COVID-NMA

- Summary of Main Results -

Introduction

Since the early months of the COVID-19 pandemic (March 2020), the COVID-NMA initiative, an international initiative working in conjunction with the World Health Organization (WHO), and led by a team of researchers from Cochrane and other institutions, has been producing relevant, accessible, up-to-date, and trustworthy synthesis of high-quality evidence about the efficacy and safety of interventions for the prevention or treatment of COVID-19, as well as mapping the trial evidence.

In our goal to aid researchers, funders, regulatory authorities, and guideline developers in their evidence-based decision making we have developed additional online tools, such as interactive online data visualization, which map the registered trials assessing treatments and vaccines for Covid-19. These tools allow the user to visualize all planned and ongoing trials, filtering, for example, by their status, country, design, registration date, type of treatment or vaccine being studied.

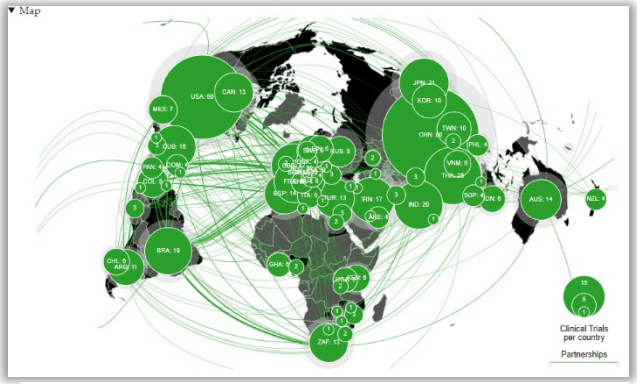

Figure 1: Screenshot of the living data visualization tool

The living systematic review identifies weekly new trials, and all data are extracted in duplicate, assessed for risk of bias, and analysed biweekly. We produce forest plots for all comparisons and use GRADE to assess the certainty of the evidence.

The app (metaCOVID) also allows the user to perform their own analyses using the data extracted. They can select particular populations of interest, define subgroups and set additional exclusion criteria based on risk of bias, publication status and missing outcome data.

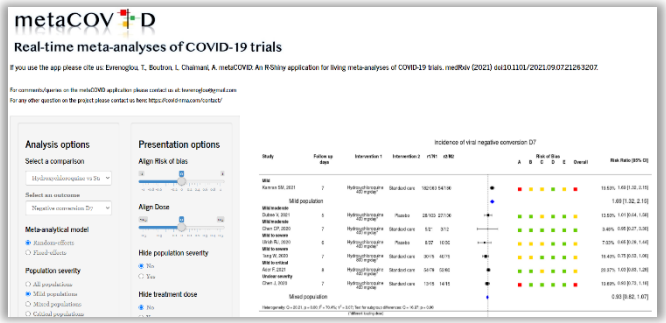

Figure 2: Screenshot of the tool to do meta-analyses and generate forest plots in real time (metaCOVID)

As part of a broader strategy to disseminate the results of the COVID-NMA initiative more effectively, we will be generating monthly reports summarizing our main findings. Our goal is to present an overview of what is known with moderate or high certainty, highlighting the interventions that appear to be effective or not, to make it easy for researchers and guideline developers to stay up to date with the current evidence on the prevention and treatment of COVID-19.

The information in this first edition of the Summary of Main Results report represents the COVID-NMA results up to **April 4th, 2022**. Given the living nature of this review, though, the most up to date results will be available on covid-nma.com, and any studies pending data extraction are available here.

As this is the first Summary of Main Results report, any feedback will be particularly valued. Feel free to get in touch with us using our contact form and to disseminate this document on twitter (@Covid-NMA).

Recent publications from the COVID-NMA team

The following articles from the COVID-NMA team have recently been published:

- Interleukin-1 blocking agents for treating COVID-19 (Davidson M et al, Cochrane Library) Read
- Interleukin-6 blocking agents for treating COVID-19: a living systematic review (Ghosn L et al, Cochrane Library) Read
- The COVID-NMA Project: Building an Evidence Ecosystem for the COVID-19 Pandemic (Boutron I et al. Annals Intern Med 2020) Read
- Research response to COVID-19 needed better coordination and collaboration: a living mapping of registered trials (Nguyen et al. J Clin Epidemiol 2020) Read
- Interventions for the prevention and treatment of COVID-19: a living mapping of research and living network meta-analysis (Boutron I et al, Protocol, Cochrane Library) Read
- Day-to-day discovery of preprint-publication links (Cabanac G et al, Scientometrics) Read
- Changes in evidence for studies assessing interventions for COVID-19 reported in preprints: meta-research study (Oikonomidi T et al, BMC Medicine) Read

What is the current evidence regarding treatment of hospitalized Covid-19 patients?

Updated on April 4th, 2022

Pharmacologic treatments in hospitalized patients

Critical outcomes of interest: Clinical improvement (around day 28 or day 60), WHO Clinical Progression Score ≥ 7 (around day 28 or day 60), all-cause mortality (around day 28 or day 60), viral negative conversion (around day 7), adverse events and serious adverse events.

For most pharmacological treatments in hospitalized patients, the certainty of the evidence is still low or very low. Below is a summary of pharmacological interventions that have **results in favor of a beneficial effect** so far compared with placebo or standard care. We only highlight outcomes of moderate and high certainty; other outcomes are of low or very low certainty.

- **Anakinra** (a monoclonal antibody) probably reduces the risk of WHO score ≥7 (i.e. mechanical ventilation or death, around 28 days) in hospitalized patients, as well as slightly increases the likelihood of clinical improvement around 28 days. The risk of adverse events probably does not increase. It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Baricitinib** (a kinase inhibitor) reduces the risk of WHO score ≥7 (i.e. mechanical ventilation or death, around 28 days) in hospitalized patients, although it results in little to no difference in clinical improvement around 28 days. It is likely to reduce the risk of all-cause mortality (around 28 days and around 60 days). It probably does not increase the risk of adverse events but probably decreases the risk of serious adverse events.
- **Casirivimab + Imdevimab (REGN-COV2)** (Monoclonal antibody combination) probably reduces the risk of all-cause mortality (around 28 days), although the likelihood of clinical improvement around 28 days and around 60 days probably is not improved. It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Corticosteroids** probably reduce the risk of all-cause mortality (around 28 days) in hospitalized patients. We pooled together oral and intravenous corticosteroids of participants with various disease severity. Of note, the largest study (the RECOVERY trial) found in subgroup analysis that “differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization”, and that “the use dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.”
- **Tocilizumab** (a monoclonal antibody) is likely to reduce the risk of all-cause mortality (around 28 days) in hospitalized patients, although it probably results in little to no difference on clinical improvement around 28 days. It is one of the interventions that have been authorized in the EU to treat Covid-19.

For the treatments below there are outcomes with moderate or high certainty indicating **uncertainty of benefit or harm**

- **Remdesivir** (an anti-viral), which is one of the interventions recommended by the NIH and which has been authorized in the EU to treat COVID-19, we found that the risk estimate for all-cause mortality (around 28 days) and its wide confidence interval (RR 0.91, 95% CI 0.74 to 1.11) point to uncertainty of benefit or harm.

For the treatments below there are outcomes with moderate or high certainty indicating **no evidence of beneficial effects** (e.g. clinical improvement or reduction in mortality) or an increase in the risks of negative effects (e.g. serious adverse events) compared with placebo or standard care:

- **Aspirin** (acetylsalicylic acid), **Azithromycin** (an antimicrobial), **Hydroxychloroquine** (an antimalarial) and **Colchicine** (an anti-inflammatory) probably do not reduce the risk of all-cause mortality (around 28 days) and probably do not increase the likelihood of clinical improvement (around 28 days).
- **Bamlanivimab** (a monoclonal antibody) probably results in little to no difference on clinical improvement around day 60.
- **Canakinumab** (a monoclonal antibody) probably results in little to no difference on clinical improvement around 28 days and in little to no difference in the risk of adverse events.
- **Convalescent plasma** probably results in little to no difference on clinical improvement around 28 days or all-cause mortality (around 28 days).
- **Lopinavir + Ritonavir** (an anti-viral) probably does not reduce the risk of all-cause mortality (around 28 days).
- **Sotrovimab** (a monoclonal antibody) probably results in little to no difference clinical improvement around day 60. Furthermore, it probably increases the risk of serious adverse events. While the NIH recommends this intervention for outpatients, it has not been recommended for hospitalized patients. Similarly, this intervention has been authorized in the EU to treat COVID-19, but only in patients who do not require supplemental oxygen and are at increased risk of the disease becoming severe.
- The use of **therapeutic anticoagulants compared to the use of prophylactic anticoagulants** probably results in little to no difference on clinical improvement around 28 days.

For another intervention authorized by the European Medicines Association (Ritonavir alone) we have not yet identified randomized controlled trials reporting its effectiveness.

Summary table on next page…

Summary Table: Pharmacologic treatments in hospitalized patients

(Updated on April 4th, 2022)

Legend:

Moderate/**High** certainty of benefit
Moderate/**High** certainty of little or no difference
Moderate/**High** certainty of harm

Treatment (vs standard care or placebo unless stated otherwise)	Treatment effectiveness							Adverse events	
	Improvement			Covid-19 events					
	Viral negative conversion (D7)	Clinical improvement (D28)	Clinical improvement (D60)	WHO progression score (level ≥7) (D28)	WHO progression score (level ≥7) (D60)	All-cause mortality (D28)	All-cause mortality (D60)	Adverse events	Serious adverse events
Anakinra	low certainty	1.10 (1.00-1.20)	very low certainty	0.64 (0.42 - 0.98)		low certainty	very low certainty	1.02 (0.94-1.10)	low certainty
Aspirin		**1.02 (1.00 - 1.04)**				0.97 (0.90 - 1.04)			
Azithromycin		1.02 (0.99-1.05)		very low certainty		**0.97 (0.89-1.06)**			
Bamlanivimab (LY-CoV555)			0.98 (0.90 - 1.07)	low certainty		low certainty	low certainty		low certainty
Baricitinib		**1.02 (1.00 - 1.05)**		**0.87 (0.78 - 0.97)**		0.75 (0.58 - 0.98)	0.69 (0.56 - 0.86)	0.96 (0.88 - 1.05)	0.77 (0.64 - 0.94)
Canakinumab		1.05 (0.96-1.14)		low certainty		low certainty	very low certainty	1.02 (0.86-1.21)	low certainty
Casirivimab + Imdevimab (REGN-COV2)		1.02 (0.99 - 1.04)	1.04 (0.97 - 1.12)	low certainty		0.93 (0.86 - 1.01)	low certainty		
Colchicine		1.02 (0.96 - 1.08)		low certainty		0.99 (0.93 - 1.06)	very low certainty	low certainty	very low certainty
Convalescent plasma	very low certainty	1.00 (0.97-1.02)		low certainty	very low certainty	0.97 (0.92 - 1.03)	very low certainty	low certainty	low certainty
Corticosteroids	very low certainty	very low certainty		low certainty		**0.91 (0.85-0.98)**	very low certainty	very low certainty	very low certainty
Hydroxychloroquine	very low certainty	0.97 (0.94 - 1.01)		low certainty	very low certainty	1.07 (0.98 - 1.17)	very low certainty	low certainty	very low certainty
Lopinavir + Ritonavir	low certainty	low certainty		very low certainty	low certainty	1.02 (0.92-1.12)		low certainty	very low certainty
Remdesivir	low certainty	low certainty		low certainty		0.91 (0.74-1.11)	very low certainty	low certainty	very low certainty
Sotrovimab			1.05 (0.97 - 1.15)	low certainty		low certainty	low certainty	low certainty	2.03 (1.32 - 3.13)
Tocilizumab		**1.05 (1.00-1.09)**	very low certainty	low certainty		**0.88 (0.82-0.95)**	low certainty	low certainty	very low certainty
Therapeutic vs Prophylactic anticoagulant	very low certainty	0.99 (0.96-1.01)		very low certainty		very low certainty	low certainty	very low certainty	very low certainty

All values are RR (95% CI). Bolded results have a high level of certainty, while non-bolded results have a moderate level of certainty. Last updated: April 4th 2021. Click on the treatment to access the corresponding site at covid-nma.com.

Continues with non-pharmacologic treatments on next page…

Non-pharmacologic treatments in hospitalized patients

For most of the non-pharmacological treatments, the certainty of the evidence is still low or very low. We have moderate certainty that:

Prone position vs Standard care probably slightly reduces the risk of requiring mechanical ventilation or death (WHO progression score level 7 or above) around 28 days in hospitalized patients. There are currently nine registered trials assessing this comparison that have finished recruitment, so we soon might have more data on this intervention.

Summary Table: Non- pharmacologic treatments in hospitalized patients
(Updated on April 4th, 2022)

Legend:

Moderate/**High** certainty of benefit
Moderate/**High** certainty of little or no difference
Moderate/**High** certainty of harm

Treatment (vs standard care or placebo unless stated otherwise)	Treatment effectiveness							Adverse events	
	Improvement			Covid-19 events					
	Viral negative conversion (D7)	Clinical improvement (D28)	Clinical improvement (D60)	WHO progression score (level ≥7) (D28)	WHO progression score (level ≥7) (D60)	All-cause mortality (D28)	All-cause mortality (D60)	Adverse events	Serious adverse events
Prone position vs Standard care		low certainty		0.86 (0.76 - 0.99)		low certainty		very low certainty	very low certainty

All values are RR (95% CI). Bolded results have a high level of certainty, while non-bolded results have a moderate level of certainty. Last updated: April 4th 2021. Click on the treatment to access the corresponding site at covid-nma.com.

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