[0.74 to 0.92]; P=0.0007). This effect was higher in ventilated patients (RR 0.65 [0.48 to 0.88]; P=0.0003) and in those receiving oxygen only (RR 0.80 [0.67 to 0.96]; P=0.0021). There was no benefit among patients who did not require respiratory support at randomization (RR 1.22 [0.93 to 1.61]; P=0.14). The effect of dexamethasone was seen in patients after 7 days of symptoms onset. Of note, the 28-day mortality was higher than that reported in the literature (41% in those who required ventilation, 25% in patients who required oxygen only, and 13% in those who did not require any respiratory intervention), limiting the external validity of the results. For example, in the European RISC-19-ICU registry cohort, intensive care unit mortality was 24%[9].

A meta-analysis of 7 randomized clinical trials including 1703 critically-ill patients receiving steroids for the treatment of Covid-19 confirmed a reduction in mortality (OR 0.66 [95% CI, 0.53-0.82]; P< .001)[10].

Of note, no data are currently available on the efficacy of dexamethasone for ambulatory patients. At this stage, the only ambulatory patients who might benefit from dexamethasone are hypoxemic patients who have definitively refused hospitalization.

Dexamethasone has become the standard of care of hospitalized patients with Covid-19 and need for oxygen in Switzerland. The living WHO guidelines issued by the MAGIC group[11] emitted a strong recommendation in favor of steroids in severe and critical patients with Covid-19.

2. Remdesivir

Remdesivir is a nucleotide analogue prodrug that inhibits the SARS-CoV-2 RNA polymerase. Several trials have assessed the efficacy of remdesivir.

In the double-blind ACTT-1 trial, patients randomized to receive remdesivir (200 mg daily loading dose, then 100 mg daily for 10 days) had a shorter recovery time than patients on placebo (median 11 days [95% CI 9-12] vs. 15 days [95% CI13-19]; P<0.001)[7]. The hazard ratio (HR) for death at 14 days was 0.70 (95% CI 0.47-1.04), which was not statistically significant. In the subgroup analysis, the effect of remdesivir on mortality was significant in patients requiring supplemental oxygen (HR 0.22 [95% CI 0.08-0.59]), but not in those receiving invasive or non-invasive mechanical ventilation. An imbalance in patient severity between subgroups (less severe patients received remdesivir) makes it difficult to interpret the subgroup analysis. In the analysis stratified by duration of symptoms, the benefit of remdesivir on recovery time was larger in patients receiving the drug early after onset of symptoms (rate ratio for recovery 1.37, 95% CI 1.14-1.64 for symptom duration ≤ 10 days vs. 1.20, 95% CI 0.94-1.52 for >10 days)[7].

In a trial enrolling 237 patients (158 in the remdesivir group and 79 in the placebo group), there were no differences in time to clinical improvement between arms: median 21 days (IQR 13-28) in the remdesivir arm vs. 23 days (15-28) in the placebo arm[12]. Due to the modest sample size, only 32 deaths were reported (15% in the remdesivir group and 13% in the placebo group).

The open-label Solidarity study compared remdesivir for 10 days vs. a standard of care in more than 5400 patients[1]. Mortality was 10.9% in patients receiving remdesivir and in 11.1% in control patients (rate ratio, 0.95; 95% CI, 0.81 to 1.11; P = 0.50). Importantly, remdesivir did not reduce initiation of ventilation or hospitalization duration, although the later may be difficult to interpret due to the open label design and the fact that hospital stay may have been extended due to the planned 10-

day course. The final results of the remdesivir arm of the Solidarity study have not yet been released.

A meta-analysis of all randomized trial using remdesivir was performed by the Solidarity statistical team and it did not find a difference in mortality between remdesivir and the control group (RR 0.91 95% CI 0.79-1.05)[1]. In the patients without mechanical ventilation, a modest effect of remdesivir could not be excluded (RR 0.80, 95% CI 0.63-10.01).

The living WHO guidelines issued by the MAGIC group emitted a conditional recommendation against remdesivir in hospitalized patients with Covid-19 of any severity[11]. The position of remdesivir in the overall management of patient is probably marginal. Remdesivir may be prescribed in patients hospitalized with a severe disease (i.e. those requiring oxygen but no invasive or non-invasive ventilation or ECMO) early after symptoms occurrence.

3. Tocilizumab and other immunomodulatory drugs

Tocilizumab is an anti-human IL-6 receptor monoclonal antibody. Eight randomized clinical trials on the use of tocilizumab in patients with Covid-19 have been recently published or are in a preprint form[2,13-19]. Inclusion and exclusion criteria vary between trials, with differences in severity in the study populations making difficult to compare the outcomes among studies. While some trials did not include patients in the ICU[13,16-18], others had 30-40% of patients on mechanical ventilation[2,15]. Also, depending on the time of inclusion, studies had major differences in the rate of additional steroid use, ranging from <10% to up to 90%. Some trials were blinded while others were not.

The results of these published peer-reviewed studies were inconsistent and did not show a positive effect on mortality or time to mechanical ventilation, in particular in patients not included in the ICU at the time of receiving tocilizumab and not receiving additional steroids therapy. However, in a recent large study including 778 patients admitted at the ICU needing ventilator or circulatory support (REMAP-CAP), a longer period of ventilation-free days and a significant 8% reduction in mortality (64% vs 73% in the control group) was observed in the group of patients receiving an anti-IL6 (tocilizumab or sarilumab)[2]. Of note, more than 80% of patients additionally received dexamethasone, suggesting a possible additive effect of steroids and anti-IL6. The study is published as a preprint and the results have not yet been peer reviewed[2]. A Brazilian study however was interrupted by the DSMB in view of a possible increased mortality in patients with a severe disease and elevated inflammatory markers receiving tocilizumab[19]: death at 15 days occurred in 11 of 65 (17%) patients in the tocilizumab group compared with 2 of 64 (3%) in the standard care group (odds ratio 6.42, 95% CI 1.59 to 43.2).

More recently, the Recovery trial released the interim analysis on the effect of tocilizumab in a preprint form[14]. More than 4100 patients hospitalized with Covid-19 requiring oxygen and with a CRP of > 75 mg/l were randomized to receive tocilizumab or a standard of care. Up to 14% of patients were receving invasive ventilation and 40% non invasive ventilation. Up to 80% of patients were on steroids at the time of randomization. Mortality at 28 days was 29% (596/2022) in the tocilizumab group and 33% (694/2094) in the usual care arm (rate ratio 0·86; 95% CI 0·77-0·96; p=0·007). In patients not receiving invasive mechanical ventilation at baseline, patients randomized to the tocilizumab arm had a lower risk of the composite endpoint of invasive mechanical ventilation or death (33% vs. 38%; risk ratio 0·85; 95% CI 0·78-0·93; 52 p=0·0005). No significant higher rates of adverse events were seen in the tocilizumab arm. A metanalysis of all published

trials was also included in the publication and showed an overall mortality of 24.8% in the tocilizumab arm and 27.5% in the usual care arm (RR 0.87 95% CI [0.79-0.96], p=0.005)[14].

No clear recommendation from international societies has been given regarding the use of tocilizumab and its use is still debated (and particularly in which population it should be used). With the recent publication of the Recovery trial, we expect a role to position tocilizumab in hospitalized patients with severe Covid-19.

Another immunomodulatory drug, baricitinib (a selective inhibitor of Janus kinase 1 and 2) showed a reduction in the median time to clinical improvement of 1 day in the ACTT-2 trial when added to a remdesivir treatment, but no improvement in mortality[8].

In an unpublished phase II/III trial (press release), aviptadil, a synthetic human vasoactive intestinal peptide (VIP), showed a reduction on the length of hospital stay in patients with critical Covid-19. The exact position of aviptadil in the Covid therapeutic strategy needs to be determined once the publication is available.

4. Convalescent plasma

Convalescent plasma from recovered patients with Covid-19 has antiviral effects by neutralizing antibodies (NA) blocking the coronavirus spike protein and additional immunomodulatory effects by blocking proinflammatory cytokines and improving cellular responses.

Six randomized controlled trials have been published so far assessing the efficacy of convalescent plasma in patients with Covid-19[20-25]. The first five trials included hospitalized patients with moderate to severe disease during the second week of symptoms[20-23,25]. The titers of NA included in the plasma preparation largely varied between trials. In none of these trials, a difference in progression to severe disease or mortality was observed.

An additional trial compared early convalescent plasma (with high titers of NA) with placebo in 160 ambulatory patients older than 75 years or aged 65-74 years with comorbidities[24]. Patients had symptoms for less than 48h and were non-hypoxemic. The trial reached the primary endpoint of severe respiratory disease, with a lower incidence in the convalescent plasma arm (16%) than in the placebo group (31%) (RR 0.52, 95% CI 0.29-0.94).

In the Recovery trial, the convalescent plasma arm has been closed due to non-efficacy. A press release on January 15th 2021 stated that the interim analysis including 10,406 patients showed no significant difference in the primary endpoint of 28-day mortality (18% convalescent plasma vs. 18% usual care alone; RR 1.04, 95% CI 0.95-1.14; p=0.34).

Finally, in a non-controlled study, 17 patients with hematological malignancies receiving B-depleting antibodies with prolonged SARS-CoV-2 viral shedding (median of 56 days) and negative serology clinically and biologically improved after being treated with convalescent plasma[26].

Overall, administration of convalescent plasma seems to only be efficacious when given early after Covid-19 onset in patients with risk factors, or in patients with few or no ability to generate a protective immune response. Therefore, this indication may be expanded to severely immunosuppressed patients with protracted Covid-19, although the evidence for this is less robust.

5. Monoclonal antibodies (casirivimab/imdevimab and bamlanivimab)

Two formulations of monoclonal antibodies blocking the spike protein have been evaluated in phase I to III combined clinical trials: casirivimab/imdevimab (REGN-CoV2) and bamlanivimab (LY-CoV555). Casirivimab/imdevimab are given in combination to potentially reduce the risk of the emergence of a treatment-resistant mutant virus. Later on, a combination of bamlanivimab and etesevimab (another anti-spike protein binding to other epitopes than bamlanivimab) has been tested in the US.

REGN-CoV-2 showed a significant (although modest) reduction in viral loads and need for medical attended visits (3% vs. 6% in the placebo group) when given within 3 days after symptoms onset in non-hospitalized patients with Covid-19[27]. These differences were particularly observed in the patients who were seronegative at enrolment. REGN-CoV-2 is currently evaluated for hospitalized patients in the Recovery trial, and results are expected soon.

Bamlanivimab was given to 452 outpatients with mild or moderate Covid-19[28]. Similar results were observed as with REGN-CoV-2, namely a reduction in viral loads in patients receiving high-dose bamlanivimab and a lower proportion of medical visits (1.6% in the bamlanivimab arm, vs. 6.3% in the placebo arm). These results were confirmed in a trial evaluating the combination of bamlanivimab and etesevimab for outpatients with mild Covid-19[29]. According to a press release from the manufacturing company, bamlanivimab was effective in preventing symptomatic Covid-19 in nursing home residents and staff who tested negative for SARS-CoV-2, but the results of the trial have not been published so far (https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented).

Bamlanivimab efficacy was also assessed in hospitalized patients with mild to severe Covid-19[30]. No differences in clinical improvement or any clinical outcome (hospital discharge, death) was seen among groups. The trial was prematurely stopped for futility after enrollment of 314 patients.

Overall, it seems that monoclonal antibodies may to some degree reduce the progression of Covid-19 when given early after onset of symptoms (similar to convalescent plasma). Given the high price and significant logistic hurdles (slow perfusion and surveillance to detect potential allergic reactions) the indication of these drugs should be further evaluated. It may be given in patients at high risk for complications, either early after the first symptoms occurs (for example in nosocomial infection, when the time of the exposure is known and the follow-up tight) or in post exposure prophylaxis, in particular in seronegative patients. Prophylactic use for patients at risks may be an interesting option, due to the mechanism of action. On note, data on efficacy and safety of both monoclonal antibodies in immunocompromised patients are not available.

Casirivimab/imdevimab and bamlanivimab are not available in Switzerland.

6. Colchicine

Colchicine has anti-inflammatory effects by targeting the inflammasome, inhibiting cellular adhesion molecules and inflammatory chemokines. In a recent trial not yet peer-reviewed, 4488 patients with mild Covid-19 were randomized to receive either colchicine for 30 days or compared to placebo[31]. In this study, 4.7% of the patients in the colchicine group and 5.8% of those in the placebo group (OR 0.79; 95%CI, 0.61 to 1.03; P=0.08) were hospitalized or died. This difference was statistically significant if only the 4159 patients with PCR-confirmed Covid-19 were taken into account (4.6% vs. 6.0% OR, 0.75; 95%CI, 0.57-0.99; P=0.04). Colchicine was generally well-tolerated, with only diarrhea being more common than in the placebo group. The number needed to treat for

avoiding one hospitalization/death was 64. If these results are confirmed, colchicine may be used in the outpatient setting in patients with risk factors for hospitalization, early in the course of the disease. A potential benefit of colchicine has also been suggested in a small Greek open-label trial in 105 hospitalized Covid-19 patients: colchicine was associated with a reduction in clinical deterioration compared to standard of care (2-point decrease on 7-grade WHO clinical status scale 1.8% vs. 14.0%; OR 0.11, 95% CI 0.01- 0.96)[32]. The very modest, and borderline significance of colchicine in outpatients population treated early after the diagnosis does not warrant any recommendation for its routine use in Switzerland. Positioning colchicine later on in the Covid-19 course, may provide different results.

In the Recovery trial, several thousands of patients have received colchicine in one of the therapeutic arms. Additional data is therefore expected soon.

7. Hydroxychloroquine

HCQ inhibits SARS-CoV-2 *in vitro* through several mechanisms, including the inhibition of viral fusion and nucleic acid replication. Several large well-conducted clinical trials in inpatients and outpatients with Covid-19 investigating HCQ for treatment as well as post-exposure prophylaxis, have confirmed no clinical or virological effect of HCQ for Covid-19[1,4,33-37].

In the Recovery trial, mortality was not significantly different in patients receiving HCQ (418/1561; 26.8%) or standard of care (788/3155; 22%; RR 1.09, 95% CI 0.96-1.23)[4]. In the Solidarity trial, mortality was 10.9% (104 of 947) in patients receiving HCQ and 9.2% (84 of 906) in control patients (rate ratio, 1.19; 95% CI, 0.89 to 1.59; P = 0.23)[1].

In two randomized studies performed in the outpatient setting in patients with early non-severe Covid-19, no differences were observed in the viral clearance, clinical course or need for hospitalization in patients receiving HCQ compared to the control group[36,37]. Additionally, HCQ given preemptively in persons in close contact with Covid-19 patients did not show any reduction in the incidence of new infections[33,35].

The living WHO guidelines issued by the MAGIC group emitted a strong recommendation against HCQ in hospitalized patients with Covid-19 of any severity[11].

8. Lopinavir/ritonavir

LPVr inhibits SARS-CoV-2 protease. In the Recovery trial, mortality was not significantly reduced in the LPVr arm (353/1596; 22.1%) vs. the standard of care arm (719/3376; 21.3%; RR 1.04, 95% CI 0.91-1.18)[5]. In the Solidarity trial, no reduction in mortality in the LPVr arm (148 of 1399) vs. the standard of care (146 of 1372) arm was observed (rate ratio, 1.00; 95% CI, 0.79 to 1.25; P = 0.97)[1]. In a small Chinese trial, the 28-day mortality was not different in the LPV/r group when compared with the standard care group[38].

The living WHO guidelines issued by the MAGIC group emitted a strong recommendation against LPVr in hospitalized patients with Covid-19 of any severity[11]. LPVr is tested in Switzerland and in Brazil as a component of a post-exposure prophylactic regimen.

9. Interferon

In an open-label randomized clinical trial, 86 patients received LPVr, ribavirin, and interferon beta-1b (three doses of 8 Mio units) and were compared to 41 patients receiving LPVr alone[39]. The

combination group had a significantly shorter viral clearance (7 days vs. 12 days). No patient died during the trial. In the Solidarity trial, mortality was 11.8% (243 of 2050) in patients receiving interferon-beta and 10.5% (216 of 2050) in control patients (rate ratio, 1.16; 95% CI, 0.96 to 1.39; P = 0.11)[1].

10. Anticoagulants

Hypercoagulability may contribute to adverse outcomes including arterial and venous thromboembolism, organ dysfunction, and death in patients with Covid-19, especially in intensive care[40,41]. Preliminary non-adjudicated interim results from a large multiplatform RCT including three global clinical trial networks (REMAP-CAP, ACTIV-4a, ATTACC) comparing therapeutic dose anticoagulation and usual care thromboprophylaxis in hospitalized Covid-19 patients have been recently released (https://www.remapcap.org/media). In 1398 moderately ill patients, full dose anticoagulation with heparin for 14 days or until discharge was superior to usual care thromboprophylaxis in improving the primary endpoint of organ support-free days/mortality (OR 1.5; 95% CI, 1.1-2.2 [OR>1 represents benefit]; major bleeding 1.6% vs. 0.9%). In patients requiring ICU level care at enrollment (n=895), recruitment was halted due to futility in December 2020, with full dose anticoagulation failing to show a benefit, and even suggesting harm compared to usual care thromboprophylaxis (OR 0.76; 95% CI, 0.60-0.97; major bleeding 3.7% vs. 1.8%). If these results are confirmed with the complete, adjudicated and peer-reviewed trial data (in particular with additional information regarding the inclusion and exclusion criteria), therapeutic anticoagulation should be considered in hospitalized Covid-19 patients with moderate illness without contraindications, but discouraged in critically ill patients (in the absence of other indications). This would be in contrast to most current recommendations from societies, which (in the absence of peer-reviewed published randomized trials) suggest prophylactic dose over intermediate or therapeutic dose anticoagulation in hospitalized non-ICU patients[42-44]. In Covid-19 patients needing intensive care there is not enough evidence reported to recommend for or against the use of higher than prophylactic dose anticoagulation. Several trials comparing different anticoagulation regimens in in- and outpatients are ongoing.

11. Other drugs

Several compounds are currently under investigation in clinical trials, including antivirals (favipiravir, ivermectin, nitazoxanide), immunomodulatory drugs (infliximab, anakinra, ruxolitinib, eculizumab…), and others such as vitamin D or zinc. No robust data including mortality or hospitalization rate as the primary endpoint are currently available from these trials.

In particular, ivermectin has gained some attention as early therapy in outpatients with mild Covid-19. Ivermectin has shown antiviral effects in vitro at doses up to 100-times higher than the dose currently approved in humans[45]. A preprint of a systematic review and meta-analysis including small published and unpublished randomized trials has recently been released, suggesting a mortality reduction with ivermectin. However, none of the 6 trials included in the meta-analysis on mortality were peer-reviewed published papers (2 unpublished, 4 preprints), which precludes any meaningful critical appraisal of the overall results of this meta-analysis. In addition, the individual studies were small and mostly of poor study quality. A summary of existing evidence regarding ivermectin has been posted on the HUG Covid-19 guidelines website (in French), and concluded that the quality of data and level of evidence is very low.

https://www.hug.ch/sites/interhug/files/structures/coronavirus/documents/ivermectine-et-covid-19.pdf.

While several trials are ongoing, current data is insufficient to recommend ivermectin for treatment of Covid-19. The National Institutes of Health, NIH, Bethesda, USA panel advises a neutral position with regards to the use of ivermectin on the basis of the current data. https://www.covid19treatmentguidelines.nih.gov/statement-on-ivermectin/. The Covid-19 Treatment Guidelines Panel states that results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.

Vitamin D may modulate antiviral and anti-inflammatory responses against SARS-CoV-2. The current evidence however does not allow to conclude that Vitamin D supplementation prevents Covid-19 infections, hospitalizations, or death. A large US base randomized clinical trial is currently been conducted (VIVID-trial; https://clinicaltrials.gov/ct2/show/NCT04536298). A recent randomized controlled trial including 120 patients hospitalized with Covid-19 did not find significant differences in length of stay among patients receiving a single dose of 200,000 IU of vitamin D (7.0 [4.0-10.0] days) vs. placebo (7.0 [5.0-13.0] days, p=0.59)[46]. There were no differences in mortality, admission at the ICU and need ofr mechanical ventilation, although the sample size was modest to assess these secondary outcomes.

A document from the HUG summarizing the existent evidence concluded that in the absence of vitamin D deficiency, systematic administration of vitamin D in patients with Covid-19 is not justified.

https://www.hug.ch/sites/interhug/files/structures/coronavirus/documents/vitamine-d-et-covid-19.pdf

The Swiss Society of osteoporosis will issue recommendations with regards of Vitamin D use in Switzerland. Vitamin D supplementation is currently indicated for patients with bone fragility at risk of osteoporosis.

Unresolved issues

Several drugs for treatment or prevention of Covid-19 are currently being evaluated in adequately powered, well-designed clinical trials. In the coming weeks, we expect that more data will be available to better position some antiviral and immunomodulatory drugs in the routine clinical practice, in particular tocilizumab, anticoagulation therapy, colchicine and the specific monoclonal antibodies against SARS-CoV-2. An update of the PB will be written if any of these trials show significant results for improving the management of patients with Covid-19.

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