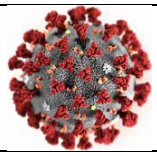
National COVID-19 Science Task Force (NCS-TF)



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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 last version of this policy brief in February 2021. 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, casirivimab/imdevimab may reduce the need for hospitalization in patients with mild disease, but their efficacy in hospitalized patients, admitted early after infection with a negative serology, warrant full attention.

Main text

Since the beginning of the pandemic, thousands 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[1-4].

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 313 published randomized controlled clinical trials (249 on treatments, 17 on prevention and 47 on vaccines (covid-nma.com, data extracted on July 1st, 2021).

In addition, several platform adaptative trials including thousands of patients are currently ongoing worldwide and have already produced some significant interim results. The most important ones are 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 in a second phase. After analyses showing the absence of clinical benefit of HCQ[5], LPVr[6], azithromycin[7], convalescent plasma[8] and the confirmed efficacy of dexamethasone and tocilizumab (see below), additional preliminary results suggest a 20% mortality reduction with casirivimab/imdevimab in hospitalised patients with sero-negative anti-SARS-CoV-2 antibody status treated early after infection[9]. In addition, preliminary results showing no benefit of aspirin[10] or colchicine[11] have been released. The current trial design includes baricitinib, high-dose vs. standard-dose corticosteroids, and dimethyl fumarate. The trial has currently included more than 40,000 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 to test artesunate, imatinib and infliximab.

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)[12]. 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[13].

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 published[4]. The trial has currently enrolled more than 6800 patients with Covid-19.

ANTICOV (https://dndi.org/research-development/portfolio/anticov/) is an an adaptative platform trial testing repurposed drugs for mild to moderate Covid-19 and carried out at 19 sites in 13

countries by the ANTICOV consortium, which includes 26 preminent African and global research and development organizations, coordinated by the Drugs for Neglected Diseases initiative (DNDi).

Together (https://www.togethertrial.com/) is a randomized adaptative platform trial to investigate the efficacy of repurposed treatments for COVID-19 among high-risk adult outpatients. The trial was started in June 2020, and enrollment into a fluvoxamine arm began in January 2021. As of August 15th, a planned interim analysis was released and showed a significant effect of fluvoxamine to reduce emergency room visits (>6 hours) and hospitalization. Neither the pre-print nor the published version of the manuscript has been shown.

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

Drugs studied in randomized clinical trials

1. *Glucocorticoids*

Systemic 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[14]. Overall, the use of dexamethasone was associated with a 17% reduction in 28-day mortality (relative risk [RR] 0.83 [0.75 to 0.93]; P<0.001). This effect was higher in ventilated patients (RR 0.64 [0.51 to 0.81]) and in those receiving oxygen only (RR 0.82 [0.72 to 0.94]). There was no benefit among patients who did not require respiratory support at randomization (RR 1.19 [0.92 to 1.55]). The effect of dexamethasone was seen in patients after 7 days of symptoms onset. Of note, the 28-day mortality in the placebo group was higher than that reported in the literature (41% in those who required ventilation, 26% in patients who required oxygen only, and 14% 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%[15].

A meta-analysis of 7 randomized clinical trials including 1703 critically-ill patients receiving systemic steroids for the treatment of Covid-19 confirmed a reduction in mortality (OR 0.66 [95% CI, 0.53-0.82]; P< .001)[16].

Of note, no data are currently available on the efficacy of systemic glucocorticoids for ambulatory patients. At this stage, the only ambulatory patients who might benefit from systemic glucocorticoids such as 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[17] emitted a strong recommendation in favor of systemic steroids in severe and critical patients with Covid-19.

Budenoside, an inhaled glucocorticoid, has been investigated for the treatment of Covid-19 in outpatients. An open label randomized trial of budenoside compared to usual care in 146 outpatients with mild Covid-19 found a reduction in Covid-19-related urgent care visits including emergency department visits and hospitalizations (3% vs. 15%, difference in proportions 0.123, 95% CI 0.033 to 0.213)[18]. Mortality was not specifically investigated. The results need to be interpreted in light of certain limitations, including the lack of blinding (potentially resulting in detection bias),

the small sample size due to early termination of the study, and the limited generalizability (population with a mean age 44 years recruited from a single community in the UK). A large, randomized, controlled, open label trial in 4700 participants receving budesonide (n=1073), usual care (n=1988) or usual care plus an intervention (n=1639) reported an improvement in time to recovey, with a "chance of also reducing hospital admission and deaths", but without meeting the superiority threshold. Non-hospitalized patients over the age of 50 (with comorbidities) or over 65 were enrolled. No concerning safety signals were observed. The author conclude that budesonide should be considered in patients with COVID-19 and a higher risk of a complictaive course. [19]

The choice of steroids (are all steroids interchangeable?), as well as the doses are still issues under investigation and results are expected soon.

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)[20]. 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)[20].

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[21]. 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[22]. 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 are expected to be released soon.

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)[22]. 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[17]. 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. Anti-human IL-6 receptors (Tocilizumab and Sarilumab)

Tocilizumab is an anti-human IL-6 receptor monoclonal antibody. Nine randomized clinical trials on the use of tocilizumab in patients with Covid-19 have been recently published[2,4,23-29] . 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[23,25,26,28], others had 30-40% of patients on mechanical ventilation[30,31]. 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 studies were inconsistent at first. In a recent large study including 803 patients admitted at the ICU needing ventilator or circulatory support (REMAP-CAP), a longer period of ventilation-free days and a significant 9% reduction in mortality (27% vs 36% in the control group) was observed in the group of patients receiving an anti-IL6 (tocilizumab or sarilumab)[4]. Of note, more than 80% of patients additionally received dexamethasone, suggesting a possible additive effect of steroids and anti-IL6. 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[29]: 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 published the results of the effect of tocilizumab[2] . 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 receiving 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 31% (621/2022) in the tocilizumab group and 35% (729/2094) in the usual care arm (rate ratio 0·85; 95% CI 0·76-0·94; p=0·0028). 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 (35% vs. 42%; risk ratio 0·84; 95% CI 0·77-0·92; p<0·0001). 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 25% in the tocilizumab arm and 28% in the usual care arm (RR 0.86 95% CI [0.78-0.94], p=0.0017)[2].

Most international societies, including the WHO[32], recommend the administration of tocilizumab in patients with respiratory failure who do not rapidly respond to steroid therapy[33].

4. Other immunosuppressive therapy

Two inhibitors of Janus kinases, baricitinib and tofacitinib, have been tested in well-performed clinical trials. Baricitinib (an 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[13].

Swissmedic has approved baricitinib for hospitalized patients, in need of oxygen, but not intubated, in conjunction with remdesivir.

In a recently published randomized controlled trial from Brazil including 289 patients, tofacitinib (an inhibitor of Janus kinase 1 and 3) showed a significant 40% relative reduction in mortality or respiratory failure as compared to placebo (18% vs. 29%, respectively)[34]. The position of these immunomodulatory drugs in the context of a widespread use of steroids and tocilizumab is yet to be determined.

In a multicenter trial perfomed in the Netherlands, 400 patients with Covid-19 requiring oxygen therapy were randomized to receive either imatinib (a tyrosine-kinase inhibitor) or placebo. While the time to discontinuation of ventilation and supplemental oxygen (primary endpoint) was not significantly different between the two groups, patients in the imatinib group had lower mortality (8% vs. 14%, HR 0.51 [0.27-0.95])[35].

According to a pre-print publication, aviptadil, a synthetic human vasoactive intestinal peptide (VIP), resulted in a higher likelihood of the combined endpoint of respiratory recovery and survival to 60 days compared to placebo in a trial of critically ill patients with Covid-19[36]. The exact position of aviptadil in the Covid therapeutic strategy needs to be determined once the peer-reviewed publication is available, and when fully-powered trials (ACTIV-3) will be completed.

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.

Several randomized controlled trials have been published so far assessing the efficacy of convalescent plasma in patients with Covid-19[8,37-42]. None of the trials including hospitalized patients with moderate to severe disease during the second week of symptoms observed a difference in progression to severe disease or mortality, except for one recently published trial suggesting an improvement in 28-day mortality but not clinical status in 223 participants from New York City and Rio de Janeiro[43]. The titers of NA included in the plasma preparation largely varied between trials, which may account for the negative trials.

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[44]. 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, convalescent plasma was administered to 5'795 patients and compared to 5'763 patients who received usual care[8]. No significant difference in the primary endpoint of 28-day mortality was observed (24% convalescent plasma vs. 24% usual care alone; RR 1.00, 95% CI 0.93-1.07; p=0.95).

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[45]. A retrospective case-control study confirmed the beneficial effect of convalescent plasma in patients

with hematological malignancies, showing a significant reduction in mortality by using a propensity score analysis (HR, 0.52; 95% CI, 0.29-0.92)[46].

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. The positioning of convalescent plasma is still to be determined in the context of potent monoclonal humanized antibodies showing a survival benefit, including in hospitalized patients[9].

5. Monoclonal antibodies (mAbs) (casirivimab/imdevimab, bamlanivimab/etesevimab, and sotrovimab*)*

Several formulations of monoclonal antibodies blocking the spike protein have been evaluated in phase I to III combined clinical trials: casirivimab/imdevimab (Regeneron/Roche), bamlanivimab/etesevimab (Eli Lilly), regdanvimab (Celltrion), tixagevimab/cilgavimab (Astrazeneca) and sotrovimab (Vir-Biotechnology/GSK). Most recent mAbs are given in combination to potentially reduce the risk of the emergence of treatment-resistant mutant viruses, and bamlanivimab monotherapy is no longer FDA-validated for Emergency Use Authorization.

- There seems to be differences on the activity of these monoclonal antibodies according to the viral variant, although the clinical experience is limited and most data rely on *in vitro* experiments on pseudoviruses. As of today, data suggest that casirivimab/imdevimab and sotrovimab both conserve activity to the dominant delta variants, while *a modest decrease in in vitro susceptibility to the combination of bamlanivimab and etesevimab was observed, although the clinical implications of this finding are not fully known (https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_111.pdf).*

5.1 Casirivimab/imdevimab

A large phase 3 trial published in a preprint version confimed these results, with a statistically significant absolute reduction of the primary endpoint consisting in hospitalization and/or death of 2.9% (4.11% in the placebo group vs. 1.19% in the casirivimab/imdevimab group)[48]. Results did not differ according to serum antibody status at baseline.

In the Recovery trial, casirivimab/imdevimab was evaluated for hospitalized patients with moderate to severe Covid-19. A publication in a preprint form has shown that, when used at a high dose, the combination casirivimab/imdevimab reduced overall mortality, but only in patients that were seronegative at the time of hospitalization (24% in the casirivimab/imdevimab group vs. 30% in the control group in seronegative patients, but 20% and 21% mortality, respectively, if all patients were included)[9].

As a summary, REGN COV-2 (the name sometimes used to refer to both imdevimab and casirivimab) can be used both for ambulatory and hospitalized patients, providing certain conditions are met.

5.2 Bamlanivimab +/- etesevimab

Bamlanivimab was given to 452 outpatients with mild or moderate Covid-19[49]. Similar results were observed, 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[50].

Bamlanivimab efficacy was also assessed in hospitalized patients with mild to severe Covid-19[51]. No differences in clinical improvement or any clinical outcome (hospital discharge, death) were seen among groups. The trial was prematurely stopped for futility after enrollment of 314 patients.

Bamlanivimab was also evaluated as post-exposure prophyalxis in 1175 residents and staff of nursing homes in contact with confirmed Covid-19 index cases, from August to November 2020. In this population, bamlanivimab significantly reduced the incidence of mild or worse Covid-19, as compared to placebo (8.5% vs 15.2%; odds ratio, 0.43 [95% CI, 0.28-0.68]). This effect was exclusively seen in residents, but not in staff receiving bamlanivimab[52]. All patients who died were in the placebo group (n=4/482 of those who were seronegative and n=1/66 of those who were seropositive at baseline). This study was performed before the advent of SARS-CoV-2 variant of concerns. Given the reduced activity of bamlanivimab to these new variants, the current utility of this drug needs to be determined.

Due to the changes in the virus ecology and the occurrence of new variants, bamlanivimab as a sole antibody will not be positioned in the current formulary of drugs and has been downgraded by the FDA.

5.3 other mAbs: Sotrovimab, regdanvimab, tixagevimag/cilgavimab

There is a number of new mAbs being developed and in late clinical developement, and we decide to cite some of their preliminary results for completeness. Sotrovimab has shown a relative 85% reduction in the risk of hospitalisation or death in high-risk adult outpatients compared to placebo (7% in placebo group vs. 1% in the sotrovimab group)[53]. Similarly, regdanvimab reduced the risk of hospitalization or death to 3.1% compared to 11.1% in the placebo group among high-risk patients with mild Covid-19[54]. Of note, the study testing sotrovimab in hospitalized patients was prematurely stopped due to a possible worsening of the COVID-19. The main interest of sotrovimab in the current mAbs armentarium resides in its theoretical ability to retain activity against most recent variants[47], including the Delta variant. Tixagevimab/cilgavimab, a long acting antibody combination, failed to meet its primary endpoint of preventing symptomatic Covid-19 compared to placebo when given as post-exposure prophylaxis in unvaccinated adults[55].

Overall, it seems that monoclonal antibodies may reduce the progression of Covid-19 when given early after onset of symptoms (similar to convalescent plasma) or possibly as a post-exposure prophylaxis (although this indication is not funded yet in the Swiss system).

In Switzerland, casirivimab/imdevimab can be provided to patients at high-risk for complications (immunocompromised patients, very elderly, comorbidities), when given early after the first symptoms occur (either in the outpatient or inpatient settings). On note, data on efficacy and safety of both monoclonal antibodies in immunocompromised patients is very scarce. It is likely that the combination of casirivimab/indevimab will also be useful for hospitalized patients, in need of oxygen, and hospitalized early after the first symptoms occur (serology still negative).

6. Colchicine

Colchicine has anti-inflammatory effects by targeting the inflammasome, inhibiting cellular adhesion molecules and inflammatory chemokines. In a recent trial, 4488 patients with mild Covid-19 were randomized to receive either colchicine for 30 days or placebo[56]. 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)[57]. However, this was not confirmed in the Recovery trial, were more than 5000 hospitalized patients with Covid-19 received colchicine as compared to the standard of care. Mortality was similar between groups (RR 1.01 [0.94-1.03]), as published in a preprint version of the manuscript[11].

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.

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[5,22,58-62].

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)[5]. 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)[22].

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[61,62]. Additionally, HCQ given preemptively in persons in close contact with Covid-19 patients did not show any reduction in the incidence of new infections[58,60].

The living WHO guidelines issued by the MAGIC group emitted a strong recommendation against HCQ in hospitalized patients with Covid-19 of any severity[17].

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)[6]. 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)[22].

In a small Chinese trial, the 28-day mortality was not different in the LPV/r group when compared with the standard care group[63].

The living WHO guidelines issued by the MAGIC group emitted a strong recommendation against LPVr in hospitalized patients with Covid-19 of any severity[17]. 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[64]. 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)[22].

10. Antithrombotic drugs (anticoagulants and antiplatelet therapy)

Hypercoagulability may contribute to adverse outcomes including arterial and venous thromboembolism, organ dysfunction, and death in patients with Covid-19, especially in intensive care[65,66].

A randomized trial including adults admitted to the ICU for COVID-19 in Iran (n=562) compared intermediate-dose and standard-dose prophylactic anticoagulation. No difference was observed in the composite of venous or arterial thrombosis, extracorporeal membrane oxygenation or death in the two groups, but major bleeding was more frequent in the intermediate-dose group (2.5% vs. 1.4% in the standard-dose group)[67]. Similarly, an open-label trial in the US did not show a significant difference in mortality or thrombosis among patients with severe Covid-19 (n=173) randomized to intermediate-dose or standard dose prophylactic anticoagulation[68]. An open label trial in 615 hospitalized patients with Covid-19 of any severity in Brazil compared therapeutic (in-hospital rivaroxaban, enoxaparin, or heparin, followed by rivaroxaban until day 30) and standard in-hospital prophylactic anticoagulation (enoxaparin or heparin). The primary efficacy outcome consisting of a hierarchical analysis of time to death, duration of hospitalization, or duration of supplemental oxygen to day 30 did not differ among the two groups, with an increased risk of clinically relevant bleeding with therapeutic anticoagulation[69]. Recently, 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 published[70,71]. In 1098 severly ill patients, full dose anticoagulation failed to show a benefit, and may even confer harm compared to usual care thromboprophylaxis (OR 0.83; 95% CI, 0.67-1.03 for organ support-free days; major bleeding 3.8% vs. 2.3%)[71]. In contrast, among 2219 non-critically ill patients, therapeutic anticoagulation resulted in a benefit compared to usual care pharmacological thromboprophylaxis with regard to organ support free days (OR 1.27, 95% CI 1.03-1.58) and survival (adjusted absolute increase in survival to hospital discharge without organ support 4.0%, 95%CI 0.5-7.2% with therapeutic anticoagulation). Major bleeding events were rare, but numerically more frequent in the therapeutic anticoagulation group (1.9% vs. 0.9%)[70].

In summary, there is currently no evidence suggesting that intermediate- or therapeutic-dose anticoagulation reduces mortality or the need for organ support in critically ill patients with Covid-19 and not other indication for therapeutic anticoagulation. Conversely, for non-critically ill

hospitalzed patients with Covid-19, data from the largest currently published randomized trial support a beneficial effect of therapeutic anticoagulation with heparine compared to usual-care pharmacologic thromboprophylaxis on survival. This finding is 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[72-74]. Several trials comparing different anticoagulation regimens in in- and outpatients are ongoing.

Antiplatelet treatment with aspirin has not been shown to reduce mortality or progression to invasive ventilation or death compared to placebo in more than 14,000 patients hospitalized with Covid-19 from the Recovery-Trial, according to a pre-print[10].

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[75]. Some meta-analyses including small published and unpublished randomized trials have suggested a mortality reduction with ivermectin[76,77], while others have not[78]. The majority of randomized trials included in these meta-analyses on mortality were non-peer-reviewed preprint articles, with additional limitations including concerns regarding study quality and small sample size of individual studies with low numbers of outcome events. One of these study has even be suspected from medical fraud and the large meta-analysis led by Andrew Hill's was retracted due to this. 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. The WHO does not recommend the use of ivermectin for treatment of Covid-19 except in the context of a clinical trial[17].

Fluvoxamine, a selective serotonin reupteake inhibitor, has raised some attention after the publication of preliminary data showing an effect of this drug to prevent clinical deterioration, defined as oxygen saturation <92% or shortess of breath with or without hospitalization in high-risk outpatients in Brazil[79]. New data from the TOGETHER platform are expected soon.

Vitamin D may modulate antiviral and anti-inflammatory responses against SARS-CoV-2. A recently published systematic review and meta-analysis of randomized trials conducted in the pre-Covid-19

era found a small reduction in the risk of acute respiratory infections with vitamin D supplementation compared to placebo[80]. The current evidence however does not allow to conclude that Vitamin D supplementation prevents Covid-19 infections, hospitalizations, or death. A large US based randomized clinical trial is currently being conducted (VIVID-trial; https://clinicaltrials.gov/ct2/show/NCT04536298). A recent randomized controlled trial including 237 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)[81]. There were no differences in mortality, admission at the ICU and need for mechanical ventilation, although the sample size was modest to assess these secondary outcomes.

Unresolved issues

Several drugs for treatment or prevention of Covid-19 are currently being evaluated in adequately powered, well-designed clinical trials

Today, dexamethasone and tocilizumab are part of the standard of care in Switzerland. The optimised positioning of other immunomodulatory drugs remains to be discussed

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