Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews

RAPID REVIEW – June 16th, 2020.
(The information included in this review reflects the evidence as of the date posted in the document. Updates will be developed according to new available evidence)

Disclaimer

This document includes the results of a rapid systematic review of current available literature. The information included in this review reflects the evidence as of the date posted in the document. Yet, recognizing that there are numerous ongoing clinical studies, PAHO will periodically update these reviews and corresponding recommendations as new evidence becomes available.

Ongoing Living Update of Potential COVID-19 Therapeutics: summary of rapid systematic reviews

Take home message thus far:

• We examined 24 therapeutic options thus far; currently, there is no evidence of any important benefit from any therapeutic option (though remdesivir is revealing promise as one option based on 2 randomized controlled trials, and while not peer-reviewed and published, preliminary findings from the RECOVERY Trial (Oxford University Group) using the corticosteroid dexamethasone, indicates a reduction in mortality in COVID-19 patients hospitalized and requiring respiratory support) and that conclusively allows for safe and effective use to mitigate or eliminate the causative agent of COVID-19; the same can be said about prophylaxis. Nearly 200 therapeutic options or their combinations are being investigated in more than 1,700 clinical trials.

• Preliminary findings from the RECOVERY Trial showed that low doses of dexamethasone (6 mg of oral or intravenous preparation once daily for 10 days) significantly reduced mortality by one-third in ventilated patients and by one fifth in patients receiving oxygen only.

• Patients with COVID19, frequently older adults and with established comorbidities such as diabetes, hypertension, obesity, cardiovascular disease, kidney disease, and liver disease as well as malignancy, are receiving multiple concomitant medications, without considering possible adverse events and interactions. This is an area of research that is being overlooked and the potential toxicity due to concomitant treatments must be urgently addressed.

• The use of medications such as ivermectin, antivirals, and immunomodulators, among others, should be done in the context of patient consented, randomized clinical trials that evaluate their safety and efficacy.

• Countries should follow WHO guidance on the ethical use of drugs in emergencies, including use on unauthorized indications and compassionate use.

• The safety of the patient suffering from COVID19 is a key priority to improve the quality of care in the provision of health services.

• There remains an urgent need for additional high-quality randomized controlled trials that includes patients with COVID-19 before any therapeutic options can be administered with any confidence. The importance of an adequately designed and reported clinical trial is paramount in evidence-based medicine.

What this rapid review adds

Corticosteroids (dexamethasone):

RECOVERY Trial on Dexamethasone (June 16th 2020)
Follow-up complete for 94% of patients
Limitation as only studied patients in hospital
Dexamethasone reduces death by about 1/3 in hospitalized patients with severe respiratory illness and complications (COVID-19 patients)
Appears to be effective in reducing death in severely ill COVID patients needing respiratory support
The study is not yet published

- 2,104 patients randomized to dexamethasone 6 mg once daily (orally or IV) for 10 days and compared to 4,321 patients randomized to standard care alone
- Dexamethasone reduced deaths by 1/3 in ventilated patients (rate ratio 0.65, 95% CI 0.48 to 0.88, p=0.0003), and by 1/5 in other patients receiving oxygen only (rate ratio 0.80, 95% CI 0.67 to 0.96, p=0.0021), and no benefit in those who did not need respiratory support (rate ratio 1.22, 95% CI 0.86 to 1.75, p=0.14).
- Reduces 28-day mortality by 17%, p=0.0007

Remdesivir:

- We found n=3 RCT comparative studies to present whereby we could meta-analytically pool n=2 of them, with both comparing remdesivir to placebo; a 3rd RCT compared duration of treatment 5 vs 10-day course
- The modelling approach considered both a fix-effect and a random effects approach and sensitivity analysis is presented (Table 1)
- The fixed-effect approach was the principle approach (when the number of pooled studies is small e.g. <3, the fix-effect approach allows for more weight to be given to the study (s) with the larger sample size/events/data) and revealed reductions in mortality (RR=0.67, 95% CI 0.46 to 0.97, p=0.03; moderate certainty), time to clinical improvement (3.95 less days, from 3.86 days less to 4.05 less days, p<0.0001; moderate certainty), serious adverse events (RR=0.77, 95% CI 0.63 to 0.94, p=0.010; moderate certainty) and all adverse events (RR=0.87, 95% CI 0.79 to 0.96, p=0.004; moderate certainty).
- Based on GRADE, all certainty was rated as 'moderate', underpinned mainly by imprecision concerns (small numbers of events, small sample sizes, wide 95% confidence intervals)
- GRADE concerns emerged for issues of imprecision (small numbers of events) and inconsistency (elevated I^2).
- Analysis found that remdesivir does have a modest and significant reduction in mortality (only when using Fixed-effect modeling), the time to clinical improvement, all adverse events, and the number of serious adverse events.

- These results are promising for remdesivir and while there were elevated deaths in the drug group, analysis did uncover a significant though modest reduction.

- These results are promising and indicates benefit yet it is more than likely that as an anti-viral, remdesivir is not sufficient on its own and may be suitable in combination with other treatments. Additional research is needed and is ongoing to clarify and contextual these promising findings (Figures 2-3).

Table 1: Sensitivity analyses for all outcomes by fixed-effect versus random-effects modeling

Outcomes	Fixed-effect modeling	Random-effect modeling
Mortality (14-day follow up)	RR 0.67 (95% CI 0.46 to 0.97)	RR 0.72 (95% CI 0.42 to 1.23)
Time to clinical improvement (days)	MD -3.92 (-4.01 to -3.83)	MD -3.01 (-4.97 to -1.05)
Serious adverse effects	RR 0.77 (95% CI 0.63 to 0.94)	RR 0.77 (95% CI 0.63 to 0.94)
All adverse events	RR 0.87 (95% CI 0.79 to 0.96)	RR 0.91 (95% CI 0.74 to 1.11)

Hydroxychloroquine-chloroquine:

- We found n=38 studies to this date, with 8 Randomized controlled trials (RCTs) and 30 observational studies (prospective, retrospective, and case-series with or without some form of matching or adjustment (though limited)) assessing the following combination of treatments (2 studies were retracted)
  - HCQ vs no HCQ or SoC or placebo control (n=14)
  - HCQ vs lopinavir/ritonavir (n=2)
  - HCQ high dose vs low dose (n=1)
  - HCQ + Azithromycin (AZ) vs SoC (n=13)
  - HCQ + AZ case series (n=2)
  - HCQ + doxycycline (n=1)
  - CQ vs historical controls (n=2)
  - HCQ +AZ +zinc vs combinations (n=2)
  - HCQ usage among health-care workers (HCWs) (n=1)

- The certainty or quality of studies using the GRADE approach was underpinned by typically high-risk biased estimates of effect and all were rated as very low certainty, except for one rated at low-moderate certainty and one at low certainty evidence
- There is currently sufficient evidence on the benefits of hydroxychloroquine and the vast majority of research thus far on hydroxychloroquine suggests no benefit. Moreover, even with the low methodological quality of the underpinning research, there is some accumulating evidence of harm of hydroxychloroquine use e.g. Figure 1 and no difference on the impact on all-cause mortality (Figure 2).
- While some agencies are completing RCTs to definitively answer the question on HCQ/CQ effectiveness, the vast majority of research is underpinned by weaker observational studies yet predominantly pointing to no benefit. Since January 2020, the quality of the published

research even for observational research has improved, but generally still very poor across COVID-19 research and HCQ research.

- We found n=1 RCT assessing hydroxychloroquine versus placebo as postexposure prophylaxis for COVID-19. Hydroxychloroquine did not prevent the incidence of new illness compatible with COVID-19 within 4 days after exposure.

Figure 1: Adverse effects of hydroxychloroquine use in RCTs

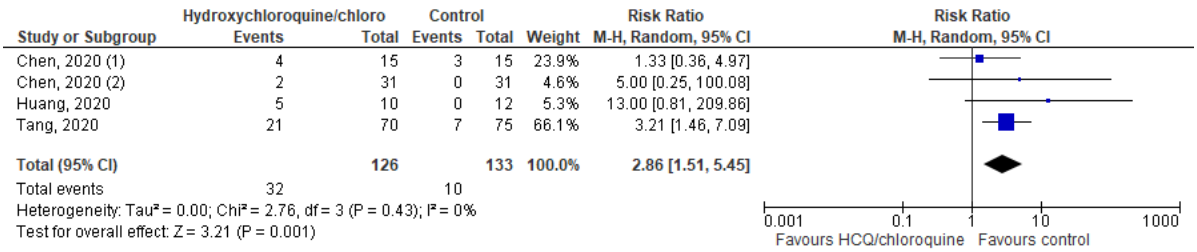
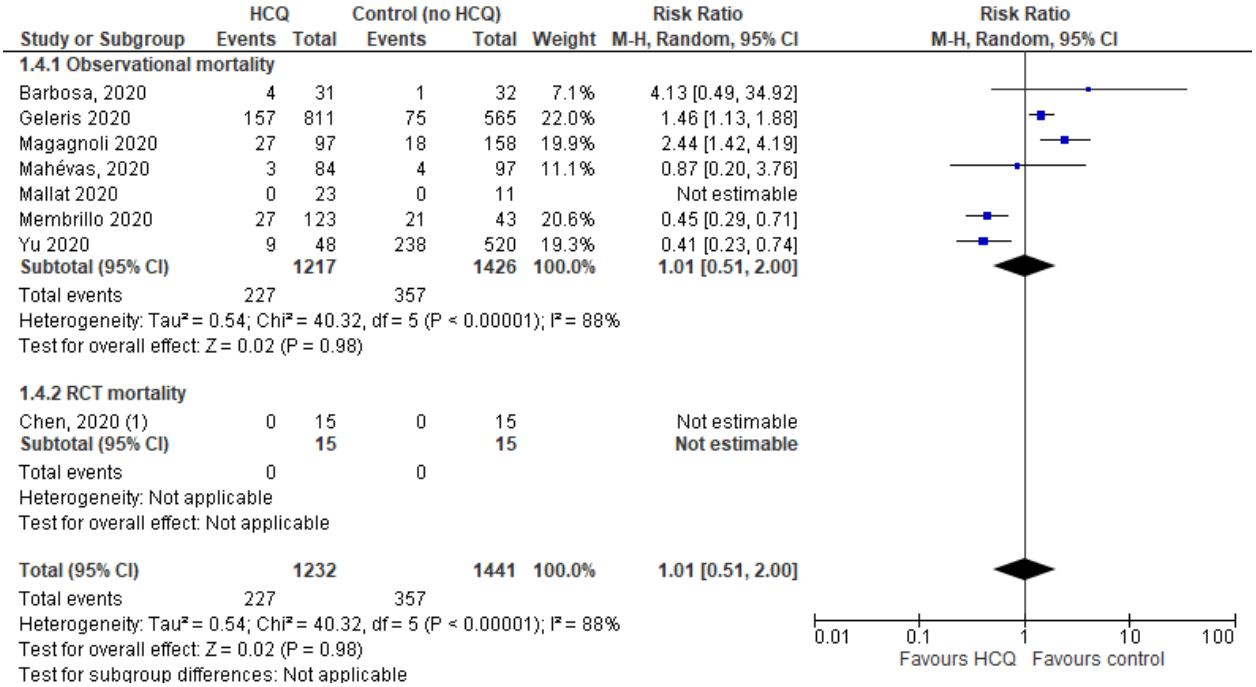


Figure 2: All-cause mortality of hydroxychloroquine use in principally nonrandomized observational cohort studies in COVID-19 patients (high heterogeneity)



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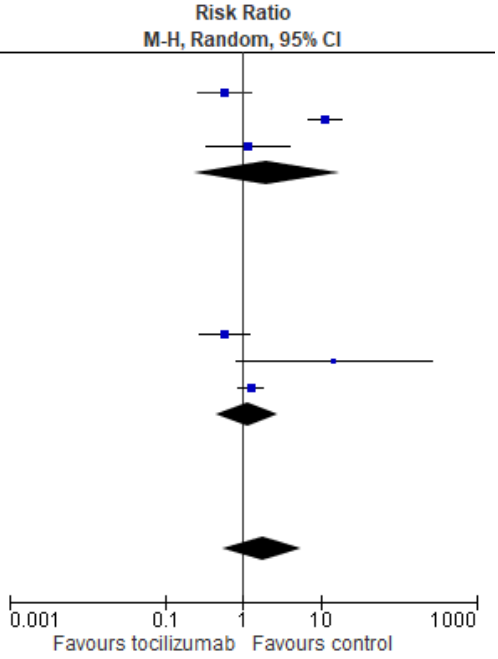
Convalescent Plasma:

- At this time, the research on convalescent plasma (CP) is underpinned by largely observational studies that are confounded, very small sample sizes and events. This limits any confidence in the findings.
- We have found 12 studies of which one is a RCT (n=1).
- The RCT looked at CP (n=52 patients) vs standard treatment alone (n=51) with a median age of 70 and 58.3% of patients being male.
- Hypertension, cardiovascular disease, diabetes, kidney disease, and liver disease were the principle types of co-morbidities.
- The trial was stopped early before arriving at its targeting sample size of 200 suggestive that it was underpowered.
- Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the CP group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; p= 0.03); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the CP group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; p = .83) (P for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; p = .30) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; p = .12). CP treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; p < .001). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care.
- The RCT was pen-label, randomization and concealment appeared reasonably well done. Methodologically an improvement from among the COVID-19 research published to date. Larger sample sized RCTs are needed urgently to establish the benefit (or harm) of CP, and whether this treatment option will be stand-alone or work optimally in combination with other therapeutics.

Tocilizumab (IL-6):

Eleven Tocilizumab studies (10 stand-alone and one review) are presented. These studies have not been definitive and are largely observational, while showing preliminary information that suggests urgent examination in large RCTs. We provide preliminary pooling of the data for mortality (unadjusted and adjusted) that at this time suggests no benefit. Given the high risk of bias and methodological concerns in the body of evidence, the confidence in estimates is very low. It is anticipated that ongoing RCT data will become available soon and this will be updated.

Study or Subgroup	Tocilizumab Events	Tocilizumab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Adjusted						
Garcia 2020	8	77	17	94	18.1%	0.57 [0.26, 1.26]
Martinez-Sanz 2020	61	260	20	969	19.1%	11.37 [6.99, 18.48]
Ramaswamy 2020	3	21	8	65	16.2%	1.16 [0.34, 3.98]
Subtotal (95% CI)		**358**		**1128**	**53.4%**	**2.02 [0.24, 17.34]**
Total events	72		45			
Heterogeneity: Tau² = 3.41; Chi² = 45.15, df = 2 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.1.2 Unadjusted						
Kimming 2020	8	32	12	28	18.3%	0.58 [0.28, 1.22]
Quartuccio 2020	4	42	0	69	8.9%	14.65 [0.81, 265.46]
Wadud 2020	27	44	24	50	19.4%	1.28 [0.88, 1.85]
Subtotal (95% CI)		**118**		**147**	**46.6%**	**1.14 [0.46, 2.80]**
Total events	39		36			
Heterogeneity: Tau² = 0.38; Chi² = 6.57, df = 2 (P = 0.04); I² = 70%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**476**		**1275**	**100.0%**	**1.78 [0.55, 5.73]**
Total events	111		81			
Heterogeneity: Tau² = 1.80; Chi² = 79.98, df = 5 (P < 0.00001); I² = 94%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						



Some key drug specific contraindications and cautions[116]

Lopinavir/ritonavir
Severe hepatic insufficiency
Co-administration with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. This includes alfuzosin, ranolazine, amiodarone, dronaderone, fusidic acid, neratinib, venetoclax, colchicine, astemizole, terfenadine, lurasidone, pimozide, quetiapine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir, lovastatin, simvastatin, lomitapide, avanafil, sildenafil, vardenafil, midazolam, triazolam, ciclosporin, tacrolimus, sirolimus, rivaroxaban and vorapaxar. It may be appropriate to temporarily withhold such concomitant medication while the patient is receiving lopinavir/ritonavir. For patients who are receiving warfarin, additional INR monitoring is advised.

Corticosteroid
Known contra-indication to short-term low-dose corticosteroid.

Hydroxychloroquine
Known prolonged QTc interval*
Caution: Co-administration with medications that prolong the QT interval (e.g. macrolides, quinolones) is not an absolute contraindication, but it may be appropriate to check the QT interval by performing an ECG.

Azithromycin
Known prolonged QTc interval*
Co-administration with chloroquine or hydroxychloroquine
Known hypersensitivity to macrolide antibiotic

Tocilizumab
Known hypersensitivity to tocilizumab.
Evidence of active TB infection
Clear evidence of active bacterial, fungal, viral, or other infection (besides COVID-19)

Note: Pregnancy and breastfeeding is not an exclusion

Convalescent Plasma
Known moderate or severe allergy to blood components
Not willing to receive a blood product[116]

Background:

The vast amount of data that will be coming will present important challenges and it must be interpreted quickly so that the correct most optimal treatment decisions can be made with as least harm to patients, and that manufacturers and supply chains can scale up production rapidly. This will ensure that reportedly successful drugs can be administered to as many patients and in as timely a manner as possible. Moreover, if evidence indicates that a medication is potentially sub-optimal and not effective, then the many ongoing clinical trials could change focus and pivot onto more promising alternatives**Error! Bookmark not defined.**. Additionally, many are using drugs already in huge volumes and also via compassionate or single use applications[1]. It is absolutely imperative therefore that prescribers be given the most updated research evidence fast to inform if what was done was optimal or if it is not optimal or even harmful to patients. The following evidence-database was complied to orient the

published studies thus far and will endeavour to add to this table list as research is released into the public space. The drugs currently under review are (Box 1):

Box 1: Therapeutics reviewed

Drug name	**Number of studies published thus far (RCT and observational)**
Meplazumab	1
Ivermectin	4
Siltuximab	1
Danoprevir	1
Tocilizumab (IL-6)	11
Favipiravir	2
Darunavir	1
Nelfinavir	1
Remdesivir	5
Chloroquine or hydroxychloroquine	38 (2 retracted)
Convalescent plasma	12
Corticosteroids	6
Arbidol/Umifenovir	8
Lopinavir/ritonavir	9
Interferon-alpha	3
Interferon-beta	3
heparin (anti-coagulants)	4
α-Lipoic acid	1
Ruxolitinib	1
IVIG	1
Sarilumab	1
Famotidine	1

[1] WHO. Off-label use of medicines for COVID-19. Scientific brief. March 31st, 2020. https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19

Lenzilumab	1
Leflunomide	1

Methods:

MEDLINE and EMBASE electronic databases were searched from 2020 to present (June 16th 2020) using a mix of keywords such as COVID-19 and respective drug names, along with any relevant variants. The search did not use a randomized controlled trial filter. For example, the COVID-19 terms were 'exp Coronavirus Infections/ or exp Coronavirus/ or exp Severe Acute Respiratory Syndrome/ or exp SARS Virus/ or coronavirus.mp. or severe acute respiratory syndrome coronavirus 2.mp. or 2019 nCoV.mp. or 2019nCoV.mp. or 2019 novel coronavirus.mp. or new coronavirus.mp. or novel coronavirus.mp. or SARS-CoV-2.mp. or SARS CoV-2.mp. or COVID 19.mp. or COVID-19.mp. or COVID19.mp.' The decision was to also search by a specific drug name under study.

PubMed was also searched daily during this period as a means to gain a rapid assessment of any emergent publications. Searches were conducted daily from March 15th to present to uncover any new evidence. Evidence was considered from additional sources such as manuscript reference lists, clinical trials registers (such as the International Clinical Trial Registry Platform) and online trial portals that pre-publish studies not yet having completed the peer-review process. For example, we have searched and will continue to search the largest clinical medicine preprint repository, medRxiv.org, on a daily basis.

The focus has been on any types of comparative effectiveness research (ideally RCTs studies) for all of the included therapeutic pharmacological interventions (adults and children) and this review was open to any study that could be informative, including case-series and observational designs. Adults and children exposed to or with confirmed or suspected COVID-19 were and will be included. Trials that compare interventions head-to-head or against no intervention or placebo is the focus. We have focused on comparative effectiveness studies that provide evidence on patient-important outcomes, but were open to all reported outcomes at this time[2]. No electronic database search restrictions were imposed. If meta-analytical pooling was and is possible from retrieved evidence, this review would seek to do this to derive more precise estimates of effect and derive additional statistical power.

A risk of bias assessment was applied to RCTs as well as observational studies focusing on randomization, allocation concealment, blinding, attrition, or other relevant biases to the estimates of effect, as well as selection bias, residual confounding bias, statistical adjustment, matching (propensity score), stratification, or restriction, respectively[3]. The GRADE 'outcome-centric' method was applied to individual outcomes per study to derive a certainty/quality of evidence rating

[2] World Health Organization. R&D Blueprint novel Coronavirus. Outline of trial designs for experimental therapeutics. WHO reference number WHO/HEO/R&D Blueprint (nCoV)/2020.4. Available at: https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1

[3] Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011.

to establish how much confidence one could have in the estimates of effect. These are principally single studies and the approach was to consider the outcomes per study in a rapid manner to establish some sense of GRADE 'lite' rating per outcome and then to derive an overall rating. The

overall rating is based on the lowest rating from among the critical/important patient outcomes. The reporting in these studies was very poor, scarce, and the general methodologies were very weak. This has been a rapid, albeit sub-optimal application of GRADE methods, while seeking to apply as much rigor to a flawed body of evidence emerging from the current reporting across COVID-19 research in general[4].

For any meta-analytical pooling if and when data allows, we planned to pool all peer-reviewed studies with non-peer-reviewed studies. We will present the combined analysis. However, we will also apply a sensitivity analysis and separate out peer-review studies to examine the estimates of effect based on the higher quality studies that would have undergone scientific scrutiny and will present these separately. There were some drug instances whereby we provide systematic-review (meta-analysis) evidence indirectly related to COVID-19 patients e.g. corticosteroids in patients with ARDS.

Results of Risk of Bias and GRADE certainty of evidence assessment

Risk of bias

Overall, our risk of bias assessment for the limited reported RCTs resulted in high risk of bias due to sub-optimal randomization, allocation concealment, and blinding (as well as other methodological and reporting concerns). RCTs were also very small in size and had small event numbers. The methods were very poor overall and the reporting was very sub-optimal. For the observational studies which comprised the bulk of studies presently published (including a vast proportion being pre-publications that are non peer-reviewed), we had concerns with the representativeness of study groups (selection bias) and imbalance of the known and unknown prognostic factors (confounding). Many studies are also at risk of being confounded by indication. Most are not prospective in nature and the outcome measures are mainly heterogeneous with wide variation in reporting across the included studies. In general, follow-up was short and as mentioned, confounded potentially by severity of disease, comorbidities, previous or concomitant COVID-19 treatment.

GRADE certainty of evidence

Overall, our certainty (or confidence) in the evidence was very limited since the studies were largely not randomised and they failed to use reliable methods to measure their results and confounded (high risk of bias). Furthermore, studies typically had only a small number of participants as well as events, and the methods were very sub-optimal in general. Our ratings of certainty was typically very low (with a few rated as low certainty) across the breath of COVID-19 research thus far.

[4] Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013;66(7):719–25. Epub 2013/01/15. pmid:23312392.

Table 2: All COVID-19 *in vitro* lab and *in vivo* (clinical) human studies published from January 2020

Author; study design; year	Treatment arm vs comparator; sample size; age (mean/median); male %	Patient co-morbidities; additional medications reported besides the intervention/ control	Reported findings and author's stated conclusion Note: methodological concerns	Risk of bias (RoB)*; GRADE certainty of evidence rating**
Meplazumab (monoclonal antibody) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
OBSERVATIONAL (clinical)				
Bian[1]; observational treatment group with hospitalized concurrent control; 2020	Add-on 10 mg meplazumab (n=17 patients) vs hospitalized patients in the same period as controls (n=11); 28; mean 56.1; 53.5%	32% hypertension, 10.7% cardiovascular disease, 10.7% diabetes; lopinavir/ritonavir, recombinant human interferon α-2b, glucocorticoid, and antibiotics.	Meplazumab treatment significantly improved the discharge (p=0.006) and case severity (p=0.021) in the critical and severe patients vs control; the time to being virus negative in treatment was reduced relative to the control group (median 3, 95% CI (1.5–4.5) vs. 13, (6.5–19.5); p=0.014, HR=0.37, 95% CI (0.155–0.833)); suggested the need for further study in clinical trials as a potential therapeutic option in COVID-19. Note: non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Ivermectin **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
in vitro				
Caly[2]; observational; 2020	One group: a single addition to Vero-hSLAM cells 2 hours post infection with SARS-CoV-2 isolate Australia/VIC01/2020 at a MOI of 0.1, followed by the addition of 5 µM ivermectin; NA	NA	Following a single addition to Vero-hSLAM cells 2 hours post infection, ivermectin at 24 hours contributed to a 93% reduction in viral RNA present in the supernatant of the samples treated with ivermectin compared to the vehicle DMSO. By 48 hours, there was an ~5000-fold reduction in viral RNA at 48 hours. Researchers concluded that ivermectin administration *in vitro* resulted in the effective loss of essentially all viral material by 48 hours, supporting further clinical study in COVID-19 patients. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Did not apply GRADE
OBSERVATIONAL (clinical)				
Patel[24]; observational (registry-based); 2020	Ivermectin (150 mcg/Kg once following initiation of mechanical ventilation) vs SoC (no ivermectin); 1,970; not reported; not reported	Not reported	A survival benefit was reported for ivermectin (mortality rate 18.6% vs 7.7%; HR 0.18, 95% CI (0.07-0.48), log rank (Mantel-Cox) p<0.001; length of hospital stay 10.9 +/- 6.1 days vs 15.7 +/- 8.1 days and ICU stay was 6.0 +/- 3.9 days vs 8.2 +/- 6.2 days, both p<0.001.	High; Very low certainty[1]

			Note: pre-print. non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	
Patel[41]; observational propensity-matched case-controlled (prospectively collected data); 2020	Ivermectin (150mcg/Kg) administered once compared with COVID-19 patients receiving medical therapy without ivermectin (704 ivermectin treated and 704 controls); 1,408; mean 53.5; 55.1%	CAD 11.1%, diabetes 11.3%, COPD 2.8%, hypertension 24.8%, immune-compromised 2.8%; hydroxychloroquine, azithromycin and corticosteroids	In patients needing mechanical ventilation, a lesser number of patients died in the ivermectin group (7.3%) vs 21.3% control and the overall mortality rates were lower with ivermectin (1.4%) vs 8.5% with a corresponding HR 0.20, CI 95% 0.11-0.37, p<0.0001). Ivermectin also contributed to reduced hospital length of stay. Note: apparent pre-print. non-randomized, potentially confounded, though propensity score matched on several variables and statistical adjustment, could not account for all unknown confounders, small events, judged as sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	Moderate-high; Very low certainty[3]
Rajter [103]; observational retrospective; 2020	Ivermection vs usual care (173 ivermectin, 107 usual care); 280; mean age 59.6 years (SD 17.9); 54.6 % male	Diabetes 32.1%, cardiac 15.4%, pulmonary 10%, obesity 40.7%, renal 8.6%, hypertension 17.9%, cancer 6.1%, neurologic 10%, HIV 3.2%; NR	Univariate analysis revealed reduced mortality in the ivermectin group (25.2% versus 15.0%, OR 0.52, 95% CI 0.29-0.96, P=0.03); mortality was also lower among 75 patients with severe pulmonary disease treated with ivermectin (38.8% vs 80.7%, OR 0.15, CI 0.05-0.47, P=.001), but there was no significant difference in successful extubation rates (36.1% vs 15.4%, OR 3.11 (0.88-11.00), p=.07). After adjustment for between-group differences and mortality risks, the mortality difference remained significant for the entire cohort (OR 0.27, CI 0.09-0.85, p=.03; HR 0.37, CI 0.19-0.71, p=.03). Note: non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Siltuximab (monoclonal antibody) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
OBSERVATIONAL (clinical)				
Gritti[3]; observational (prospective cohort study); 2020	One group: patients received siltuximab at a median dose of 900 mg, ranging from 700 to 1,200 mg; received a second dose of siltuximab; 21; median 64.0 (IQR 48-75); 85.7%	43% had hypertension, 23.8% diabetes, 19% cardiovascular disease, 4.7% malignancies, 4.7% chronic kidney disease, and 4.7% cerebrovascular disease; no other medication reported but siltuximab	The results suggest a potential role of siltuximab in treating patients with ARDS secondary to SARS-CoV-2 infection. Note: pre-print, non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Danoprevir (antiviral) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
OBSERVATIONAL (clinical)				
Chen[4];	Treatment experienced	18% hypertension;	After 4 to 12-day treatment with danoprevir boosted by	High;

observational; 2020	(n=9) vs naïve patients (n=2), treatment naïve patients never received any antiviral therapies such as lopinavir/ritonavir and interferon nebulization before switching to danoprevir (all treated with danoprevir boosted by ritonavir in the presence or absence of interferon nebulization (the background therapy)); 11; median 44 (range 18-66); 36%	not reported	ritonavir, all patients (n=11) discharged from the hospital based on normal body temperature for at least 3 days; there was substantial improvements in respiratory symptoms; the CT lung imaging revealed absorption and recovery of acute exudative lesions; there were 2 consecutive RT-PCR negative tests of SARS-CoV-2 nucleotide acid; researchers concluded that repurposing of danoprevir for COVID-19 should be considered within clinical trials. Note: pre-print, non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	Very low certainty[1]
Tocilizumab/IL-6 (monoclonal antibody) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
OBSERVATIONAL (clinical)				
Xu[5]; observational (retrospective cohort); 2020	All patients treated with tocilizumab; 21; mean 56.8 ± SD 16.5, ranged from 25 to 88 years; 85.7%	43% hypertension, 23.8% diabetes, 9.5% CHD, 4.8% COPD, 4.8% CKD, 4.8% bronchiectasis, 4.8% brain infarct, 4.8% auricular fibrillation; none reported	75.0% lowered oxygen intake and one patient required no oxygen therapy. CT scans showed lung lesion opacity was absorbed in 90.5%. The percentage of lymphocytes in peripheral blood returned to normal in 52.6% patients on the fifth day following treatment. Abnormally elevated C-reactive protein declined significantly in 84.2% of patients. No adverse reactions reported and 90.5% (n=19) discharged from hospital mean 13.5 days following the treatment with tocilizumab and the rest; 2 are undergoing good recovery; researchers concluded that tocilizumab should be considered within clinical trials for COVID-19. Note: pre-print, non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Cellina[34]; observational case-series (1 patient); 2020	2 doses of tocilizumab (8 mg/kg), 12 hours apart, on day 7 and 8; 1 patient; 64; male	None reported; none reported	Patient without significant clinical history presented with syncope with normal vitals; ear temperature was 38 °C, oxygen saturation 99% on room air, chest X-Rays showed mild linear densities in the lower and middle left lung fields, laboratory investigations showed increased white blood cell count (10.900 per µL), elevated serum lactate level (250 U/L) and elevated reactive C protein (RCP) (89 mg/dL), other blood tests normal; COVID-19 detected in a throat swab sample by RT-PCR. Due to the worsening of the blood tests on the day 2, patient admitted; day 6, the patients developed dyspnea; decreased of oxygen saturation (90%) and further increase of CRP 336 mg/dL; white blood cell count was 10.800 per µL; interleukin-6 was 80 ng/L; day 7, unenhanced chest CT showed the presence of diffused bilateral air space opacities, including ground glass opacities and consolidation; assisted ventilation started; patient administered 2 doses of tocilizumab (8 mg/kg), 12 hours apart, on day 7 and 8; day 9, CRP declined to 96 mg/dL and white blood cell count to 2.360 per µL; patient clinical condition gradually improved and ventilatory support was gradually stopped; day 14, repeat chest CT revealed mark improvement (size reduction of air cells opacities, density reduction of consolidations, some ground glass opacities, peripheral reticular	Not applied; Not applied

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			opacities, reduction of pleural effusion and mediastinal lymphadenopathy).	
Roumier[44]; observational retrospective; 2020	Treated with IL-6 vs no IL-6 in matched controls group; 59 (n=30 IL-6 group and 29 in no IL-6 group); median age 50 years; 80%	Hypertension 30.5%, cardiovascular disease 14.7%, cerebrovascular disease 5%, chronic kidney disease 8.5%, HIV/AIDS 5%, immunosuppressive therapy 11.8%; 2 patients on IL-6 got azithromycin and 2 got methyl-prednisolone	Tocilizumab significantly reduced need for subsequent mechanical ventilation (weighted OR: 0.42; 95% CI [0.20-0.89]; p=0.025), unadjusted analysis showed a trend towards a reduction of mortality (OR: 0.25 95% CI [0.05-0.95], p=0.04), this significance faded with weighted analysis; in addition, based on only 23 patients (and 16 controls) treated outside of the ICU, tocilizumab significantly reduced the risk of subsequent ICU admission (weighted OR: 0.17; 95% CI [0.06-0.48]; p=0.001); as of April 4th 2020, based on the 30 patients treated with tocilizumab, 3 (10%) died, while 4/7 (57%) and 6/30 (20%) were discharged from the ICU and from hospital, respectively; tocilizumab was well-tolerated, there is mild hepatic cytolysis in n=2 and ventilator-acquired pneumonia in n=1. Note: nonrandomized, confounded, optimal adjustments and steps not employed but the matching in the control group was an improvement (though not clear where the source of the control group was taken from e.g. was it drawn from the same population as treatment), small sample size, small events, and not optimally comparative. See reference 3 as these results differ from those of Gritti et al. who treated more severe patients requiring non-invasive ventilation with siltuximab (another IL-6R-targeted therapy). This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Quartuccio [6]; observational retrospective case-control; 2020	Tocilizumab (TOCI) vs SoC; 111 (42 TOCI vs 69 SoC); mean age of 58·5±13·6 years; 69.4% male	Not reported; not reported	In the TOCI group, 62% of the cases were ventilated and there were 3 deaths (17·8±10·6 days, mean follow up) with 7/26 cases remaining on ventilators, without improvement, and 17/26 developing bacterial superinfection; researchers reported 1 death in the 15 TOCI cases treated on noninvasive ventilation and 1 serious bacterial superinfection; the 69 SoC cases had no fatalities and no bacterial complication; TOCI group had higher baseline CRP and IL-6 elevations. Researchers reported more elevated inflammatory markers, more superimposed infections and poorer outcomes in ventilated TOCI cases relative to ward based TOCI therapy. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes	High; Very low certainty[1]
Wadud [77]; observational (retrospective case-control); 2020	Tocilizumab (n=44) vs control (n=50); 94; median age was 55.5 years in the study group and 66 in the control group; 76.5%	Additional medications (not optimally reported by groups etc.) were hydroxychloroquine, azithromycin, Steroids - hydrocortisone/ methylprednisolone/ dexamethasone).	Average HS score was 114 in the tocilizumab group and 92 in the control group, reported difference was statistically significant with p< 0.0001 when compared to the control group; length of stay was reportedly longer, average 17.9 days in the tocilizumab; survival rate was much lower at 48 % in the control group and 61.36 % in patients who received tocilizumab with significant at p value of < 0.00001. Note: nonrandomized, confounded, optimal adjustments and steps not employed but the matching (while not fully described) was an improvement (though not clear where the source of the control group was taken from e.g. was it drawn from the same population as treatment), small sample size, small events, and not optimally comparative.	High; Very low certainty[1]
Ramaswamy [78]; observational case-control; 2020	Tocilizumab (dosed at either 400 mg fixed dose or 8 mg/kg weight-based dose with maximum single dose	Diabetes 11.6%, COPD 26.7%, hypertension 20.9%, hypertension 4.7%,	3 deaths tocilizumab, 8 deaths in untreated control; cox models and treatment effects models revealed short-term survival benefit; an associated 75% reduction in the risk of inpatient death when treated (HR 0.25; 95% CI 0.07-0.90) with	High; Very low certainty[1]

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	of 800mg) (n=21) vs no tocilizumab (n=65); 86; mean 63.7 (15.7); 66% male	cancer 2.3%, vascular disease 2.3%, atrial fibrillation 7%, stroke 2.3%; corticosteroids 20.9%, ACE 10.5%, hydroxychloroquine 67.4%	tocilizumab; 52.7% reduced risk of dying while hospitalized compared to those not treated (RR 0.472; 95% CI 0.45-0.49). Note: nonrandomized, confounded, some adjusted analysis but not optimal, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This data is also to be considered hypothesis generating, calling for well-designed randomised clinical studies.	
Kimmig [85]; observational retrospective; 2020	Tocilizumab (400 mg flat dosing of tocilizumab with the potential for redosing based on clinical response (e.g. oxygenation status, hemodynamic stability, inflammatory marker response) n=28 vs no tocilizumab n=32; 60; not reported; not reported	Not reported, not reported.	Tocilizumab was associated with a higher incidence of secondary bacterial infections including hospital acquired pneumonia and ventilator associated pneumonia (64.3% vs. 31.3% p=0.010); logistic regression modeling showed that tocilizumab administration was independently associated with presence of secondary bacterial infections (OR: 3.96 (95% CI 1.35-11.61), p=0.033).	High; Very low certainty[1]
Martinez-Sanz [98]; observational cohort; 2020	Tocilizumab (n=260) vs control (n=969); 1229; median treatment 65 (55 - 76), control 68 (57 - 80); 62.2%	Hypertension 22%, diabetes 22.7%, CHF 2.9%, CAD 7.9%, CKD 5.2%	Larger observational study, a total of 1,229 and 10,673 person/days were analyzed. In the adjusted marginal structural models, a significant interaction between tocilizumab use and high Creactive protein (CRP) levels was detected. Tocilizumab was associated with decreased risk of death (aHR 0.34, 95% CI 0.16–0.72, p=0.005) and ICU admission or death (aHR 0.38, 95% CI 0.19–0.81, p=0.011) among patients with baseline CRP >150 mg/L, but not among those with CRP ≤150 mg/L. Exploratory subgroup analyses yielded point estimates that were consistent with these findings. In sum, tocilizumab was associated with a lower risk of death or ICU or death in patients with higher CRP levels. Note: nonrandomized, confounded, adjusted analysis, methodology much improved over prior published COVID-19 research; as with any observational study, there is still a risk of unmeasured confounding	High; Very low certainty[1]
Garcia [99]; observational; 2020	Tocilizumab (n=77) vs control (n=94); 171; mean (SD) age of 61.5 (12.4) and 61.4 (16) years; 65.4% male	Hypertension 44%, heart disease 19.3%, respiratory diseases 11.7%, diabetes 15.2%	77 patients received tocilizumab and 94 did not. The tocilizumab group had less ICU admissions (10.3% vs. 27.6%, P= 0.005) and need of invasive ventilation (0 vs 13.8%, P=0.001). In multivariable analysis, tocilizumab remained as a protective variable (OR: 0.03, CI 95%: 0.007-0·1, P=0.0001) of ICU admission or death. Note: nonrandomized, confounded, adjusted analysis, methodology much improved over prior published COVID-19 research; as with any observational study, there is still a risk of unmeasured confounding.	High; Very low certainty[1]
Formina [111]; observational, 2020	89 patients received tocilizumab (TCZ), 17 of these patients (19%) were on mechanical ventilation, 72 (81%) treated with supplemental oxygen without mechanical ventilation (No MV); 89; 36% < 50 years, 51% 50-69 years, 14% > 70 years; 59.6% males	Hypertension 33%, diabetes 11%, lung disease 7%, obesity 26%	Among the 89 patients who were treated with TCZ, 74 had been treated for a median of 9 days with hydroxychloroquine+ azithromycin + lopinavir/ritonavir before TCZ treatment, 4 had been treated for a median of 9 days with HCA + AZ before TCZ treatment and 11 had been treated for a median of 9 days with lopinavir/ritonavir before TCZ treatment. Sixty three of 72 patients were discharged from hospital, one patient died, and 8 remained in hospital at time of writing. Among 17 patients receiving mechanical ventilation, despite a rapid decrease in CRP levels from 89 to 35 mg/L (p = 0.014) and early improvements in NEWS2 scores in 10 of 17, ten patients died and seven remain in hospital at time of writing. Overall, mortality was only seen in patients who had markedly elevated CRP levels (>30 mg/L) and low lymphocyte counts	High; Very low certainty[1]

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			(<1000*UL*) before TCZ administration. Note: nonrandomized, confounded, unadjusted analysis, no matching, stratification, and methodology somewhat improved over prior published COVID-19 research; as with any observational study, there is still a risk of selection bias and unmeasured confounding.	
SYSTEMATIC REVIEW/META-ANALYSIS (clinical evidence)				
Kahn[58]; review, using observational retrospective case-series and case-reports; 2020	5 retrospective studies (tocilizumab, n=2 case series and two case reports; siltuximab, n=1 case series); 59; NR	Diabetes 23.8% to 27%, hypertension 42.8% to 60%; lopinavir and methylprednisolone	Xu et al 2020: All had resolution of fever within 24 hours; 75% had reduced oxygen support; CRP and lymphocytes returned to normal in 84% and 53% respectively. 91% had radiological improvement; 91% discharged; 9% remain stable Luo et al 2020: 20% died; 13% had worsening of disease; 67% demonstrated clinical stability; median CRP fell from 126.9 to 11.2 mg/L. Drop in IL-6 in 67% Gritti et al 2020: 33% improved; 43% stable; 24% worsened or died Zhang et al 2020: By Day 4 – Resolution of fever; discontinuation of supplemental oxygen therapy; radiological improvement in ground glass changes; CRP dropped from 225mg/L to 33mg/L Michot et al 2020: At 72 hours – Resolution of chest symptoms; IL-6 levels returned to normal Note: high risk of selection bias, unclear how the patients were enrolled, unclear information on interventions and comparators and outcomes, key design details missing and methods just overall very very poor; multiple treatments, small sample sizes and events.	High; Very low certainty[1] AMSTAR II [7] critical appraisal of the review: low-quality, serious concerns
Favipiravir (antiviral) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
RCT (clinical)				
Chang[7]; RCT (open-label); 2020	120 assigned to favipiravir group (116 assessed, routine treatment + 1600 mg on the first day twice a day, 600 mg from the second day to the end, twice a day) and 120 to arbidol group (120 assessed, 200 mg, 3 times a day to the end of the trial); 236; not reported clearly; 46.6%	27.9% hypertension, diabetes 11.4%, 95% COVID-19 pneumonia; none reported	Clinical recovery rate of day 7 between two groups, 61.2% favipiravir vs 5.7% arbidol (total patients), 71.4% vs 55.6% (moderate cases) respectively, 5.5% vs 0.0% (serious cases) respectively; patients with hypertension and/or diabetes 54.7% favipiravir vs 51.4% arbidol; adverse events 37/116 favipiravir vs 28/120 arbidol, note, 18 severe patients in the favipiravir group vs 9 severe patients in the arbidol group (imbalanced). Note: pre-print, sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, and use of active comparator with unknown effectiveness for COVID-19.	High; Very low certainty[1]
OBSERVATIONAL (clinical)				
Cai[6]; observational (nonrandomized open-label); 2020	Oral FPV (Day 1: 1600 mg twice daily; days 2–14: 600 mg twice daily) plus interferon (IFN) α by aerosol inhalation in the FPV arm vs LPV/RTV (days 1–14: 400 mg/100 mg twice daily) plus IFN-α; 80 (n=35 FPV and n 45=in LPV/RTV); median 47 (35.75–61); 43.8%	None reported; no additional medications reported, standard care included oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, and antiemetic drugs.	Viral clearance median time for FPV (Group A), was estimated to be 4 days (IQR: 2.5–9) and significantly shorter than the time for patients in control group (Group B), which was 11 d (IQR: 8–13) ($P < 0.001$); for chest CT changes, on the 14th day after treatment, the improvement rates of the chest CT in FPV significantly higher than those in the control arm (91.4% versus 62.2 %, 32/35 versus 28/45, $p = 0.004$). Adverse reactions in the FPV n=4 was four, significantly fewer than the 25 adverse reactions in the control arm ($p < 0.001$). Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-	High; Very low certainty[1]

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			optimal reporting of methods and outcomes, and active, retrospective comparator with unknown effectiveness for COVID-19. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	
Darunavir (antiviral) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
in vitro				
De Meyer[8]; observational; 2020	Examined the *in vitro* antiviral activity of darunavir against a clinical isolate from a patient infected with SARS-CoV-2.	NA	Darunavir showed no activity against SARS-CoV-2 at clinically relevant concentrations (EC50 >100 µM). Remdesivir, used as a positive control, showed potent antiviral activity (EC50 = 0.38 µM). Present findings do not support the use of darunavir for treatment of COVID-19. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	Definitely high[2] (risk of bias assessed for *in vitro* studies using OHAT tool); Very low certainty[1]
Nelfinavir (antiviral) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
in vitro				
Yamamoto [9]; observational; 2020	Assessed the 50% effective concentration (EC50), the 50% cytotoxic concentration (CC50), and the selectivity index (SI, CC50/EC50); C max-EC50 ratio (C max/EC50) and C trough-EC50 ratio (C trough/EC50) were also calculated to evaluate the safety and efficacy of the 9 antivirals (plus lopinavir, ritonavir, saquinavir, atazanavir, tipranavir, amprenavir, darunavir, and indinavir).	NA	Nelfinavir effectively obstructs replication of SARS-CoV-2; the effective concentrations for 50% and 90% inhibition (EC50 and EC90) of nelfinavir was the lowest from among the 9 HIV-1 protease inhibitors. Present *in vitro* findings are positive and support further clinical study of nelfinavir in COVID-19 patients. The methodology indicates a high risk of bias. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	Definitely high[2] (risk of bias assessed for *in vitro* studies using OHAT tool); Very low certainty[1]
Remdesivir (antiviral) **Remdesivir does have a modest and significant reduction the time to clinical improvement, all adverse events, and the number of serious adverse events.There is insufficient evidence to draw a definitive conclusion on benefits to reduce mortality.** **The effectiveness is being evaluated in various randomized clinical trials.**				
OBSERVATIONAL (clinical)				
Holshue [10]; case-report; 2020	1 COVID-19 patient (first in USA), aged 35 years, male, treated with remdesivir on compassionate use authorization	NA	Treatment with IV remdesivir began on the evening of day 7, and no adverse events were observed in association with the infusion. Vancomycin was discontinued on the evening of day 7, and cefepime was discontinued on the following day, after serial negative procalcitonin levels and negative nasal PCR testing for methicillin-resistant *Staphylococcus aureus*. On hospital day 8 (which was illness day 12), it was found that the patient's clinical condition improved significantly, whereby the supplemental oxygen was discontinued, and his oxygen saturation values improved to 94 to 96% while he was breathing ambient air. Bilateral lower-lobe rales were no longer present. Appetite improved, and the patient was asymptomatic aside from intermittent dry cough and rhinorrhea. All symptoms resolved.	Not applied; Not applied

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Grein,[11]; case-series; 2020	Remdesivir; 53; median IQR 64 (48–71); 75	Hypertension 25%, diabetes 17%, hyperlipidemia 11%, asthma 11%; none reported	Researchers reported that at baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving ECMO. Based on a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) has died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation. Thirty-two patients incurred adverse events in follow-up. Small sample size, no control group, short duration follow-up. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, and not optimally comparative. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
RCT (clinical)				
Beigel [87]; RCT; 2020	541 were assigned to the remdesivir group and 522 to the placebo group; 1063; mean 58.9 ± 15; 64.3% male	Hypertension 49.6%, obesity 37%, diabetes 29.7%; not reported clearly	Those who received remdesivir showed a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).	Low; Moderate[3] See Figure 5
Wang [60]; RCT; 2020	IV remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) n=158 vs the same volume of placebo n=79 infusions for 10 days	Hypertension 43%, diabetes 23.7%, CHD 7.2%; interferon alfa-2b 32.2%, lopinavir–ritonavir 28.4%, antibiotics 91.1%, corticosteroids 65.6%	Researchers reported that remdesivir use was not associated with a significant difference in time to clinical improvement (HR 1.23 [95% CI 0.87–1.75]); remdesivir patients had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (HR 1.52 [0.95–2.43]); 102 (66%) of 155 remdesivir recipients had adverse events relative to 50 (64%) in 78 placebo recipients; remdesivir was stopped early due to adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early; 22 persons died in the treatment group vs 10 in the control group. Note: randomization and allocation concealment appear much better than traditional COVID-19 methods; however, insufficient statistical power to detect real differences in the outcomes (50% power instead of the needed 80% power), heavy death in treatment and control of about 14% of patients and its a huge problem; numerically higher death in remdesivir; 22 deaths vs 10 deaths; this patient group were not as sick, not as ill to begin with and so this should have meant not many deaths for they were not ill, not many on mechanical ventilation (approx. 1% to start); and so the patients should have had less bad outcomes; the remdesivir group of patients suffered many deaths (22) and it could have been remdesivir and as such, longer terms RCTs with larger sample sizes (adequately powered) are urgently needed; in addition, there were many adverse effects in the group on remdesivir; 102 patients or 66% in the remdesivir group had adverse effects.	Low; Moderate[3]
Goldman [91]; RCT (open-label); 2020	200 patients for 5 days and 197 for 10 days (200 mg of remdesivir on day 1, followed by 100 mg of remdesivir once daily for the	Diabetes 22.6%, hyperlipidemia 22.4%, hypertension 49.8%, asthma 12.3%; not clearly	Deaths n=16 vs 21 (5 vs 10 days treatment); at baseline, patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group (p=0.02); at day 14, a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients	Low; Moderate[3]

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	subsequent 4 or 9 days. Both treatment groups continued supportive therapy at the discretion of the investigator throughout the duration of the trial); 397; median 5 days 61 (50-69) vs 10 days 62 (50-71); 63.7%	reported.	in the 5-day group and in 54% in the 10-day group; after adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to that among patients in the 5-day group (p=0.14); the most common adverse events were nausea (9% of patients), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).	
Chloroquine/hydroxychloroquine **Studies appears to show no significant benefit in reducing mortality or other primary outcomes** **The effectiveness is being evaluated in various randomized clinical trials.** **Cardiovascular adverse events should be closely monitored** **(see GRADE Table and Figure in appendix)**				
RCT (clinical)				
Chen [12]; RCT; 2020	Hydroxychloroquine (HCQ) 400 mg per day for 5 days vs control (conventional treatment); 30 (15:15); 48.5 mean; 70%	None reported; nebulization with interferon alpha, and 80% patients in the experimental group received abidol vs 66.7% in control, 2 received lopinavir / ritonavir.	Nucleic acid of throat swabs was negative in 13 (86.7%) HCQ cases and 14 (93.3%) cases in the control group (*P*>0.05), median duration from hospitalization to virus nucleic acid negative conservation was 4 (1-9) days in HCQ group, which is comparable to that in the control group [2 (1-4) days, median time for body temperature normalization in HCQ group was 1 (0-2) after hospitalization, which was also comparable to that in the control group 1(0-3), radiological progression was shown on CT images in 5 cases (33.3%) in the HCQ group and 7 cases (46.7%) in the control group. Researchers concluded that the standard dose of hydroxychloroquine sulfate does not show clinical effects in improving patient symptoms and accelerating virological suppression. Note: sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, and imbalanced co-treatment assignment.	High; Very low certainty[1] See Figure 1, Table 1
Chen[13]; RCT; 2020	5-day HCQ (n=31) (400 mg/d), control (n=31) received SoC; 62; 44.7 mean (SD 15.3); 46.8%	None reported; none reported	Body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group (mean days and SD was 2.2 (0.4) in the HCQ groups vs 3.2 (1.3) in the control, p=0.0008. They also reported a greater proportion of patients with improved pneumonia (on chest CT) in the HCQ treatment group (80.6%, 25 of 31) relative to the control group (54.8%, 17 of 31). Four patients in the control group developed severe illness (none in the treatment group) and there were 2 mild adverse events in the HCQ group. Note: the study group was generally younger, and the illness was mild on entry, suggestive that this was not an overly ill group to begin with and patients may have recovered on their own. No accounting of whether patients were taking any other medications prior to study entry or during the study; sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, and imbalanced co-treatment assignment.	High; Very low certainty[1]
Huang [14]; RCT; 2020	Twice-daily oral of 500 mg Chloroquine (n=10) versus 400/100mg Lopinavir/Ritonavir (n=12) for 10 days; 22; 44.0 mean (36.5 to 57.5); 59.1%	None reported; none reported	Using RT-PCR, on day 13, all patients in the chloroquine group were negative, and 11 of 12 in the control group (lopinavir/ritonavir) were negative on day 14. Via lung CT on day 9, 6 patients in chloroquine group achieved lung clearance versus 3 in the comparison group. At day 14, the rate ratio based on CT imaging from the Chloroquine group was 2.21, 95% CI 0.81-6.62) relative to the control group. Five patients in the chloroquine group had adverse events versus no patients in the control group. Note: this small RCT appeared to show better effectiveness of chloroquine over lopinavir/ritonavir in moderate to severely ill	High; Very low certainty[1]

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			COVID-19 patients; plagued with sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, and use of active comparator with uncertain treatment effectiveness against COVID-19.	
Silva Borba[15]; RCT; 2020	CQ (600mg CQ twice daily for 10 days or total dose 12g); or low dose CQ (450mg for 5 days, twice daily only on the first day, or total dose 2.7g); 81 (41 high doses vs 40 low dose); 51; 75	Hypertension 46.2%, diabetes 25.9%, alcoholism 26%, heart disease 9.2%, asthma 6.2%, CKD 7.5%, rheumatic disease 5.6%, liver disease 3.7%, TB 3.7%, HIV/AIDS 1.9%; corticosteroids 5.4%, ACE inhibitors 10.3%, oseltamivir 89.6%	There were 11 deaths (13.5%) in high dose and low dose users; the high dose CQ arm presented more QTc>500ms (25%), and a trend toward higher lethality (17%) than the lower dosage. Fatality rate was 13.5% (95%CI=6.9–23.0%), overlapping with the CI of historical data from similar patients not using CQ (95%CI=14.5-19.2%). In 14 patients with paired samples, respiratory secretion at day 4 was negative in only one patient; preliminary findings suggest that the higher CQ dosage (10-day regimen) should not be recommended for COVID-19 treatment because of its potential safety hazards. Note: sub-optimal randomization with randomization occurring before laboratory confirmation of SARS-CoV-2 infection, small sample size, small event number, and comparison of dose-comparison concurrent trial without a placebo control.	Low-moderate; Moderate certainty[3]
Tang[16]; RCT; 2020	HCQ (a loading dose of 1, 200 mg daily for three days followed by a maintained dose of 800 mg daily for the remaining days) vs SoC; 150; mean 46.1±14.7; 54.7%	Diabetes 14.0%, hypertension 6%, others 31%; 80 patients used other drugs after randomization (not clearly reported)	The overall 28-day negative conversion rate was not different between SOC plus HCQ and SOC group (85.4% versus 81.3%, p=0.34). Negative conversion rate at day 4, 7, 10, 14 or 21. A significant efficacy of HCQ on alleviating symptoms was observed (HR, 8.83, 95%CI, 1.09 to 71.3). There was a significantly greater reduction of CRP (6.98 in SOC plus HCQ versus 2.72 in SoC, milligram/liter, p=0.045) conferred by the addition of HCQ, which also led to more rapid recovery of lymphopenia, albeit no statistical significance. Adverse events found in 8.8% of SoC and 30% of HCQ recipients with two serious adverse events in the HCQ group. Note: sub-optimal randomization, allocation concealment, no blinding, small sample size, small event number, and comparison of dose-comparison concurrent trial without a placebo control.	High; Low certainty[1]
Barbosa[28]; quasi-RCT; 2020 (submitted to NEJM for peer review, abstract form and available in the referenced blog)	HCQ + supportive care vs supportive care alone; 63 (32 HCQ vs 31 control);	Not reported; not reported (will be updated as the authors published in full)	HCQ administration was associated with worse outcomes. Note: this paper was cited on a blog and appears to be a released paper submitted to NEJM; we felt the data is important as shed important light but we do not wish this reference or material to be cited out of regard to the originating authors; what we include we have taken from the blog as referenced (https://blogs.sciencemag.org/pipeline/about-derek-lowe)	High; Low certainty[1]
Horby [101]; RCT; 2020	RECOVERY Trial, 1542 patients were randomised to hydroxychloroquine and compared with 3132 patients randomised to usual care alone; not clearly reported and will be updated as the manuscript is published.		There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10). There was also no evidence of beneficial effects on hospital stay duration or other outcomes. Researchers reported that the data convincingly rule out any meaningful mortality benefit of hydroxychloroquine in patients hospitalised with COVID-19. The RECOVERY trial has shown that hydroxychloroquine is not an effective treatment in patients hospitalised with COVID19. Note: Unclear thus far; will be updated as the study is published in full	High; Low certainty[1] This assessment is based on the full authored peer-reviewed manuscript not yet being available.
Boulware [107]; RCT; 2020	Postexposure prophylaxis with hydroxychloroquine after exposure to Covid-19, HCQ (n=441) vs placebo (n=407); 821; median HCQ	Hypertension 12.1%, 7.6%; not reported	No deaths were reported for either group; incidence of new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was −2.4 percentage points (95%	Low-moderate; Moderate certainty[3]

	41 (33-51), placebo 40 (32-50); 48.2% male		confidence interval, −7.0 to 2.2; P=0.35). Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%); no serious adverse reactions were reported. Note: relatively larger sample size, small events, randomization and concealment much more adequate than usually seen in COVID-19 research	
OBSERVATIONAL (clinical)				
Gautret[17]; observational (open-label non-randomized trial); 2020	HCQ 600 mg daily 6 d n=26 (AZ added depending on clinical presentation); 42; 26 HCQ, 16 control; 45.1 ± 22.0 (mean/SD); 41.7%	None reported; none reported	Researchers reported that 6 patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D 6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin (Z-Pak) added to hydroxychloroquine was significantly more efficient for virus elimination. Researchers concluded that hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure. Note: clinical follow-up and occurrence of side-effects were not discussed in the paper; non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Gautret[18]; observational (uncontrolled non-comparative observational study); 2020	200 mg of HCQ three times per day for ten days combined with AZ (500 mg on D1 followed by 250 mg per day for the next four days); 80; 52.5 median, 52.5%	Cancer 6.3%, diabetes 11.2%, CAD 7.5%, hypertension 16.3%, chronic respiratory disease 10%, obesity 5%; immune-suppressive treatment 5%, non-steroid anti-inflammatory treatment 2.5%	Nasopharyngeal viral load tested by qPCR and negative on day 8 was found in 93.7% of patients, not contagious (with a PCR Ct value<34) at day 10 was found in 98.7%, negative virus cultures on day 5 was found in 98.7%, and length of stay in ICU (days) was a mean 4.6 days ± 2.1 SD (n=65). Researchers reported that patients were rapidly discharged from highly contagious wards with a mean length of stay of five days. Note: this study was judged to be at high risk of biased estimates due to it being a case-series observational study with no control group. Based on reporting, the cohort appears to be younger and the NEWS risk scoring system placed them all at very low risk of deteriorating, leaving one to speculate on if they would have recovered on their own. This group appears to be COVID-19 patients with mild illness. Patients may have recovered on their own; non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Molina[19]; observational (narrative review); 2020	HCQ 600 mg/d for 10 days and AZ 500 mg Day 1 and 250 mg days 2 to 5; 11; 58.7 mean, 64%	None reported; none reported	One patient, hydroxychloroquine and azithromycin were discontinued after 4 days because of a prolongation of the QT interval from 405 ms before treatment to 460 and 470 ms under the combination; They report that in the 10 living patients, repeated nasopharyngeal swabs were positive for COVID-19 RNA in 8 of the 10 patients (80%) at days 5 to 6 following treatment initiation. Researchers also questioned the one death and 3 ICU transfers[14] that suggest a worsening clinical outcome. They conclude that there is "no evidence of a strong antiviral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment of our hospitalized patients with severe COVID-19".	High; Very low certainty[1]

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			Note: this was a small consecutive series of patients followed to describe the response to the treatment, high risk of biased estimates; non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	
Lane[20]; network cohort and case-series; 2020	Network cohort and self-controlled case series study that involved 956,374 and 310,350 users of HCQ and sulfasalazine, and 323,122 and 351,956 users of HCQ-azithromycin and HCQ-amoxicillin.	ARDS 58%, COPD 5%, depression 14.5%, diabetes 13.2%, hyperlipidemia 30%, pneumonia 5.7%, renal impairment 4.2%, UTI 14.2%	Data comprised 14 sources of claims data or electronic medical records from Germany, Japan, Netherlands, Spain, UK, and USA. Researchers found no excess risk of SAEs was when 30-day hydroxychloroquine and sulfasalazine use were compared. However, when azithromycin was added to hydroxychloroquine, researchers reported an increased risk of 30-day cardiovascular mortality HR 2.19 (95% CI 1.22-3.94), chest pain/angina HR 1.15 (95% CI 1.05-1.26), and heart failure HR 1.22 (95% CI 1.02-1.45)). The conclusion was that short-term hydroxychloroquine treatment was safe, but when azithromycin is added, it can induce heart failure and cardiovascular mortality, likely due to synergistic effects on QT length. Researchers urged caution in the use of this combination in COVID-19. Note: very confusing methods, non-randomized, confounded, not optimally comparative (e.g. comparison of hydroxychloroquine compared to hydroxychloroquine with azithromycin was not reported), sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
Chorin[21]; observational (retrospective cohort study); 2020	HQC plus azithromycin; 84; mean 63 ±15; 74%	CAD 11%, hypertension 65%, CKD 7%, diabetes 20%, COPD 8%, congestive heart failure 2%; Levofloxacin, Lopinavir/Ritonavir, or Tacrolimus 8%, Norepinephrine, Phenylephrine, or Vasopressin 13%, Amiodarone 7%	The QTc was prolonged maximally from baseline (days 3-4) and in 25 patients, the QTc increased more than 40ms. They also found that in 9 patients (11%), the QTc increased to >500 ms, indicative of a high-risk group for malignant arrhythmia and sudden cardiac death. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Mahévas[22]; observational (retrospective cohort study); 2020	HCQ at a daily dose of 600 mg in the first 48 hours after hospitalisation vs no HCQ; 181; median 60 years (IQR 52 to 68 years); 71.1% Note: in the HCQ group, 20% received concomitant azithromycin	Respiratory disease 11%, heart failure 3.3%, hypertension (cardiovascular illnesses) 51.9%, diabetes 8.3%, CKD 5%, immuno-depression 11.6%; none reported	In terms of deaths or transfer to the ICU, 19% vs 21.6% occurred in the HCQ vs no HCQ groups respectively (RR 0.93 (0.48 to 1.81)), for day 7 mortality, 3.6% died in HCQ group vs 4.1% in the no-HCQ group (RR 0.61 (0.13 to 2.90)), occurrence of acute respiratory distress syndrome, 28.6% occurred in HCQ group vs 24.1% in no HCQ group (RR 1.15 (0.66 to 2.01)); in the 84 patients receiving HCQ within the first 48 hours, 8 (9.5%) experienced ECG modifications requiring HCQ discontinuation at a median of 4 days (3-9) after it began. Researchers report that the results do not support HCQ use in patients admitted to hospital with covid-19 who require oxygen Note: one of the stronger methodologies from among COVID-19 research releases; inverse probability of treatment weighting (IPTW) approach was used to closely approximate randomisation and try to balance the differences in baseline prognostic variables between treatment groups; some potentially important prognostic variables were not balanced in the modelling; overall, nonrandomized, confounded, optimal adjustments and steps such as masking not applied, small	Low-moderate; Very low certainty[1]

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			sample size, small events, and not optimally comparative. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	
Magagnoli[42]; observational (retrospective analysis study); 2020	One of three cohorts based on medication exposure to hydroxychloroquine (HC) and azithromycin (AZ): 1) HC-treated (97); 2) HC- and AZ-treated (113); or 3) HC-untreated (158), all received standard support care; 368; median age (IQR) HC 70 (60-75), HC + AZ 68 (59-74), no HC 69 (59-75); 100%	Hyperlipidemia 15.7%, asthma 5.9%, 4.9%, congestive heart failure 20.4%, peripheral vascular disease 17.4%, cerebrovascular disease 12.8%, COPD 19.6%, diabetes 67.6%, renal disease 25%, cancer 16%, liver disease 1.1%; ACE inhibitor 13.9%, ARBs 8.9%	27 deaths (27.8%) HC group, 25 deaths (22.1%) HC+AZ group, 18 deaths (11.4%) no HC group, mechanical ventilation in 13.3% HC group, 6.9% HC+AZ group, and 14.1% no HC group (Table 4). Relative to the no HC group, there was higher risk of death from any cause in HC group (adjusted HR, 2.61; 95% CI, 1.10 to 6.17; p=0.03) but not in HC+AZ group (adjusted HR, 1.14; 95% CI, 0.56 to 2.32; P=0.72), no significant difference in the risk of ventilation in either the HC group (adjusted HR, 1.43; 95% CI, 0.53 to 3.79; p=0.48) or the HC+AZ group (adjusted HR, 0.43; 95% CI, 0.16 to 1.12; p=0.09), compared to the no HC group; no evidence that HCQ, with or without AZ, reduced the risk of mechanical ventilation and an association of increased overall mortality in HCQ alone. Note: adjusted for a large number of confounders including comorbidities, medications, clinical and laboratory abnormalities; however, even with propensity score adjustment for a large number of relevant confounders, one cannot discount the potential of selection bias or residual confounding; 100% male with median age was over 65 years, so not applicable directly to women or younger hospitalized populations; most were black; small sample size, small events number, though reporting was an improvement over COVID-19 reporting in general. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Ramireddy[57]; observational case-series; 2020	HCQ 10%, Azithromycin 28%, both 62%; 98; mean age 62±17; 61% Note: 73 patients COVID-19 positive and 25 suspected	Heart failure 20%, hypertension 60%, diabetes 22%, CKD 14%, COPD 26%; none reported	Significant prolongation was observed only in males (18±43 ms vs -0.2±28 ms females, p=0.02); researchers reported 12% of patients reached critical QTc prolongation, multivariable logistic regression, age, sex, Tisdale score, Elixhauser score, and baseline QTc were not associated with critical QTc prolongation (p>0.14). HCQ + AZ revealed the greatest changes in QTc relative to each drug; changes were highest with combination treatment relative to either drug, with many-times greater prolongation using combination vs. azithromycin alone (17±39 vs. 0.5±40 ms, p=0.07); researchers reported that no patients experienced torsades de pointes. Note: pre-publication and not yet peer-reviewed, nonrandomized, potentially confounded even with adjustments, small sample size, sub-optimal reporting. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Mathian [62]; case-series; 2020	HCQ treatment in SLE patients; 17; median age 53.5 (26.6–69.2); 23%	CHD 12%, cerebrovascular disease 18%, hypertension 35%, cancer 6%, COPD 12%, CKD 47%; prednisone 71%, ACE inhibitors 35%, anticoagulants 29%	HCQ did not prevent COVID-19 in severe forms, in patients with SLE. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data in this SLE patient group with SARS-CoV-2 infection is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Yu [63]; observational (retrospective); 2020	HCQ for 7–10 days (200 mg twice per day) vs no HCQ (basic treatment); all 568 critically ill COVID-19 patients who were confirmed	Hypertension 44%, CHD 10.4%, COPD 2.8%, diabetes 17.1%;	Died=247 patients, 8 in HCQ and 238 in non-HCQ; time of hospital stay before patient death was 15 (10 to 21) days and 8 (4 to 14) days for the HCQ and NHCQ groups, respectively (p<0.05). The level of inflammatory cytokine IL-6 was significantly lowered from 22.2 (8.3 to 118.9) pg/mL at the	Moderate to high; Very low certainty[1]

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	by pathogen laboratory tests; median 68 (57-76); 63% Note: HCQ age 68 (60-75) vs 68 (57-77)		beginning of the treatment to 5.2 (3.0 to 23.4) pg/ml ($p<0.05$) at the end of the treatment in the HCQ group but there is no change in the NHCQ group; researchers concluded that HCQ seemed to play a role in decreased mortality in critically ill patients with COVID-19 via a role in mitigating the inflammatory cytokine storm. Note: nonrandomized, small sample sized and events (especially in HCQ group), not optimally comparative; conducted adjusted analysis (Cox regression) including baseline drugs, but still cannot account for all known and unknown confounders; methods were sub-optimal but an improvement over the general methods across COVID19 and the reporting was not optimal but still an improvement.	
Chorin [64]; observational case-series; 2020	HCQ/Azithromycin combination; 251; 64 +-13; 75% Note: HCQ orally at 400 mg BID for one day (loading dose) followed by 200 mg BID for 4 days. Azithromycin orally at a dose of 500 mg daily for 5 days.	CAD 12%, hypertension 54%, CKD 115, diabetes 27%, COPD 7%, congestive heart failure 3%; not reported	Researchers reported that QTc was prolonged in parallel with increasing drug exposure and incompletely shortened following its completion; of concern was the extreme new QTc prolongation to > 500 ms which is an established marker of high risk for TdP and this developed in 15.9% of patients; reporting suggested that 1 patient developed TdP requiring emergent cardioversion and 7 patients required premature termination of therapy; HCQ combined with azithromycin macrolide significantly prolonged the QTc in patients with COVID-19 and the prolongation may be responsible for life threating arrhythmia in the form of TdP. Note: nonrandomized, confounded, some logistic regression adjustments employed but optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes; weaker evidence but raises concern about the combination of HCQ and AZ. Note, adjusted analysis is an improvement over unadjusted analysis whereby the estimates are very unreliable but still is unable to adjust for all unknown confounders.	High; Very low certainty[1]
Mallat [66]; observational retrospective cohort; 2020	HCQ; 34 (23 HCQ vs 11 non-HCQ); median age 37; 73.5% male	Asthma 8.8%, diabetes 5.9%, hypertension, 14.7%, malignancy 8.8%, chronic heart failure 2.95, chronic kidney disease 29%; immunosuppressive 2.9%, NSAID 11.8%	Researchers reported that HCQ treatment was independently associated with longer time to SARS-CoV-2 test negativity; at day 14, virologic clearance was significantly higher in patients who did not receive HCQ, and HCQ treatment did not result in improvement of inflammatory markers or lymphopenia rate. Note: nonrandomized, confounded, steps such as masking not applied, small sample size, small events, adjustment could not control for all unknown confounders and did not adjust for key prognostic variables, sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
Huang [67]; observational prospective; 2020	197 CQ patients and 176 patients as historical controls; 373; mean age 44.78; 46.9% male	Hypertension 6.4%, diabetes 2.4%; not reported	53 adverse events in CQ vs 57 in non-CQ group; time to undetectable viral RNA, median no. of days (IQR) CQ 3.0 (3.0, 5.0) vs non-CQ 9.0 (6.0, 12.0) (absolute difference in medians -6.0 days; 95% CI -6.0 to -4.0); length of hospital stay, median no. of days (IQR) CQ 19.0 (16.0, 23.0) vs non-CQ 20.0 (15.8, 24.0). Note: nonrandomized, confounded, sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
Membrillo et al. [69]; observational cohort; 2020	166 patients, HCQ 123 and 43 no HCQ; 166; mean age HCQ 61.5 (16.2) vs 68.7 (18.8) non HCQ; 62% male	Hypertension 42.7%, diabetes 17.4%, cardiopathy 22.2%, malignancy 13.8%, pulmonary disease 14.4%, dyslipidaemia	Hydroxychloroquine treatment was associated with an increase in the mean cumulative survival; HCQ group 22% vs 48.8%; mean hospital stay days mean 6 (SD 5) HCQ vs 5 (7) non HCQ group; median (IQR) from symptoms begin to the start of treatment with HCQ: 7(6) days.	High; Very low certainty[1]

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		28.3%; none reported	Note: nonrandomized, confounded design, small sample sized, small number of events, plagued by selection bias, residual confounding bias.	
Geleris [71]; observational prospective; 2020	HCQ (n=811) vs no HCQ (n=565), HCQ 600 mg twice on day 1, then 400 mg daily for a median of 5 days; n=118 <40 yrs, n=287 40-59 yrs, n=485 60-79 yrs, and n=206 >=80 yrs, 58.5% males (propensity score matched HCQ 811 vs 274 matched controls	Chronic lung disease 17.9%, diabetes 36.4%, hypertension 50.1%, cancer 13.2%, chronic kidney disease 17.8%, transplantation, HIV infection, or immune-suppressive medications 4.7%; statin 38.5%, ACEi or ARBs 29.5%, corticosteroid 23.7%, anticoagulant 9.2%, azithromycin 54.1%, antibiotic 72.5%, tocilizumab 6.2%, remdesivir 2.5%	Primary end point of respiratory failure developed in 346 patients (25.1%); 180 patients were intubated; 166 died without intubation; in unadjusted analysis, patients who had received hydroxychloroquine were more likely to have had a primary end-point event than were patients who did not (HR 2.37; 95% CI 1.84 to 3.02); there was no significant association between hydroxychloroquine use and the composite primary end point (HR 1.04; 95% CI 0.82 to 1.32); there was no significant association between treatment with azithromycin and the composite end point (HR 1.03; 95% CI 0.81 to 1.31). Researchers concluded that results do not support the use of hydroxychloroquine unless within confines of randomized clinical trials testing. Note: nonrandomized, potentially confounded design, decent sample sized though control group markedly smaller, small number of events, compositive end-point (time to intubation or death), plagued by selection bias, residual confounding bias even with propensity-score matching and adjustment (these steps strengthen the weaker nonrandomized design but still is unable to correct for selection and residual confounding/confounded by indication biases).	Low-moderate; Very low certainty[1]
Carlucci [72]; observational retrospective; 2020	n=411 HCQ (400 mg load followed by 200 mg twice daily for five days) plus Azithromycin (500 mg once daily) plus zinc (220 mg capsule containing 50 mg elemental zinc twice daily for five days) plus SoC vs n=521 HCQ plus Azithromycin plus SoC; mean age zinc 63.19 + 15.18 vs no zinc 61.83 + 15.97; 63% males	Hypertension 38.8%, hyperlipidemia 26.5%, CAD 8.2%, heart failure 5.1%, COPD 11.3%, diabetes 25.2%, cancer 6%, CKD 9.7%, BMI zinc 29.17 (25.8-33.42) vs no zinc 29.29 (25.77-33.2); NSAID 13.6%, anticoagulant 97%, ACE or ARB 33.5%, corticosteroid 9.3%, beta blocker 23.9%	Reporting suggested that zinc did not impact the length of hospitalization, duration of ventilation, or ICU duration; based on univariate analyses, zinc sulfate increased the frequency of patients being discharged home (p=0.003), and decreased the need for ventilation (p=0.014), admission to the ICU (p=0.004), and mortality (p<0.0001) or transfer to hospice (p=0.004) for patients who were never admitted to the ICU. Adjusted comparison of categorical hospital outcomes when zinc sulfate was added, an increased frequency of being discharged home (OR 1.53, 95% CI 1.12-2.09, p=0.008) reduction in mortality (p=0.002) or transfer to hospice remained significant (OR 0.449, 95% CI 0.271-0.744, p=0.002). Note: nonrandomized, potentially confounded design, decent sample sized, roughly small number of events in terms of OIS, compositive end-point (hospice/death), plagued by selection bias, residual confounding bias even with the adjusted analysis (these steps strengthen the weaker nonrandomized design but still is unable to correct for selection and residual confounding/confounded by indication biases).	Low-moderate; Very low certainty[1]
Davido et al. [74]; observational retrospective; 2020 RETRACTED	Day 1 with 800 mg/day was administered followed by maintenance dose of 400 mg/day up to 600 mg/day in case of obesity (body mass index (BMI) > 30) for a total 10 days plus 500 mg of azithromycin was prescribed the first day, followed by 250 mg for 4 days n=45 vs other treatments (n=87) azithromycin alone (n=28) lopinavir/ritonavir (n=14) no targeted therapy (n=36) HCQ+AZI <48 hours (n=9) before achieving the primary outcome; 132; mean 58.6	Cardiovascular disease 45.1%, COPD 16.6%, diabetes 18.9%, CKD 3%, obesity 10.6%, immunodepression 8.3%; not reported clearly.	Researchers reported that 91.1% of cases who received HCQ and AZ had a favourable outcome (OR=6.2, p=0.002) versus others regimen (n=87); for patients that needed transfer to ICU (n=27) (for mechanical ventilation), median delay for transfer was 2 days (IQR 1-3); there was one case with an adverse event (a prolonged QT interval on EKG) in which HCQ was stopped. Note: nonrandomized, potentially confounded design (though there is adjustment but not optimal), small sample sized (n=132), small number of events, plagued by selection bias, residual confounding bias.	High; Very low certainty[1]

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	years; 65% males			
Rosenberg [75]; observational retrospective; 2020	HCQ + AZ vs HCQ alone vs AZ alone, or neither alone; 735 (51.1%) received hydroxychloroquine + azithromycin, 271 (18.8%) received hydroxychloroquine alone, 211 (14.7%) received azithromycin alone, and 221 (15.4%) received neither drug; 1438; Median patient age was similar in the 4 groups (hydroxychloroquine + azithromycin, 61.4 years; hydroxychloroquine alone, 65.5 years; azithromycin alone, 62.5 years; and neither drug, 64.0 years; 59.6% male	Obesity 30.5%, cancer 3.8%, kidney disease 13%, diabetes 35%, cardiovascular disease 30.4%; none reported clearly	Patients receiving hydroxychloroquine, azithromycin, or both were more likely than those not receiving either drug to have diabetes, respiratory rate >22/min, abnormal chest imaging findings, O_2 saturation lower than 90%, and aspartate aminotransferase greater than 40 U/L; the overall in-hospital mortality was 20.3% (95% CI, 18.2%-22.4%); the risk of death for patients receiving HCQ + AZ was 189/735 (25.7% [95% CI, 22.3%-28.9%]), HCQ alone, 54/271 (19.9% [95% CI, 15.2%-24.7%]), AZ alone, 21/211 (10.0% [95% CI, 5.9%-14.0%]), and neither drug, 28/221 (12.7% [95% CI, 8.3%-17.1%]); compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving HCQ + AZ (HR, 1.35 [95% CI, 0.76-2.40]), HCQ alone (HR, 1.08 [95% CI, 0.63-1.85]), or AZ alone (HR, 0.56 [95% CI, 0.26-1.21]); compared with patients receiving neither drug cardiac arrest was significantly more likely in patients receiving HCQ + AZ (adjusted OR, 2.13 [95% CI, 1.12-4.05]), but not HCQ alone (adjusted OR, 1.91 [95% CI, 0.96-3.81]) or AZ alone (adjusted OR, 0.64 [95% CI, 0.27-1.56]); a greater proportion of patients receiving HCQ + AZ experienced cardiac arrest (15.5%) and abnormal ECG findings (27.1%), as did those in the HCQ alone group (13.7% and 27.3, respectively), compared with AZ alone (6.2% and 16.1%, respectively) and neither drug (6.8% and 14.0%, respectively); there were no significant differences in the relative likelihood of abnormal electrocardiogram findings. Note: nonrandomized, potential residual confounding, confounded by indication, small sample size and events in certain groups, patients were selected by hospital-stratified random sampling; potential confounders such as inflammatory markers associated with severity of COVID-19 in prior studies were not frequently measured and thus not available for modeling; adjusted analysis was a step in the right direction and the methods used in this observational study is somewhat improved from the typical COVID-19 research methods	Low-moderate; Very low certainty[1]
Million [81]; observational retrospective; 2020	SARS-CoV-2 positive tested patients treated for at least three days with the following regimen: HCQ (200 mg three times daily for ten days) + AZ (500 mg on day 1 followed by250 mg daily for the next four days); 1061; mean age 43.6 (15.6); 46.4%	Cancer 2.6%, diabetes 7.4%, CAD 4.3%, hypertension 14%, respiratory illness 11.5%, obesity 5.8%; diuretics 3.3%, metformin 1.9%, selective beta blocking agents 3.2%, dihydropyridine derivatives 3.2%, angiotensin II receptor blockers 3.8%, HMG CoA reductase 3.6%	Prolonged viral carriage was observed in 47 patients (4.4%) and was associated with a higher viral load at diagnosis ($p < 0.001$) but viral culture was negative at day 10; all but one, were PCR-cleared at day 15; poor clinical outcome (PClinO) was observed for 46 patients (4.3%) and 8 died (0.75%) (74–95 years old). All deaths resulted from respiratory failure and not from cardiac toxicity. Five patients are still hospitalized (98.7% of patients cured so far). PClinO was associated with older age (OR 1.11), severity of illness at admission (OR10.05) and low HCQ serum concentration. PClinO was independently associated with the use of selective beta-blocking agents and angiotensin II receptor blockers ($p < .05$). A total of 2.3% of patients reported mild adverse events (gastrointestinal or skin symptoms, headache, insomnia and transient blurred vision). Note: nonrandomized, selection bias, potential residual confounding, confounded by indication, some adjustment conducted but not optimal and not controlling for all unknown confounding factors, small sample size and events in certain groups	Low-moderate; Very low certainty[1]
Singh [83]; observational retrospective (propensity-matched); 2020	Propensity matched, HCQ (n=910) vs no HCQ (n=910); 1820; mean age HCQ 62.17±16.81 vs no 62.55±17.62; 54.4% males	Hypertension 61.5%, diabetes 35.2%, obesity 30%, ischemic heart disease 28.8%,	Treatment Hydroxychloroquine vs Control (Matched Cohorts) Mortality 30-Day treatment 11.43% (104) vs control 11.98% (109) RR 0.95 (0.74-1.23); Treatment Hydroxychloroquine combined with Azithromycin vs. Control (Matched Cohorts) Mortality treatment 12.27% (86) vs control 10.27% (72) RR	Moderate-high; Very low certainty[1]

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		kidney disease 32.4%, heart failure 18.6%, prolonged QT interval 2.5%, COPD 14.2%, cerebrovascular 14.9%, asthma 13.1%, liver disease 9.9%	1.19 (0.89-1.60); treatment hydroxychloroquine vs control (matched cohorts) mechanical ventilation treatment 5.05% (46) vs control 6.26% (57) RR 0.81 (0.55-1.18); the analysis of a large retrospective cohort of hospitalized COVID-19 patients treated with HCQ did not show benefits in mortality or the need for mechanical ventilation when compared to a matched cohort of patients who did not receive HCQ. Note: nonrandomized, selection bias, potential residual confounding, confounded by indication, some matching adjustment conducted but not optimal; all unknown confounding factors uncontrolled for, small sample size	
Yu [84]; observational retrospective; 2020	HCQ vs no HCQ (48 vs 502); 550; median 68 (59–77); 62.5% male	Hypertension 45.8%, CHD 10.7%, COPD 2.9%, diabetes 17.1%; not clearly reported	Deaths HCQ 9/48 (18,8%) vs 238/502 (47.4%) p<0.001; Hospital stay time before death (d) HCQ 15 (10–21) vs 8 (4–14) p= 0.027 Note: nonrandomized, confounded, adjusted analysis but not fully optimal, small events, sub-optimal reporting of methods and outcomes.	Moderate-high; Very low certainty[1]
Mehra [86]; observational retrospective; 2020 RETRACTED	One of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide) vs control group with none of the drugs; 96,032 whereby 14 888 patients were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 81 144 patients were in the control group; 53·8 years (SD 17·6); 53.7% male	29, 510 [30·7%] were obese with BMI ≥30 kg/m², 64220 (66·9%) were white, 9054 (9·4%) were black, 5978 (6·2%) were Hispanic, and 13 519 (14·1%) were of Asian origin (appendix p 4). In terms of comorbidities, 30 198 (31·4%) had hyperlipidaemia, 25 810 (26·9%) had hypertension, 13 260 (13·8%) had diabetes, 3177 (3·3%) had COPD, 2868 (3·0%) had an underlying immunosuppressed condition; 12 137 (12·6%) had coronary artery disease, 2368 (2·5%) had a history of congestive heart failure, and 3381 (3·5%) had a history of arrhythmia; use of other antivirals was recorded in 38 927 (40·5%) patients as treatment for COVID-19. The most common antivirals were lopinavir with ritonavir (12 304 [31·6%]), ribavirin (7904 [20·3%]), and oseltamivir (5101	10698 (11·1%) patients died in hospital; control group (n=81 144) 7530 (9·3%) deaths, Chloroquine (n=1868) 307 (16·4%) deaths, Chloroquine with macrolide* (n=3783) 839 (22·2%) deaths, Hydroxychloroquine (n=3016) 543 (18·0%) deaths, Hydroxychloroquine with macrolide* (n=6221) 1479 (23·8%) deaths; after controlling for multiple confounding factors (age, sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), when compared with mortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% CI 1·223–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·218–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated with an increased risk of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6·1%; 2·369, 1·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; 3·561, 2·760–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalisation. Note: nonrandomized, confounded, adjusted analysis but not fully optimal though a very strong approach methods wise in the adjustment but adjustment cannot adjust for all unknown confounders	Low-moderate; Very low certainty[1]

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		[13·1%]).		
Ip [89]; observational retrospective; 2020	HCQ vs no-HCQ (Hydroxychloroquine, 2) Hydroxychloroquine in combination with Azithromycin, 3) Azithromycin alone, and 4) neither drug); 2,512; median 64 (52 - 76); 62.3% males Note: 134 patients received tocilizumab in the ICU	Diabetes 32.3%, COPD 14.9%, hypertension 55.2%, coronary disease 15.8%, cancer 11.5%, renal failure 7.5%, cerebrovascular disease 4.9%, obesity 35.1%; not reported	Hospitalized patients; researchers reported that after adjusting for imbalances via propensity modeling, relative to receiving neither drug, there were no significant differences in associated mortality for patients receiving any hydroxychloroquine during the hospitalization (HR, 0.99 [95% CI, 0.80-1.22]), hydroxychloroquine alone (HR, 1.02 [95% CI, 0.83-1.27]), or hydroxychloroquine with azithromycin (HR, 0.98 [95% CI, 0.75-1.28]); the 30-day unadjusted mortality for patients receiving hydroxychloroquine alone, azithromycin alone, the combination or neither drug was 25%, 20%, 18%, and 20%, respectively; among 547 evaluable ICU patients, including 134 receiving tocilizumab in the ICU, an exploratory analysis found a trend towards an improved survival association with tocilizumab treatment (adjusted HR, 0.76 [95% CI, 0.57-1.00]), with 30 day unadjusted mortality with and without tocilizumab of 46% versus 56%. Note: nonrandomized, potentially confounded, though there is adjusted analysis via some propensity score matching, possible misclassification, small sample sizes/events limited analysis, selection bias.	Low-moderate; Very low certainty[1]
Ahmad [90]; observational, case-series; 2020	Case-series, all received HCQ and doxycycline; 54; median 68 (22-97); 61% males	Hypertension 91%, diabetes 40%, CAD 58%, CHD 18%, COPD 38%; not reported	A series of fifty-four (54) high-risk patients, who developed a sudden onset of fever, cough, and shortness of breath (SOB) and were diagnosed or presumed to have COVID-19, were started with a combination of DOXY-HCQ and 85% (n=46) patients showed clinical recovery defined as: resolution of fever and SOB, or a return to baseline setting if patients are ventilator-dependent.; 11% (n=6) of patients were transferred to acute care hospitals due to clinical deterioration and 6% (n=3) patients died in the facilities; indirect comparison suggests these data were significantly better outcomes than the data reported in MMWR (reported on March 26, 2020) from a long-term care facility in King County, Washington where 57% patients were hospitalized, and 22% patients died. Note: nonrandomized, potentially confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Bhattacharya [108]; observational cohort; 2020	Cohort 1 (n=54) all the health care workers with history of intake of at least the loading dose of hydroxychloroquine prophylaxis as per ICMR guidelines; Cohort 2 (n=52), all the health care workers either no history of HCQ prophylaxis or had history of inadequate intake of HCQ as per ICMR guidelines; 106; mean HCQ 26.46 ± 3.93, no HCQ 27.71 ± 7.24; 47% male	Comorbidities in 3.7%; not reported	The comparative analysis of incidence of infection between the two groups demonstrated that voluntary HCQ usage was associated with lesser likelihood of developing SARS-CoV-2 infection, compared to those who were not on it, X2=14.59, p<0.001. None of the HCQ users noted any serious adverse effects. Note: nonrandomized, potentially confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
Oteo [109]; observational cohort; 2020	HCQ 400 mg twice in a loading dose followed by 200 mg twice for 5 days, plus AZM 500 mg on the first day followed by 250 mg daily for	32.5% had comorbidities; not reported	Twelve patients (15%), 11 of whom had pneumonia, experienced side effects affecting mainly the digestive. In another patient a QTc interval prolongation (452 msc) was observed. In total 3 of these patients had to be admitted in the Hospital, 2 because of vomiting and 1 because a QTc interval	High; Very low certainty[1]

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	5 days; 80; median 52 (22 to 75); 47% male		lengthening. None of the patients needed to stop the HCQ or AZM and all the 80 patients finished the therapeutic strategy. From the group without pneumonia only a patient developed diarrhea that did not require hospitalization or stop the medication. Note: nonrandomized, potentially confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes.	
Magagnoli [110]; Observational retrospective; 2020	Hydroxychloroquine alone (HC) n=198 or with azithromycin (HC+AZ) n=214 or no HC as treatments n=395; median age 70; 95.6% males	Hyperlipidemia 18.2%, asthma 3%, MI 5.1%, CHF 25.3%, cerebrovascular 17.7%, pulmonary disease 23.2%, diabetes with complications 28.8%, renal disease 32.8%, cancer 17.2%, liver disease 9.1%, diabetes without complications 48.5%; NR	There were 38, 49, and 37 deaths respectively in HCQ, HCQ +AZ, and no HCQ groups; relative to the no HC group, after propensity score adjustment for clinical characteristics, the risk of death from any cause was higher in the HC group (adjusted hazard ratio (aHR), 1.83; 95% CI, 1.16 to 2.89; P=0.009) but not in the HC+AZ group (aHR, 1.31; 95% CI, 0.80 to 2.15; P=0.28). Both the propensity score-adjusted risks of mechanical ventilation and death after mechanical ventilation were not significantly different in the HC group (aHR, 1.19; 95% CI, 0.78 to 1.82; P=0.42 and aHR, 2.11; 95% CI, 0.96 to 4.62; P=0.06, respectively) or in the HC+AZ group (aHR, 1.09; 95% CI, 0.72 to 1.66; P=0.69 and aHR, 1.25; 95% CI, 0.59 to 2.68; P=0.56, respectively), compared to the no HC group; researchers reported that among patients hospitalized with COVID-19, there was no significant reduction in mortality or in the need for mechanical ventilation with hydroxychloroquine treatment with or without azithromycin. Note: Nonrandomized, confounded, and fraught with selection bias and residual confounding bias, but propensity-matching performed adjusting for comorbidities, medications, clinical and laboratory values; methodology an improvement.	High; Very low certainty[1]
Bhattacharyya [112]; observational longitudinal; 2020	HCQ was given in the dose of 400 mg twice on day one, and then 400 mg weekly for seven weeks; 391 HCWs; mean age of 34±8 years; 58.6% males	Diabetes 1.9%, respiratory disease 1.2%, kidney disease 0.3%, cardiovascular disease 1.9%, liver disease 1.2%; NR	17.5% of HCW experienced adverse events due to HCQ use. This study was a descriptive report on HCW who used HCQ when infected with COVID-19. The majority of the data is based on perceptions of use. Note: case series, single arm, nonrandomized, confounded, no adjustment, no masking or stratifications, very low certainty evidence.	High; Very low certainty[1]
Macias [113]; observational retrospective; 2020	Patients with autoimmune inflammatory diseases n=722 and 40% received HCQ n=290 vs 432 non-HCQ; median age 56 (45-65) HCQ vs 58 (48-68) no HCQ; 17.1% males	NR; NR	290 (40%) patients were receiving HCQ; during the seven-week study period, five (1.7% [95% CI: 0.5%-4.0%] cases of COVID-19 were registered among patients with hydroxychloroquine and five (1.2% [0.4%-2.7%]) (p=0.523) in without hydroxychloroquine; COVID-19 was confirmed by PCR in one (0.3%, 95% CI 0.008-1.9%) patient with hydroxychloroquine and two (0.5%, 95% CI 0.05%-1.6%) without hydroxychloroquine (p=1.0); one patient on hydroxychloroquine and two subjects without hydroxychloroquine were admitted to the hospital, none of them required to be transferred to the intensive care unit and no patient died during the episode. Researchers concluded that the incidence and severity of COVID-19 among patients with autoimmune rheumatic diseases with and without hydroxychloroquine was not significantly different. Hydroxychloroquine does not seem to be an appropriate therapy for post-exposure prophylaxis against COVID-19. Note: Nonrandomized, confounded, and fraught with selection bias and residual confounding bias.	High; Very low certainty[1]
Giacomelli [114];	LPV/r + HCQ, early	NR; remdesivir	The rate of clinical improvement increased over time to 73.3%	High;

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observational retrospective; 2020	treatment n=43 vs delayed treatment n=129; 172; median age 61.7 (50.9-72.7); 72% male	(n=33, 19.2%), tocilizumab (n=36, 20.9%) or both (n=10, 5.8%).	on day 30, without any significant difference between the two groups (Gray's test p=0.213); after adjusting for potentially relevant clinical variables, there was no significant association between the timing of the start of treatment and the probability of 30-day mortality (adjusted odds ratio [aOR] ET vs DT=1.45, 95% confidence interval 0.50-4.19); 8% of the patients discontinued the treatment because of severe gastrointestinal disorders attributable to LPV/r. The timing of the start of LPV/r+HCQ treatment does not seem to affect the clinical course of hospitalised patients with COVID-19. Together with the severe adverse events attributable to LPV/r, this raises concerns about the benefit of using this combination to treat COVID-19. Note: Nonrandomized, confounded, and fraught with selection bias and residual confounding bias.	Very low certainty[1]

Corticosteroids

One preliminary RCT (RECOVERY) appears to show benefit in those needing respiratory support
The effectiveness is being evaluated in various randomized clinical trials.

OBSERVATIONAL (clinical)

Lu[23]; observational (retrospective cohort study); 2020	Corticosteroid (methylprednisolone, dexamethasone, and hydrocortisone) vs no drug; 61 (31:31); 57.5 mean; 52%	Hypertension 45%, diabetes 17.7%, CVD 6.5%, COPD 1.5%; oseltamivir, arbidol, lopinavir/ritonavir, ganciclovir, interferon-α	28-day mortality rate was 39% (12 out of 31) in case subjects and 16% (5 out of 31) in control subjects (p=0.09). Increased corticosteroids dosage was significantly associated with elevated mortality risk (p=0.003) in matched cases after adjustment for administration duration; every ten-milligram increase in hydrocortisone dosage was associated with additional 4% mortality risk (adjusted HR: 1.04, 95% CI: 1.01-1.07). Note: nonrandomized, confounded, optimal adjustments and steps such as masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. Note: nonrandomized, confounded, optimal adjustments and steps such as masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. Note: one study (Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study) by Zhou et al.[51] reported 26 of 57 deaths in COVID-19 patients taking corticosteroids vs 28/134 deaths in those not on corticosteroids. Wu et al. [52] reported that among the patients with ARDS in a retrospective cohort study, of those who received methylprednisolone treatment, 23 of 50 (46.0%) patients died, while of those who did not receive methylprednisolone treatment, 21 of 34 (61.8%) died. Guan et al. [53] reported 5 deaths among 204 who got corticosteroids vs 10 of 895 COVID-19 patients who did not. In a retrospective observational study, Shang et al [55] reported 43 deaths in 196 COVID-19 patients who received corticosteroids vs 8 of 220 who did not.	High; Very low certainty[1] See Figure 3.
Wang[54]; observational (retrospective); 2020	Methylprednisolone (n=26) 1-2mg/kg/d for 5-7 days via intravenous injection vs no drug (n=20); median 54 (48-64); 57%	Cardiovascular disease 13%, pulmonary disease 6.5%, cerebrovascular 4.3%, malignancy 4.3%, diabetes 8.7%, hypertension 30%; antiviral therapy (a-interferon),	There were 2 deaths of 26 in the treatment group vs 1 of 20 in the control group, mean days for body temperature back to the normal significantly shorter in patients with methylprednisolone ns no drug (2.06 + - 0.28 vs. 5.29 + - 0.70, p=0.010), methylprednisolone group had faster improvement of SpO2, while patients without administration of methylprednisolone had a significantly longer interval supplemental oxygen use (8.2days (IQR 7.0-10.3) versus 13.5days (IQR 10.3-16); p<0.001); there was increased absorption degree of the focus in the methylprednisolone treatment group.	High; Very low certainty[1]

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		lopinavir/ritonavir), immune-enhancement therapy (thymosin)	Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, sub-optimal reporting of methods and outcomes.	
Wang[56]; observational (retrospective); 2020	IV methylprednisolone 0.5-1.0g per day for 2-3 days; or intravenous methylprednisolone at 1-3 mg/kg per day for 3-10 days (n=73) vs n=42 in non-corticosteroid group; 115; median 59 (IQR 40-67); 50.4%	Hypertension 26%, cardiovascular 12.2%, diabetes 10.4%; empirically treated with intravenous moxifloxacin, arbidol, ribavirin, interferon-alpha, immunoglobulin	Age, C-reactive protein, D-dimer and albumin were similar in both groups, corticosteroid group had more adverse outcomes than non-corticosteroid group respectively (32.9% vs. 11.9%, p=0.013). In multivariate analysis, corticosteroid treatment was associated with a non-significant 2.155-fold increase in risk of either mortality or ICU admission (p=0.308). Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
Fadel [68]; quasi-experimental pre-post; 2020	213 patients (pre n=81 and post n=132 corticosteroid group using a composite endpoint) (early, short-course, methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days); 213; median age 62 (51-62); 51.2% male	Asthma 15.5%, CKD 46%, COPD 12.7%, CHF 12.2%, CAD 17.8%, diabetes 49.3%, hypertension 74.2%, malignancy 11.3%; empiric antibiotics 76.5%, lopinavir/ritonavir 4.7%, remdesivir 2.3%, hydroxychloroquine 75.6%, tocilizumab 6.6%, corticosteroid 63.8% (at any time)	The composite endpoint occurred at a significantly lower rate in post-corticosteroid group compared to pre-corticosteroid group (34.9% vs. 54.3%, p=0.005). Primary composite pre corticosteroid protocol vs post protocol= 54.3 vs 34.9%, OR 0.45 (0.26 – 0.79), p=0.005 Death 26.3% vs 13.6%, OR 0.45 (0.22 – 0.91), p=0.024 Respiratory failure requiring mechanical ventilation 36.6% vs 21.7%, OR 0.47 (0.25-0.92), p=0.025 Escalation from GMU to ICU 44.3% vs 21.3%, OR 0.47 (0.25 – 0.88), p=0.017 An early short-course of corticosteroid seems to reduce escalation of care and improve clinical outcomes. Note: nonrandomized, confounded, use of composite outcome though individual components were significant, small sample sized, small events, regression to the mean and maturation due to quasi-experimental study design, corticosteroid administration was not universal as per protocols, data is lacking for the pre and post corticosteroid groups discharged from hospital.	High; Very low certainty[1]
RCT (clinical)				
RECOVERY trial. Horby et al.[115]; RCT; 2020	Dexamethasone trial arm 2,104 vs 4,321 in standard care alone Based on a preliminary release from study authors.	Not yet reported	• Corticosteroids (dexamethasone), typically used to reduce inflammation: • RECOVERY Trial on Dexamethasone (June 16th 2020) • Follow-up complete for 94% of patients • Limitation as only studied patients in hospital • Dexamethasone reduces death by about 1/3 in hospitalized patients with severe respiratory illness and complications (COVID-19 patients) • Appears to be effective in reducing death in severely ill COVID patients needing respiratory support • The study is not yet published • 2,104 patients randomized to dexamethasone 6 mg once daily (orally or IV) for 10 days and compared to 4,321 patients randomized to standard care alone • Dexamethasone reduced deaths by 1/3 in ventilated patients (rate ratio 0.65, 95% CI 0.48 to 0.88, p=0.0003), and by 1/5 in other patients receiving oxygen only (rate ratio 0.80, 95% CI 0.67 to 0.96, p=0.0021), and no benefit in those who did not need respiratory support (rate ratio 1.22, 95% CI 0.86 to 1.75, p=0.14). • Reduces 28-day mortality by 17%, p=0.0007	Unable to conduct risk of bias assessment or GRADE due to use on a publication release and not the full peer-reviewed manuscript

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			• Appears to improve survival in COVID-19 patients who require oxygen in hospital	
SYSTEMATIC REVIEW/META-ANALYSIS (clinical evidence)				
Mammen[39]; meta-analysis; 2020	7 RCTs focusing on ARDS and not directly on the COVID-19 patient with ARDS; examining corticosteroids (hydrocortisone, methylprednisolone, dexamethasone, or inhaled budesonide) vs no-corticosteroids; n=851 patients; typically, > 50 years of age, hospitalized patients; typically >50 years	Not studied; not studied	Three of seven trials (43%) enrolling 51.5% of the total sample had a low risk of bias. The loss to follow-up was rare: six trials (85.7%) had a near-complete follow-up with loss that was deemed not biasing, and with only one study, we judged had attrition greater than 5%; Corticosteroids reduced all-cause mortality (risk ratio [RR] 0.75, 95% CI: 0.59 to 0.95, p=0.02, moderate certainty) and duration of mechanical ventilation (mean difference [MD] -4.93 days, 95% CI: -7.81 days to -2.06 days, p<0.001, low certainty), and increased ventilator-free days (VFD) (MD 4.28 days, 95% CI: 2.67 days to 5.88 days, p<0.001, moderate certainty), when compared to placebo. Corticosteroids also increased the risk of hyperglycemia (RR 1.12%, 95% CI: 1.01 to 1.24, p=0.03, moderate certainty), and the effect on neuromuscular weakness was unclear (RR 1.30, 95% CI 0.80 to 2.11, p=0.28, low certainty).	Low[5]; i) mortality, moderate certainty ii) duration of mechanical ventilation, low certainty iii) increased ventilator-free days, moderate iv) risk of hyperglycemia, moderate v) neuro-muscular weakness, low AMSTAR II [7] critical appraisal of the review: high-quality
CONVALESCENT PLASMA (CP) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
OBSERVATIONAL (clinical)				
Shen[25]; case-series; 2020	Convalescent plasma (CP) to all; 5; age range 36-73 years; 60% Note: CP administered to all between 10 and 22 days after admission	1 has hypertension and mitral insufficiency; antivirals (lopinavir/ ritonavir; interferon alfa-1b; favipiravir; arbidol; darunavir) and corticosteroid methylprednisolone	Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Did not apply GRADE
Duan[26]; case-series; 2020	CP to all; 10; median age was 52.5 years (IQR, 45.0–59.5); 60%	Hypertension 30%, cardiovascular and cerebrovascular disease 10%; arbidol, ribavirin, remdesivir, Interferon-α, oseltamivir, peramivir and	Following transfusion, the level of neutralizing antibody quickly increased to 1:640 in five cases, and maintained at a high level (1:640) in remaining of cases. Researchers reported that the clinical symptoms were substantially improved. They also found an increase in oxyhemoglobin saturation within 3 days. Several parameters tended to improve as compared to pre-transfusion. Improved parameters included "increased lymphocyte counts and decreased C-reactive protein. Radiological examinations	High; Did not apply GRADE

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		corticosteroid methylprednisolone	showed varying degrees of absorption of lung lesions within 7 days. The viral load was undetectable after transfusion in seven patients who had previous viremia". No severe adverse effects. Note: case-series, nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, not optimally comparative, sub-optimal reporting of methods and outcomes.	
Zhang[27]; case-series; 2020	CP to all; 4; 31, 55, 69, 73 years old and F, M, M, and pregnant F respectively	None reported; arbidol, lopinavir-ritonavir, ribavirin, interferon alpha inhalation, oseltamivir, albumin, zadaxin and immunoglobulin, antibacterial and antifungal drugs	Researchers reported no serious adverse reactions and all 4 patients recovered from COVID-19. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Did not apply GRADE
Pei[29]; case-series; 2020	CP to all three; 3; not reported; not reported	Not reported; not reported	There were 2 patients with negative conversions and 1 failure due to anaphylaxis shock (discontinued); 1st patient treated on 12th day admission, turned severe, 2nd treatment, then significantly improved (nucleic acid test became negative and symptoms improved) and met discharge criteria on 26th day, 2nd patient, treatment on 27th day, the nucleic acid test became negative 4 days later, 3rd patient was a 51-year old pregnant woman who suffered anaphylaxis shock and CP was discontinued). Note: pre-print, small, only 3 patients, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes.	High; Did not apply GRADE
Shi[48]; case-series; 2020	1 patient, 50-year old female	Antiviral therapy plus interferon-α2b, followed by lopinavir and ritonavir and empiric ceftriaxone	IVIG (20g) and thymalfasin were initiated, corticosteroid (intravenous 80 mg methylprednisolone) was also commenced and halved to 40mg two days later, symptoms deteriorated and ceftriaxone was replaced with piperacillin-tazobactam; initiated the administration of three consecutive sessions of PE with 6000ml plasma (frozen plasma served as the sole replacement solution) followed by 20g IVIG from DOI 14 to DOI 17; symptoms were almost all rapidly relieved, with three consecutive sessions of PE treatment; no adverse events or complications were seen during PE treatment; oxygenation index increased with oxygen saturation of 96%; patient was breathing ambient air oxygen and the blood pressure was re-established. Note: small case-series of n=1	High; Did not apply GRADE
Zheng [61]; retrospective observational; 2020	CP (n=6) vs no CP (15); 21; CP median 61.5 (31.5-77.8) vs control median 73 (60-79); 76%	Hypertension 19%, diabetes 28.5%, liver disease 9.5%, cardiovascular 4.7%, kidney 4.7%; antiviral treatment 76%, IVIG 90%, glucocorticoid pulse 76%. There was fever 85.7%, cough 90.5%, fatigue 67%, dyspnea 76%, bilateral pneumonia in 95%	There was respiratory failure in 100%, ARDS 85%, septic shock 52%, secondary infection 76%; 5 deaths in treatment (83%) vs 14 (93%) in control group, 100% SARS-CoV-2 clearance in treatment group vs in 4 patients (26.7%) in the control group and there was SARS-CoV-2 clearance before death in 5/5 fatal patients in treatment group vs 3/14 (21%) in control; the 6 treatment patients with respiratory failure received convalescent plasma at a median of 21.5 days after first detection of viral shedding; overall, it appears that CP treatment may halt SARSCoV-2 shedding but failed in reducing mortality in critically end-stage COVID-19 patients; researchers suggested that treatment should be stated earlier. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small	High; Very low certainty[1]

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			sample size, a small number of events, sub-optimal reporting of methods and outcomes.	
Ahn [76]; observational case-series; 2020	CP; 2; ages 67 and 71; 1 males and 1 female	Both critical; a medical history of hypertension, previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): Concomitant therapy: 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empirical antibiotics, intubation and mechanical ventilator care, IV methylpred nisolone (0.5/1 mg/kg/day daily).	Both received lopinavir/ritonavir and hydroxychloroquine but showed persistent fever, rapidly aggravated hypoxemia and progressive bilateral infiltrations in accordance with the criteria of severe ARDS; following CP infusion, the patients showed improved oxygenation and chest X-rays with decreased inflammatory markers and viral loads; researchers reported that when used with systemic corticosteroids, there is the possibility of reducing excessive inflammatory response by corticosteroids as well as promoting the reduction of viral loads by convalescent plasma simultaneously. Note: small case series of 2 patients, not blinded for outcome detectors, not adjusted for confounding.	High; Did not apply GRADE
Joyner [78]; observational (retrospective case-series); 2020	5000 patients (of 8,932 enrolled patients with COVID-19) received CP; 5000; median age 62.3 (18.5, 97.8); 63.1% male	72% respiratory failure, 63% dyspnea, 62% blood oxygen saturation ≤ 93%, 43% had lung infiltrates >50% within 24-28 hours of enrollment, 38% had a respiratory frequency ≥ 30 breaths·minute-1 , 34% had partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, 18% had multiple organ dysfunction or failure, and 15% had septic shock.	81% patients had severe or life-threatening COVID-19 and 949 (19%) were judged to have a high risk of progressing to severe or life-threatening COVID-19; prior to COVID-19 convalescent plasma transfusion, a total of 3,316 patients (66%) were admitted to the ICU; incidence of all serious adverse events (SAEs) in the first four hours after transfusion was <1%, Of the 36 reported SAEs, there were 25 reported incidences of related SAEs, including mortality (n=4), transfusion-associated circulatory overload (TACO; n=7), transfusion-related acute lung injury (TRALI; n=11), and severe allergic transfusion reactions (n=3); 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfusion by the treating physician. The seven-day mortality rate was 14.9%. Researchers suggested the CP is safe in a hospital setting to be used in COVID-19 and warrants further study. Note: large case-series, nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, not optimally comparative, sub-optimal reporting of methods and outcomes.	High; Did not apply GRADE
Liu [88]; prospective case-control; 2020	CP transfused patients; 39; 55 ± 13; 64% males Note 1:4 matching 156; 1:2 matching 74	Asthma 8%, cancer 5%, CKD 3%, COPD 3%, diabetes 21%, obesity 54%; not reported	CP patients were more likely than control patients to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14, with an odds ratio of 0.86 (95% CI: 0.75~0.98; p=0.028). Plasma recipients also demonstrated improved survival, compared to control patients (log-rank test: p=0.039). In a covariates-adjusted Cox model, convalescent plasma transfusion improved survival for non-intubated patients (hazard ratio 0.19 (95% CI: 0.05 ~0.72); p=0.015), but not for intubated patients (1.24 (0.33~4.67); p=0.752).	High; Very low certainty[1]
Salazar [93]; observational case-series; 2020	CP in patients with severe and/or life-threatening COVID-19 disease; 25; ages ranged from 19 to 77 years (median 51, interquartile range [IQR] 42.5 to 60); 44% male	40% diabetes, hypertension 32%, CKD 4%, hyperlipidemia 20%; hydroxychloroquine 100%, tocilizumab 56%, corticosteroids 36%, remdesivir 8%	At day 7 post-transfusion with CP, 9 (36%) patients had at least a 1-point improvement in clinical scale, and seven of those were discharged. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged. No adverse events as a result of plasma transfusion were observed. Whole genome sequencing data did not identify a strain genotype-disease severity correlation. The data indicate that administration of convalescent plasma is a safe treatment option for those with severe COVID-19 disease.	High; Did not apply GRADE

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			Note: small case series of 25 patients, not adjusted for confounding.	
Perotti [95]; one-arm multicenter interventional study; 2020	Hyperimmune plasma (CP); 46; mean age 63 years (SD 12); 61% male	Hypertension 46%, diabetes 17%, cardiovascular disease 14%, COPD 5%, CKD 9%, dyslipidemia 21%; antiviral 42%, antibiotics 84%, HCQ 86%, anticoagulant 98%	Twenty-four patients received one unit of plasma, 21 received two units and one patient received 3 units. Three patients (6.5%) died within 7 days (at 1, 4 and 6 days); two had important comorbidities, such as diabetes, hypertension and cancer, while the third had an extremely low PaO2/FiO2 level of 67 at the time of plasma infusion; among survivors, the severity of the condition at baseline was confirmed by the low oxygen saturation (mean 94%) and PaO2/FiO2 (mean 131); > than 89% of patients showed bilateral multilobe infiltrates at chest radiogram and all laboratory biomarkers were markedly elevated; at 7 days after plasma infusion PaO2/FiO2 increased by 112 units in survivors, the chest radiogram severity decreased in 23% of patients; CRP, Ferritin and LDH all decreased by 60, 36 and 20%, respectively; no or little improvement was present in the three deceased patients; five serious adverse events occurred in 4 patients. Note: nonrandomized, confounded, small case series of 46 patients, not optimally adjusted for confounding.	High; Very low certainty[1]
RCT (clinical)				
Li [97]; RCT; 2020	CP added to standard treatment (n=52) vs standard treatment alone (n=51); 103; median age, 70 years s (IQR, 62-78 years); 58.3% male	Hypertension 54.3%, cardiovascular disease 25%, cerebrovascular 17.5%, diabetes 10.6%, kidney disease 5.8%, liver disease 10.7%	Among 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]; $P = .03$); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the CP group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; $P = .83$) (P for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; $P = .30$) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; $P = .12$). CP treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; $P < .001$). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care. Researchers concluded that CP did not result in a statistically significant improvement in time to clinical improvement within 28 days, and no improvement in the risk of death. Note: the trial was terminated before it reached its targeted original sample size of 200 patients; only 103 were enrolled (for whom randomization was stratified by disease severity); the study was underpowered and many comparisons between the CP group and the control group were not statistically significant; open-label, randomization and concealment appeared reasonably well done. Methodologically an improvement from among the COVID-19 research published to date.	Low to moderate; Moderate[3]
Umifenovir/arbidol (antiviral) **There is insufficient evidence to draw a conclusion on benefits and harms.** **The effectiveness is being evaluated in various randomized clinical trials.**				
RCT (clinical)				
Li[30]; RCT; 2020	Lopinavir/ritonavir (LPV/r) vs arbidol vs control; 44 (21, 16, 7 respectively); mean 49.4	Some type of underlying illnesses 34%; gamma	The median time of positive-to-negative conversion of SARS-CoV-2 nucleic acid was 8.5 (IQR 3, 13) days in the LPV/r group, 7 (IQR 3, 10.5) days in the arbidol group and 4 (IQR 3,	High; Low certainty[1]

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	years; 50%	globulin 11.3%, glucocorticoids 22.7%	10.5) days in the control group (p=0.751). Researchers reported that there were no statistical differences between the three groups in the rates of antipyresis, cough alleviation, improvement of chest CT or the deterioration rate of clinical status (all $p > 0.05$). Five (23.8%) patients in the LPV/r group experienced adverse events during the follow-up period versus none in the other groups. Note: pre-print, sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, imbalanced co-treatment assignment and use of active comparator with unknown effectiveness for COVID-19.	See Figure 2, Table 2
Chen[31]; RCT; 2020	Favipiravir versus Arbidol open-label RCT; 236 (116 favipiravir, 120 arbidol); unclear; 46.6%	Hypertension 27.9%, 11.4% diabetes; moxifloxacin hydrochloride tablets, cephalosporins, antiviral drugs other than the experimental drugs, glucocorticoid and human serum albumin.	There was no significant difference in clinical recovery rate at day 7, whereby 71 (61%) recovered in the favipiravir arm and 62 (52%) in the arbidol group. In patients with hypertension and/or diabetes, 23 (54.76) recovered in the favipiravir arm and 18 (51.43) in the arbidol arm (no significant difference). There were no deaths in either arm and 1 respiratory failure in the favipiravir arm and 4 (3.33) in the arbidol arm. Researchers reported 37 adverse events in the favipiravir arm and 28 in the arbidol arm. The reporting in this study was very poor and the methodology was weak. This was described as a randomized study but it was not. No proper description of randomization, allocation concealment, or masking was provided. Note: pre-print, sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, imbalanced co-treatment assignment and use of active comparator with unknown effectiveness for COVID-19.	High; Very low certainty[1]
Chang[7]; RCT (open-label); 2020	120 assigned to favipiravir group (116 assessed, routine treatment + 1600 mg on the first day twice a day, 600 mg from the second day to the end, twice a day) and 120 to arbidol group (120 assessed, 200 mg, 3 times a day to the end of the trial); 236; not reported clearly; 46.6%	27.9% hypertension, diabetes 11.4%, 95% COVID-19 pneumonia; none reported	Clinical recovery rate of day 7 between two groups, 61.2% favipiravir vs 5.7% arbidol (total patients), 71.4% vs 55.6% (moderate cases) respectively, 5.5% vs 0.0% (serious cases) respectively; patients with hypertension and/or diabetes 54.7% favipiravir vs 51.4% arbidol; adverse events 37/116 favipiravir vs 28/120 arbidol, note, 18 severe patients in the favipiravir group vs 9 severe patients in the arbidol group (imbalanced). Note: pre-print, sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, and use of active comparator with unknown effectiveness for COVID-19.	High; Very low certainty[1]
OBSERVATIONAL (clinical)				
Deng[32]; observational (retrospective cohort study); 2020	Arbidol combined with LPV/r (n=16) vs LPV/r alone (n=17); 33; mean 44.5; 51.5%	Median number of comorbidities was 0 ·7 (range 0–2); corticosteroid therapy; a number of antibacterial therapy agents; vasopressors.	Researchers reported that COVID-19 was not detected for 12 of 16 patients' nasopharyngeal specimens (75%) in the combination group after 7 days, relative to 6 of 17 (35%) in the monotherapy group ($p < 0·05$). "After 14 days, 15 (94%) of 16 and 9 (52·9%) of 17, respectively, SARS-CoV-2 could not be detected ($p < 0·05$)". They reported that the chest CT scans were improving for 11 of 16 patients (69%) within the combination group following seven days relative to 5 of 17 (29%) in the monotherapy group ($p < 0·05$). Note: The sample was very small (n=33) and this was a nonrandomized retrospective design which is a weak design; overall, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes and use of active comparator with unknown effectiveness for COVID-19. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Wang[33];	Arbidol vs no arbidol; 67;	Hypertension 13%,	Mortality rate was 7.5%. Patients were divided into the	High;

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observational (retrospective case series); 2020	median 42.0(35.0-62.0); 46%	cardiovascular disease 12%, diabetes 10%, COPD 6%, malignancy 6%, asthma 3%, chronic hepatitis 1%; antivirals, antibiotics, antifungals, corticosteroids	SpO2≥90% group (n=55) and the SpO2 < 90% n=14; all deaths occurred in SpO2 < 90%, median age of the SpO2 <90% was 70.5, IQR 62-77, SpO2 <90% had more comorbidities (included the 5 that died) than SpO2≥90% group, 36% vs 7%, p=0.014, cardiovascular disease 36% vs 5%, p=0.07, diabetes 43% vs 2% p<0.001. SpO2 < 90% group had more fever and dyspnea; no persons died who were treated with arbidol (n=36 patients), and all 5 deaths occurred in the group that received no arbidol (n=31 patients). The study showed that elderly persons (older) with underlying medical conditions were at increased risk of death. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes.	Very low certainty[1]
Liu[37]; observational (retrospective cohort study); 2020	Arbidol vs no arbidol; 257; mean 59.1; 51.4%	52.1% pre-existing conditions; not clearly reported	Patients receiving arbidol had slightly higher SpO2 level and smaller lesion area. Mortality was 7% among patients taking arbidol vs. 24.70% among patients who did not; adjustment for gender, pre-existing condition, log(age), log (SpO2), log (lesion size), log (admission data) and hospital, the OR was 0.169 (95% CI, 0.07 to 0.34) for arbidol; in terms of lesion size based on chest CT and adjusting for patients' characteristics and antiviral medication use, the ratio of the lesion size after the treatment vs before was 85.2% (95% CI, 74.4- 97.5; p=0.02) of that among patients not taking arbidol, indicative of much quicker lesion absorption. While the methods and analysis were very confusing and generally poor, it reported that arbidol is significantly related to a reduction in mortality among hospitalized COVID-19 patients; also reported was the combination of arbidol and oseltamivir being linked to a reduction in mortality, with no benefit with Lopinavir/Ritonavir. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, sample not necessarily representative of clinical population, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes.	High; Very low certainty[1] See Figure 4
Zhu [50]; observational retrospective cohort; 2020	Arbidol group (16 cases) 0.2g arbidol, three times a day vs lopinavir/ritonavir group received 400mg/100mg of Lopinavir/ritonavir, twice a day for a week; 50; 36.02; 52%	None reported, none reported	No significant difference in baseline Ct values between the two groups (both p >0.05), day 7 following admission, viral load was undetectable in 50% of patients receiving arbidol and in 23.5% of the patients treated with lopinavir/ritonavir, day 14 after admission, viral load was undetectable in 100% patients in arbidol group vs found in 44.1% of patients who received lopinavir/ritonavir, arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group ($p < 0.01$), 3 in the lopinavir/ritonavir group and three patients in the arbidol group had an elevated level (< 125 U/L) of ALT in the first week of admission ($\chi 2 = 0.047$, $p = 0.99$). 1 patient in lopinavir/ritonavir group and two in the arbidol group diagnosed with leucopenia. Researchers suggested that a arbidol monotherapy may be potentially superior to lopinavir/ritonavir for COVID-19 patients. Note: active-comparator, nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small events, and sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
Zhou [100]; observational retrospective;	238 patients; arbidol 82, arbidol plus interferon 139; median age 55.5 years (IQR,	Hypertension 28.2%, cardiovascular disease 5.5%,	92.9% (221/238) administered arbidol, 58.4% (139/238) used arbidol combination with interferon; median time from illness onset to start arbidol was 8 days (IQR, 5-14 days) and the	High; Low certainty[1]

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2020	35-67.3 years); 42.9% male	diabetes 9.2%, chronic lung disease 3.4%, kidney disease 0.8%; antibiotics 96.2%, corticosteroids 22.7%, interferon/lopinavir 2.1%	median duration of SARS-CoV-2 virus shedding was 23 days (IQR, 17.8–30 days). SARS-CoV-2 RNA clearance was significantly delayed in patients who received arbidol >7 days after illness onset, compared with those in whom arbidol treatment was started≤7 days after illness onset (HR, 1.738 [95% CI, 1.339–2.257], P < .001). Multivariate regression analysis revealed that prolonged viral shedding was significantly associated with initiation arbidol more than seven days after symptom onset (OR 2.078, 95% CI [1.114-3.876], P .004), more than 7 days from onset of symptoms to first medical visitation (OR 3.321, 95% CI[1.559-7.073], P .002), illness onset before Jan.31, 2020 (OR 3.223, 95% CI[1.450-7.163], P .021). Arbidol combination with interferon was also significantly associated with shorter virus shedding (OR .402, 95% CI [.206-.787], P .008). Note: nonrandomized, potentially biased due to selection bias and residual confounding, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes. Adjusted analysis and generally, an improvement, methods wise.	

Lopinavir/ritonavir (LPV/r) protease inhibitor

There is insufficient evidence to draw a conclusion on benefits and harms.
The effectiveness is being evaluated in various randomized clinical trials.

RCT (clinical)

Li[30]; RCT; 2020	Lopinavir/ritonavir (LPV/r) vs arbidol vs control; 44 (21, 16, 7 respectively); mean 49.4 years; 50%	Some type of underlying illnesses 34%; gamma globulin 11.3%, glucocorticoids 22.7%	The median time of positive-to-negative conversion of SARS-CoV-2 nucleic acid was 8.5 (IQR 3, 13) days in the LPV/r group, 7 (IQR 3, 10.5) days in the arbidol group and 4 (IQR 3, 10.5) days in the control group (p=0.751). Researchers reported that there were no statistical differences between the three groups in the rates of antipyresis, cough alleviation, improvement of chest CT or the deterioration rate of clinical status (all p > 0.05). Five (23.8%) patients in the LPV/r group experienced adverse events during the follow-up period versus none in the other groups. Note: pre-print, sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, imbalanced co-treatment assignment and use of active comparator with unknown effectiveness for COVID-19.	High; Low certainty[1]
Huang [14]; RCT; 2020	Twice-daily oral of 500 mg Chloroquine (n=10) versus 400/100mg Lopinavir/Ritonavir (n=12) for 10 days; 22; 44.0 mean (36.5 to 57.5); 59.1%	None reported; none reported	Using RT-PCR, on day 13, all patients in the chloroquine group were negative, and 11 of 12 in the control group (lopinavir/ritonavir) were negative on day 14. Via lung CT on day 9, 6 patients in chloroquine group achieved lung clearance versus 3 in the comparison group. At day 14, the rate ratio based on CT imaging from the Chloroquine group was 2.21, 95% CI 0.81-6.62) relative to the control group. Five patients in the chloroquine group had adverse events versus no patients in the control group. Note: this small RCT appeared to show better effectiveness of chloroquine over lopinavir/ritonavir in moderate to severely ill COVID-19 patients; overall, sub-optimal randomization, allocation concealment, blinding, small sample size, small event number, and use of active comparator with uncertain treatment effectiveness against COVID-19.	High; Very low certainty[1]
Cao[36]; RCT; 2020	LPV/r (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care vs standard	Diabetes 11.6%, cerebrovascular 6.5%, cancer 3%; interferon on	Time to clinical improvement — median no. of days (IQR) 16.0 (13.0 to 17.0) vs 16.0 (15.0 to 18.0); Day 28 mortality — no. (%) n=19 (19.2) vs 25 (25.0) intervention vs control respectively; clinical improvement - no. (%) day 28	High; Low certainty[4]

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	care alone; 100 (99 intervention 100 control); median 58 years IQR 49 to 68 years; 60.3%	enrollment 11.1%, vasopressors 22.1%, glucocorticoid 33.7%, antibiotic 95%	n=78 (78.8) vs 70 (70.0); ICU length of stay - median no. of days (IQR) 6 (2 to 11) vs 11 (7 to 17); hospital stay - median no. of days (IQR) 14 (12 to 17) vs 16 (13 to 18); the median interval time between symptom onset and randomization was 13 days (IQR, 11 to 16 days). Note: open-label, no blinding, imbalanced viral loads between groups with higher baseline viral loads in the LPV/r group, small sample size, and small event number.	
OBSERVATIONAL (clinical)				
Ye[35]; observational; 2020	LPV/r vs plus adjuvant drugs only no LPV/r (adjuvant drugs only); 47 (42 treatment vs 5 control); aged between 5 and 68, of which 9 were under 30 and 38 were over 30; 42%	Hypertension 17%, diabetes 17%; arbidol, moxifloxacin	Improvement in body temperature for both groups admission to the 10th day treatment; body temperature of intervention group declined faster than control, some reductions in proportions of white blood cells, lymphocytes and C-reactive protein in intervention vs control, proportion with abnormal alanine aminotransferase and aspartate aminotransferase in intervention lower than control; reduced number of days testing negative in intervention group. Note: Non-randomized, confounded, optimal adjustments and steps such as stratification and masking not applied, sample not necessarily representative of clinical population, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
Deng[32]; observational (retrospective cohort study); 2020	Arbidol combined with LPV/r (n=16) vs LPV/r alone (n=17); 33; mean 44.5; 51.5%	Median number of comorbidities was 0.7 (range 0-2); corticosteroid therapy; a number of antibacterial therapy agents; vasopressors.	COVID-19 was not detected for 12 of 16 patients' nasopharyngeal specimens (75%) in the combination group arbidol plus LPV/r following 7 days, relative to 6 of 17 (35%) in the monotherapy group ($p < 0{\cdot}05$). "After 14 days, 15 (94%) of 16 and 9 (52·9%) of 17, respectively, SARS-CoV-2 could not be detected ($p < 0{\cdot}05$)". They reported that the chest CT scans were improving for 11 of 16 patients (69%) within the combination group following seven days relative to 5 of 17 (29%) in the monotherapy group ($p < 0{\cdot}05$). The sample was very small (n=33) and this was a nonrandomized retrospective design which is a weak design. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes and use of active comparator with unknown effectiveness for COVID-19.	High; Very low certainty[1]
Lan [65]; observational (retrospective); 2020	Lopinavir/ritonavir vs Lopinavir/ritonavir plus arbidol; 73 (LR 34 vs LR + Arbidol 39); mean age LR+ Arbidol 52.3±15.8 years (range, 21-81 years), 66.7% males vs mean age of LR 59.5±13.6 years (range, 30-87 years), 32.4% male.	Not reported adequately; not reported adequately	Researchers reported no indication that lopinavir–ritonavir when combined with abidol treatment improved the clinical symptoms and accelerated the virological inhibition when compared with single antiviral drug lopinavir–ritonavir treatment; moreover, time to virus turning negative and the duration of fever and cough in the combined group were greater than lopinavir–ritonavir treatment group. Note: nonrandomized, potentially biased due to selection bias and residual confounding, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Interferon-alpha α **There is no quality evidence to support a recommendation on its therapeutic use** **The effectiveness is being evaluated in randomized clinical trials.**				
OBSERVATIONAL (clinical)				
Meng[38]; observational	Medical personnel, low-risk group received rhIFN-α	Not reported; not reported	There were no new cases of COVID-19 pneumonia during follow-up in low-risk group, and no new cases were found in	High; Very low

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(retrospective); 2020	nasal drops for 28 days (n=2,415) vs the high-risk group who received rhIFN-α nasal drops combined with thymosin-α1, once a week (n=529); 2,944; 34.6; 30%		the high-risk group. Adverse effects among a few personnel included transient irritation which resolved soon after it began. Researchers suggest that in low and high-risk level hospital personnel, with the proper protective equipment (first and second-level) and at low risk to begin, when given IFN-α nasal drops with or without thymosin alpha, are effectively prevented from developing COVID-19 disease. The data on testing prior to the study and post study ending is not available which raises many questions about this study. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes. In addition, the use of thymosin-α, an agent with unknown effectiveness for COVID-19 obscures the treatment effect. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	certainty[1]
Zhou[59]; observational (retrospective); 2020	Nebulized IFN-α2b (5mU b.i.d.), arbidol (ARB) (200mg t.i.d.) or a combination of IFN-α2b plus arbidol; 77; n=7 IFN median IQR 41.3 (27-68), n=46 IFN + ARB 40.4 (25-80), n=24 ARB 64.5 (37-73); 40%	Fever 62.3%, cough 50%, fatigue 27%, myalgia 18%, headache 6.5%, chest pain 12%, expectoration 14%, diarrhea 10.4%	IFN-α2b therapy shortens duration of viral shedding; reduction of markers of acute inflammation e.g. CRP and IL6 correlated with this shortened viral shedding. Days from symptom onset to hospital admission IFN, IFN+ARB, ARB 8.0 [5.5, 15.5], 6.5 [3.0, 10.0], 10.0 [4.5, 19.5]; Days from symptom onset to treatment 8.0 [6.5, 16.0], 17.0 [10.0, 22.0], and 8.0 [5.0, 11.0] respectively. Note: nonrandomized, confounded, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes. Adjustments sub-optimal. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Pereda [104]; observational prospective; 2020	Interferon-alpha 2b (n=761) vs no interferon (n=53); 814; mean age 44.3, age IFN 42.9 (2-96) vs no IFN 66.9 (1-101); 50% male	3.2% co-morbidities in IFN group vs 56.6% in no-IFN	The proportion of fully recovered patients was higher in the IFN-treated compared with non-IFN treated group (95.4% vs 26.1%, p<0.01); the CFR for all patients was 2.95%, and for those patients who received IFN-α2b the CFR was reduce to 0.92. Note: nonrandomized, confounded, small events, not optimally comparative, and sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]

Interferon-beta β

There is no quality evidence to support a recommendation on its therapeutic use
The effectiveness is being evaluated in various randomized clinical trials.

SYSTEMATIC REVIEW/META-ANALYSIS (clinical evidence)

Mammen[40]; meta-analysis; 2020	2 RCTs focusing on ARDS and not directly on the COVID-19 patient with ARDS; examining interferon-beta vs no interferon-beta; n=392 patients; not reported; not reported	Not studied, not studied	Use of IFNβ had no significant difference on 28-day hospital mortality (risk ratio [RR] 0.59, 95% CI: 0.13 to 2.67, p=0.49, or on ventilator-free days (VFD) (MD 4.85 days, 95% CI: -3.25 days to 12.93 days, p=0.24), compared to no IFNβ. IFNβ also had no significant impact on the risk of adverse events (RR 0.98%, 95% CI: 0.94 to 1.03, p=0.47). The use of IFNβ does not appear to improve mortality, VFD or adverse events in ARDS patients; based on two small studies with limited numbers of events, which raises uncertainties in IFNβ true effects. The analysis of one study reveals increased mortality with the concomitant use of corticosteroids and IFNβ, suggesting careful consideration of drug-drug interactions with this combination.	Low[5]; i) mortality 28-day, very low certainty ii) ventilator-free days, very low certainty iii) adverse events, low certainty AMSTAR II [7] critical appraisal of the review: high-quality

RCT (clinical)				
Fan-Ngai Hung [73]; open-label Phase II RCT; 2020	n=127 combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group); 127 (86 combination and 41 control); median 52 years (IQR 32–62); 68 (54%) male	Diabetes 13.3%, 28.3% hypertension, CAD 7.9%, cerebrovascular disease 1.5%, 22.8% hyperlipidemia, malignancy 1.5%; 53.3% antibiotics, corticosteroids 6.2%	There were no deaths; combination group revealed significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days, IQR 5–11) vs the control group (12 days [8–15]; HR 4·37 [95% CI 1·86–10·24], p=0·0010); the adverse events included self-limited nausea and diarrhoea with no difference between the two groups. One patient in the control group discontinued lopinavir–ritonavir because of biochemical hepatitis. Note: randomization and concealment appeared reasonable, open-label which is a limitation, no placebo group, young ages for both groups limit generalizability to elderly populations, small sample sizes, small events, indicative of a needed Phase III study, manipulating interferon as the base treatment.	Low-moderate; Low certainty[4]
OBSERVATIONAL (clinical)				
Estébanez [82]; observational retrospective; 2020	Interferon beta1b (n=106) was given by subcutaneous injection at a dose of 250 µg on alternate days vs no interferon beta (N=150); 256; mean 63.7 (17); 59.4% males	Dyslipidaemia 30.6%, Cardiopathy 22.4%, cancer 11.4%, Pulmonary disease 14.5%; Hydroxychloroquine 77%, Lopinavir/ ritonavir 36.1%, Azythromycin 62.9%, Corticosteroids 25.8%	The overall mortality rate is 24.6% (63/256). Twenty-two patients (20.8%) in the interferon group died and 41 (27.3%) in the control group (p=0.229). In the multivariate analysis, the predictors of in-hospital mortality were i) age, ii) severity of clinical picture at admission and iii) hydroxychloroquine treatment. Note: nonrandomized, potentially confounded, optimal adjustments not applied though there was some adjusted analysis, small sample size, small events. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]

Heparin

There are specific recommendations on the use of antithrombotic agents.[46 47]
Studies are ongoing to evaluate the preventive and therapeutic use of antithrombotic agents to mitigate the thrombotic and hemorrhagic events and assess the potential drug interactions with investigational drugs.

OBSERVATIONAL (clinical)				
Negri[43]; observational, case-series; 2020	Enoxaparin 1 mg/kg SC every 24 hours (OD). Patients with a creatinine clearance under 30 mL/min received subcutaneous unfractionated heparin at a dose of 5,000 units every 8 or 6 hours; 27; mean 56 ± 17; 70%	n=15 patients had diabetes 11%, hypertension 26%, heart disease 11%, previous lung disease 7%, cancer 4%, other 26%; 10-day course of azithromycin (500mg on day 1, then 250mg daily), methylprednisolone 40mg daily if a worsening radiological pattern increase in serum LDH levels	15 (56%) discharged after an average 7.3 (± 4.0) days, 1 discharged and lost follow-up, 9 patients (33%) admitted to ICU, 3 (33%) then discharged to the ward after an average 9.3 (±4.5) days, 8 (30%) required intubation, half of which (4 patients) successfully extubated after an average 10.3 (± 1.5) days of mechanical ventilation and other half (4 patients) currently being weaned off the ventilator, 2 required a tracheostomy; no deaths or haemorrhagic complications due to heparin anticoagulation. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, and not optimally comparative. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Ayerbe [94]; observational (retrospective); 2020	Heparin; 2075; mean age 67.57(15.5); 60.5% male	Not reported; hydroxychloroquine, azithromycin, steroids, tocilizumab, a combination of lopinavir with ritonavir, and oseltamivir	There were 301 deaths (14%); researchers found that heparin was associated with lower mortality when their model was adjusted for age and gender, with OR (95%CI): 0.55 (0.37-0.82) p=0.003. This association remained significant when saturation of oxygen <90%, and temperature >37C were added to the model with OR: 0.54(0.36-0.82) p=0.003, and also when all the other drugs were included as covariates OR: 0.42 (0.26-0.66) p<0.001.	High; Very low certainty[1]

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			Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, though there was multivariate logistic regression with some adjustment, small sample size, small events, and not optimally comparative. This early data is also to be considered hypothesis generating, calling for well-designed randomised clinical studies.	
Tang [102]; observational, 2020	449 consecutive patients COVID-19 positive (severe); 99 heparin treated, 350 non-heparin treated; mean age 65.1 ± 12.0 years; 59.6% male	Hypertension 39.4%, diabetes 20.7%, heart disease 9.1%; NR	Ninety-nine (22.0%) patients received heparin treatment for at least 7 days, in which 94 received LMWH (40-60 mg enoxaparin/d) and five received unfractionated heparin (10 000-15 000 U/d), no anticoagulants other than heparin had been used for 7 days or longer in our patients. All patients received antiviral and appropriate supportive therapies after admission; D-dimer, prothrombin time, and age were positively, and platelet count was negatively, correlated with 28-day mortality in multivariate analysis. No difference in 28-day mortality was found between heparin users and nonusers (30.3% vs 29.7%, *P* = 0.910). But the 28-day mortality of heparin users was lower than nonusers in patients with SIC score ≥4 (40.0% vs 64.2%, *P* = 0.029), or D-dimer >6-fold of upper limit of normal (32.8% vs 52.4%, *P* =0 .017). Note: Consecutive patients, nonrandomized, confounded, small event number, sample size, not optimally adjusted.	High; Very low certainty[1]
Trinh [105]; observational retrospective; 2020	244 patients were included in the analysis: 161 received therapeutic anticoagulation (heparin) and 83 received prophylactic anticoagulation; 244; mean 59.6±13.2; 66% male	Diabetes 36.9%, hypertension 50%, CKD 9.8%, CHD 2.5%, CAD 12.7%, asthma 12.3%, COPD 4.1%, cerebrovascular 6.2%, anticoagulation 3.3%, malignancy 7.8%; heparin 82.6%; antibiotics 99.2%, corticosteroids 83.2%, HCQ 88.4%, tocilizumab 14.3%, sarilumab 8.6%, remdesivir 4.5%, stem cell antibodies 3.3%	Propensity score (PS) weighted Kaplan-Meier plot demonstrated a survival advantage (57% vs. 25%) at 35 days from admission to the ICU in patients who received therapeutic anticoagulation for a minimum of 5 days compared to those who received prophylactic anticoagulation during their hospital course. A multivariate Cox proportional hazard regression model with PS weights to adjust for baseline differences found a 79% reduction in death in patients who were therapeutically anticoagulated HR 0.209, [95% CI (0.10, 0.46), p <0.0001. Bleeding complications were similar between both groups. A 26.7% [95% CI (1.16, 1.39), p <0.0001. Note: nonrandomized, confounded, but adjustments performed and a stronger methodology. Propensity score matched. This early data is also to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]

α-Lipoic acid

There is no quality evidence to support a recommendation on its therapeutic use
The effectiveness is being evaluated in various randomized clinical trials.

RCT (clinical)

Zhong[44]; RCT, single-blind; 2020	α-Lipoic acid (ALA) n=8 1200 mg/d, intravenous infusion) once daily plus for 7 days plus standard care vs placebo n=9 saline infusion plus standard care for 7 days; median (IQR) 63 (59-66); 76.5%	Hypertension 47%, diabetes 23.5%, coronary heart disease 5.9%; none reported	Researchers found no significant difference in SOFA score between the placebo group and the ALA group (p=0.36); the 30-day all-cause mortality was 77.8% (7/9) in the placebo group, and 37.5% (3/8) in the ALA group (p=0.09). Note: single-blind (participants and study personnel were aware of the study-group assignments), very small number of patients, very small events, randomization, allocation concealment not optimal or clear.	High; Very low[6]

Intravenous immunoglobulin (IVIG)

There is no quality evidence to support a recommendation on its therapeutic use

The effectiveness is being evaluated in various randomized clinical trials.				
OBSERVATIONAL (clinical)				
Xie[49]; observational retrospective; 2020	When the absolute lymphocyte count fell to < 0.5× 109 /L at 20 g/day, patients given IVIG and correction for hypoalbuminemia; 58; mean 62; 62% Note: > 48 h group and ≤48 h group were divided according to the use of intravenous immunoglobulin within 48 h after admission	Not reported; all given oxygen therapy and abidor and initially given moxifloxacin, low molecular heparin anticoagulation; thymosin and glucocorticoids with IVIG	23/58 patients died within 28 days admission, 7 in ≤48 h group and 16 in > 48 h group; statistically significant difference in 28-day mortality between the two groups (p=0.009); length of stay in hospital of the ≤48 h group significantly shorter than in the > 48 h group (11.50 ±1.03 vs 16.96 ±1.62 days, p=0.005), and the length of stay in the ICU of the ≤48 h group was also significantly shorter than that of the > 48 h group (9.53±1.09 vs 13.50 ±1.63 days, p=0.045); proportion of patients requiring mechanical ventilation in the ≤48 h group significantly lower than in the > 48 h group (6.7% vs 32.1%, p=0.016). Note: nonrandomized, potentially confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, and not optimally comparative. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Sarilumab (IL-6 receptor antagonist) **There is no quality evidence to support a recommendation on its therapeutic use** **The effectiveness is being evaluated in various randomized clinical trials**				
OBSERVATIONAL (clinical)				
Gremese [80]; observational case-series; 2020	IV sarilumab medical ward vs ICU care (final injectable solution was obtained combining 2 Sarilumab 200 mg prefilled syringes mixed in 100 ml 0.9% sodium chloride solution for intravenous use); 53; median and IQR medical wards 68.0 (55.0-75.0) vs ICU care 60.5 (53.8-68.0); 90.5%	Diabetes 20.7%, hypertension 50.9%, cardiovascular disease 21.7%, COPD 8.7%, cancer 4.3%, dyslipidemia 11.7%; lopinavir/ritonavir 400/100 mg BID or darunavir/ritonavir 800/100 mg QD, orally); hydroxychloroquine, azithromycin, heparin.	Within medical wards, 7(17.9%) required ICU admission, 4 of whom were re-admitted to the ward within 5-8 days. At 19 days median follow-up, 89.7% of medical inpatients significantly improved (46.1% after 24 hours, 61.5% after 3 days), 70.6% were discharged from the hospital and 85.7% no longer needed oxygen therapy; within patients receiving sarilumab in ICU, 64.2% were discharged from ICU to the ward and 35.8% were still alive at the last follow-up. Overall mortality rate was 5.7% after sarilumab administration: 1(2.5%) patient died in the Medical Ward whilst 2(14.2%) patients died in ICU, respectively. Note: nonrandomized, potentially confounded, adjustments conducted but considered not optimal, small sample size, small events, and not optimally comparative. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Ruxolitinib **Findings are encouraging and informative to future trials to test efficacy of ruxolitinib in a larger population**				
RCT (clinical)				
Cao [92]; RCT; 2020	Ruxolitinib 5mg (n=22) twice a day plus standard-of-care (SoC); the control group (group A) (n=21), which was treated with placebo (100mg vitamin C) twice a day with SoC; 43; median 63 years (interquartile range [IQR], 58 to 68 years); 58.5%	Hypertension 39%, diabetes 19.5%, CAD 7.3%; vasopressor 7.3%, glucocorticoid 70.7%, IVIG 43.9%, antivirals 90.2%, antibiotics 48.8%, arbidol 73%, oseltamivir 27%	Researchers found that treatment with ruxolitinib plus SoC was not significantly associated with accelerated clinical improvement in severe patients with COVID-19, although the ruxolitinib group had a numerically faster clinical improvement; 18 (90%) patients from the ruxolitinib group showed CT improvement at D14 compared with 13 (61.9%) patients from the control group (P = 0.049); three patients in the control group died of respiratory failure, with 14.3% overall mortality at D28; no patients died in the ruxolitinib group; overall, ruxolitinib was reportedly well tolerated with low toxicities and no new safety signals; researchers found that the levels of 7 cytokines were significantly decreased in the ruxolitinib group in comparison to the control group. Note: RCT (randomization and allocation concealment relatively well done and describe), small sample size and events.	Low-moderate; Low certainty[8]

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			This study has yielded promising results and warrants further RCT study with larger sample sizes.	
Famotidine **Findings are encouraging and informative to future trials to test efficacy in a larger population**				
OBSERVATIONAL (clinical)				
Freedberg [96]; observational (retrospective); 2020	Famotidine, classified as present if famotidine was received within 24 hours of hospital admission and otherwise classified as absent; 1,620; unclear, 43.8% male	Diabetes 20.6%, hypertension 28.2%, CAD 7.2%, pulmonary disorders 7.5%, CKD 8.7%	142 (8.8%) patients were intubated and 238 (15%) died; 340 (21%) patients met the composite study outcome (death or intubation); researchers found that the use of famotidine was associated with reduced risk for death or intubation (adjusted hazard ratio (aHR) 0.42, 95% CI 0.21-0.85) and also with reduced risk for death alone (aHR 0.30, 95% CI 0.11-0.80). After balancing baseline patient characteristics using propensity score matching, these relationships were unchanged (HR for famotidine and death or intubation 0.43, 95% CI 0.21-0.88). Proton pump inhibitors, which also suppress gastric acid, were not associated with reduced risk for death or intubation. Note: nonrandomized, potentially confounded, propensity score matched but considered not optimal, small sample size, small events, and not optimally comparative. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Very low certainty[1]
Lenzilumab **Findings are encouraging and informative to future trials to test efficacy in a larger population**				
OBSERVATIONAL (clinical)				
Temesgen [106]; observational case-series; 2020	Lenzilumab 600 mg intravenously; 12; median 65 (52-70); 67% males	Diabetes 58%, hypertension 58%, obesity 50%, CKD 17%, CAD 17%, COPD 17%; not clearly reported	Clinical improvement was observed in 11 out of 12 (92%) patients treated with lenzilumab; median time to discharge of 5 days; researches report a significant improvement in oxygenation; proportion of patients with SpO2/FiO2 < 315 at the end of observation was 8% vs. compared to 67% at baseline (p=0.00015). A significant improvement in mean CRP and IL-6 values on day 3 following lenzilumab administration was also observed (137.3 mg/L vs 51.2 mg/L, p = 0.040; 26.8 pg/mL vs 16.1 pg/mL, p = 0.035; respectively). Cytokine analysis showed a reduction in inflammatory myeloid cells two days after lenzilumab treatment. There were no treatment-emergent adverse events attributable to lenzilumab, and no mortality in this cohort of patients with severe and critical COVID-19 pneumonia. Note: Case-series, nonrandomized, confounded, small sample size, no adjustments, uncertain findings, but suggests further research examination	High; Very low certainty[1]
Leflunomide **Findings are encouraging and informative to future trials to test efficacy in a larger population**				
OBSERVATIONAL (clinical)				
Wang [117]; observational comparative; 2020	Hospitalized adult patients (≥18 years of age) with radiologically confirmed pneumonia and SARS-CoV-2 positive for more than 28 days despite standard care were assigned to receive standard of care (SOC, grp I) or leflunomide + SOC (grp 2), 12 in group 1 vs 15 group 2; 27; median age 62 (43-70); 52% male	Hypertension 26%, diabetes 7%, hyperlipidemia 19%, cardiovascular 11%, cancer 4%; NR	By day 14, the median time to SARS-CoV-2 clearance was 6.0 days (range 1-12, IQR 1-12) for grp 2 patients. In grp 1, two patients converted to viral negative on days 1 and 6 (P=0.002). The 14-day discharge rate was 73.3% (11/15) for the grp 2 versus 8.3% (1/12) for grp 1 (P=0.001). The 30-day discharge rate was 100% (15/15) for the grp 2 versus 66.7% (8/12) for grp 1. No severe adverse events or deaths were reported. Researchers concluded that leflunomide is effective in enhancing SARS-CoV-2 clearance and hospital discharge in refractory COVID-19 patients. The addition of leflunomide to SOC did not increase adverse events versus SOC. Note: nonrandomized, selection bias, small sample size and	High; Very low certainty[1]

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			events, single center. Findings suggest the need for further RCT study.	

Notes and considerations:

*ratings are high vs moderate-low vs low RoB; note, high risk for RCTs would be for serious flaws in randomization, allocation concealment, blinding, severe data loss, baseline imbalances etc. and for observational non-randomized studies (single or two-arm), there could be no adjustment for confounders, no masking, stratification etc.
**ratings are high, moderate, low, very low certainty (GRADE); note using GRADE, RCTs start as high certainty/quality evidence, observational studies start as low certainty/quality; for imprecision, the focus is on sample size, number of reported events, width of confidence intervals (if reported); note also that the use of GRADE in this application for RCTs and observational studies focuses mainly on risk of bias and imprecision given we are dealing with single studies and domains of consistency (heterogeneity), indirectness, and publication bias are not ideally applicable. However, we would consider indirectness if the evidence emerged from a study that used a different patient group e.g. if looking at lopinavir/ritonavir in COVID-19 patients, but the evidence emerged from HIV infected persons, we would downgrade for indirectness. Though we are focusing at present on COVID-19 patients. We would consider the magnitude of effect, dose-response, and plausible residual confounding for observational study designs.
[1]risk of bias (potentially selection bias and residual confounding bias if observational and not randomized in design) and imprecision (small sample sizes, small event numbers, 95% CI spans both sides of line of no effect and thus a different decision could be made at either end), downgrade one level each (one may argue that since observational studies start as low certainty that the risk of bias due to lack of randomization etc. is already accounted for and no need to downgrade for risk of bias; in any case, one downgrade for imprecision still leads to very low; in some sense in the use of the ROBINS-I tool for risk of bias in nonrandomized studies that is suggested to start at high certainty, eventually, certainty will become low due to the challenges of nonrandomization, selection bias, confounding bias etc.).
[2]risk of bias for in vitro studies uses OHAT risk of bias tool/NTP
url: Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Available online: http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf whereby questions such as i) was administered dose or exposure level adequately randomized ii) was allocation to study groups adequately concealed and iii) can we be confident in the exposure characterization, were answered. Rating are definitely high, probably high, probably low, definitely low.
[3]imprecision downgrade one level due to small sample size and/or events.
[4]risk of bias downgrade due to open-label and imprecision due to small sample size and events; down-grade of two levels
[5]Low risk of bias based on application of AMSTAR II tool (url: https://amstar.ca/Amstar_Checklist.php).
[6]Very low RCT due to single downgrade risk of bias and double for imprecision
[7]AMSTAR II critical appraisal of systematic review and/or meta-analysis, url: https://amstar.ca/docs/AMSTAR-2.pdf (Accessed on April 1st 2020); citation: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21; 358: j4008.
[8] Double downgrade due to imprecision (small number of events and sample size)

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Appendix

Figure 1: Adverse events combined in use of HCQ / CQ (pre-publications, non-peer review)

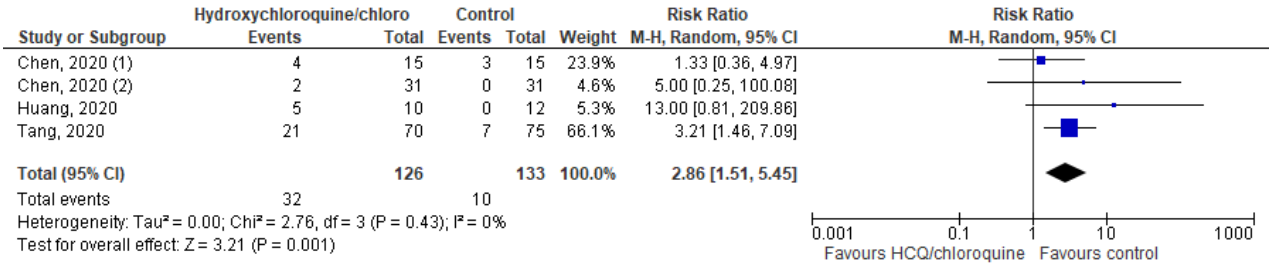

Table 1: GRADE certainty hydroxychloroquine/chloroquine adverse events (all combined)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine/chloroquine	no HCQ/CQ or control	Relative (95% CI)	Absolute (95% CI)		
Adverse outcomes (all combined)												
4	randomised trials	serious [a]	not serious	not serious	serious [b]	none	32/126 (25.4%)	10/133 (7.5%)	**RR 2.86** (1.51 to 5.45)	**140 more per 1,000** (from 38 more to 335 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. unclear/absent randomization, concealment, blinding, sub-optimal outcomes, imbalanced co-treatment assignment

b. small sample size, small number of events (OIS not met)

Figure 2: Adverse events combined in use of arbidol (pre-publications, non-peer review)

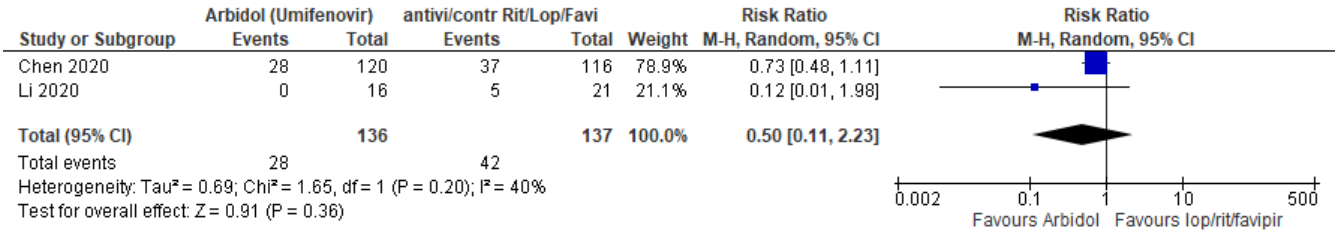

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Table 2: GRADE certainty arbidol adverse events (all combined)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	arbidol	no arbidol/control	Relative (95% CI)	Absolute (95% CI)		
Adverse outcomes (combined)												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	28/136 (20.6%)	42/137 (30.7%)	**RR 0.50** (0.11 to 2.23)	**153 fewer per 1,000** (from 273 fewer to 377 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Sub-optimal randomization, allocation concealment, blinding etc.

b. Small sample size, small event number, OIS not met, wide CIs, 95% CI crosses benefits and harms

Figure 3: Adverse events combined in use of corticosteroids (pre-publications, non-peer review)

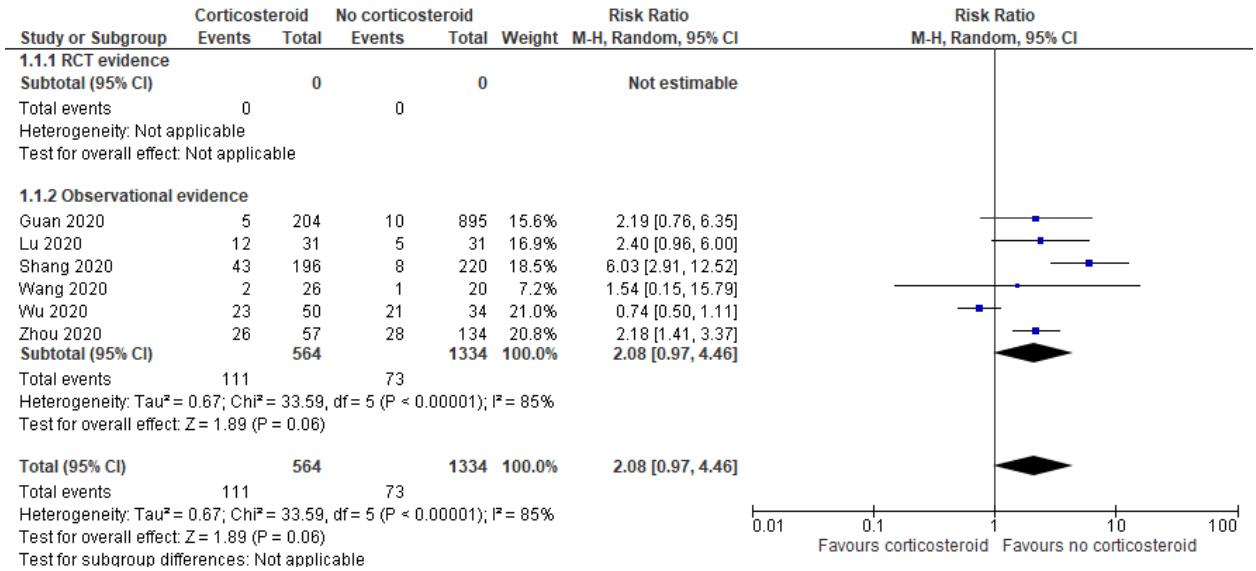

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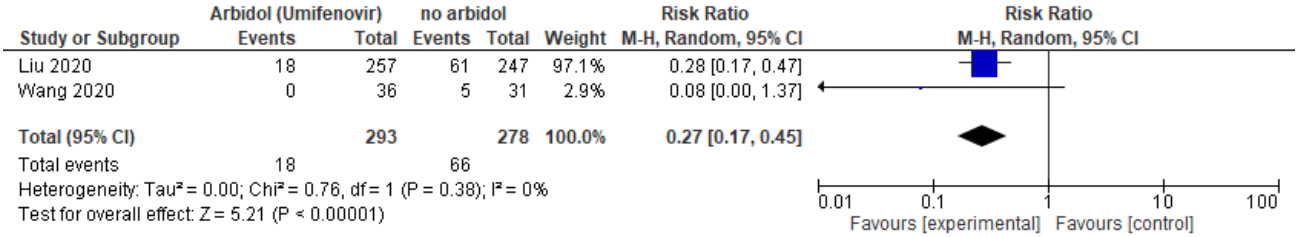
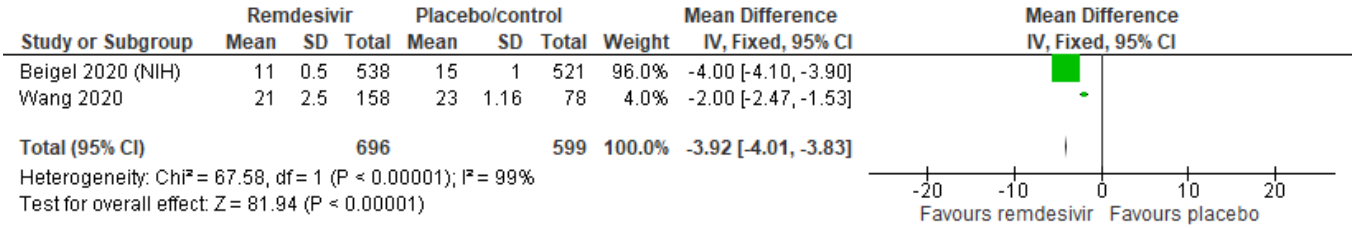
Figure 4: Mortality using arbidol (pre-publications, non-peer review)

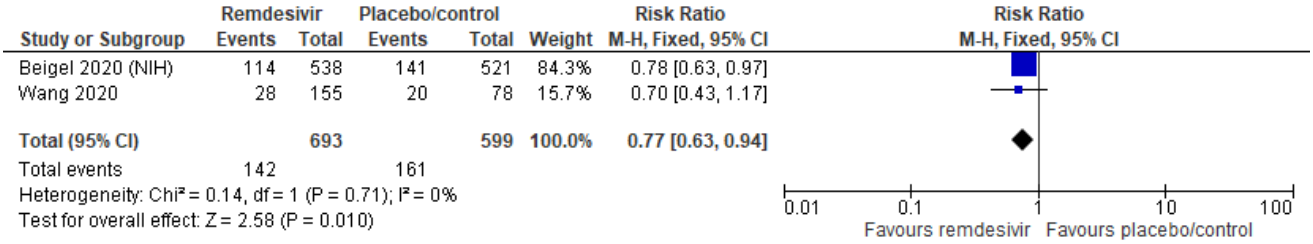


Figures 5a-d: Remdesivir

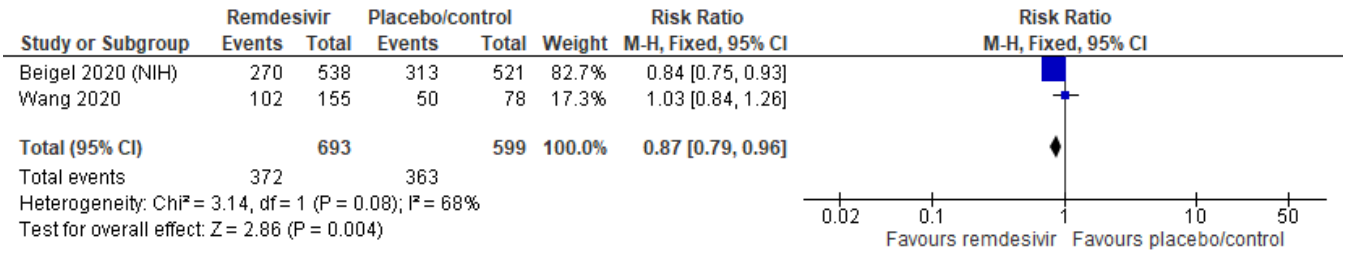
a. Time to clinical improvement



b. Serious adverse events



c. All adverse events



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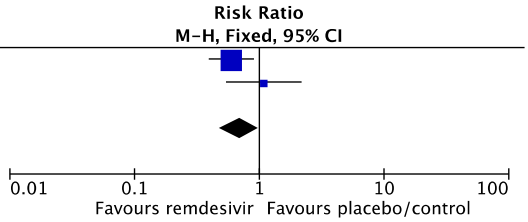
d. Mortality

Study or Subgroup	Remdesivir Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Beigel 2020 (AC)	32	451	54	454	80.1%	0.60 [0.39, 0.91]
Wang 2020	22	158	10	78	19.9%	1.09 [0.54, 2.18]
Total (95% CI)		**609**		**532**	**100.0%**	**0.69 [0.49, 0.99]**
Total events	54		64			

Heterogeneity: $Chi^2 = 2.09$, df = 1 (P = 0.15); $I^2 = 52\%$
Test for overall effect: Z = 2.02 (P = 0.04)



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