



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Guidelines

ESCMID COVID-19 living guidelines: drug treatment and clinical management

Michele Bartoletti^{1,2,*}, Ozlem Azap³, Aleksandra Barac^{4,5}, Linda Bussini¹, Onder Ergonul⁶, Robert Krause⁷, José Ramón Paño-Pardo^{8,9}, Nicholas R. Power¹⁰, Marcella Sibani¹¹, Balint Gergely Szabo^{12,13}, Sotirios Tsiodras¹⁴, Paul E. Verweij¹⁵, Ines Zollner-Schwetz⁷, Jesús Rodríguez-Baño¹⁶

¹ Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico di Sant'Orsola, Bologna, Italy

² Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

³ Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Başkent University, Ankara, Turkey

⁴ Clinic for Infectious and Tropical Diseases, Clinical Centre of Serbia, Belgrade, Serbia

⁵ Faculty of Medicine, University of Belgrade, Belgrade, Serbia

⁶ Koc University Research Centre for Infectious Diseases, Istanbul, Turkey

⁷ Division of Infectious Diseases, Department of Internal Medicine, Medical University of Graz, Graz, Austria

⁸ Fundación Instituto de Investigación Sanitaria Aragón (IIS Aragón), Biomedical Research Centre of Aragón (CIBA), Zaragoza, Spain

⁹ Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

¹⁰ Royal College of Physicians of Ireland, Setanta Pl, Dublin, Ireland

¹¹ Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy

¹² South Pest Central Hospital, National Institute of Haematology and Infectious Diseases, Budapest, Hungary

¹³ School of PhD Studies, Semmelweis University, Budapest, Hungary

¹⁴ Fourth Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece

¹⁵ Department of Medical Microbiology and Radboudumc-CWZ Centre of Expertise for Mycology, Radboud University Medical Centre, Nijmegen, the Netherlands

¹⁶ Clinical Unit of Infectious Diseases and Microbiology Virgen Macarena University Hospital and Department of Medicine, University of Seville, Institute of Biomedicine of Seville, Seville, Spain

ARTICLE INFO

Article history:

Received 7 September 2021

Received in revised form

29 October 2021

Accepted 4 November 2021

Available online 22 November 2021

Editor: L. Leibovici

Keywords:

COVID-19

Disease progression

Guidelines

Mortality

Treatment

ABSTRACT

Scope: In January 2021, the ESCMID Executive Committee decided to launch a new initiative to develop ESCMID guidelines on several COVID-19-related issues, including treatment of COVID-19.

Methods: An ESCMID COVID-19 guidelines task force was established by the ESCMID Executive Committee. A small group was established, half appointed by the chair, and the remaining selected with an open call. Each panel met virtually once a week. For all decisions, a simple majority vote was used. A long list of clinical questions using the PICO (population, intervention, comparison, outcome) format was developed at the beginning of the process. For each PICO, two panel members performed a literature search with a third panellist involved in case of inconsistent results. Voting was based on the GRADE approach.

Questions addressed by the guideline and recommendations: A synthesis of the available evidence and recommendations is provided for each of the 15 PICOs, which cover use of hydroxychloroquine, bamlanivimab alone or in combination with etesevimab, casirivimab combined with imdevimab, ivermectin, azithromycin and empirical antibiotics, colchicine, corticosteroids, convalescent plasma, favipiravir, remdesivir, tocilizumab and interferon β -1a, as well as the utility of antifungal prophylaxis and enoxaparin. In general, the panel recommended against the use of hydroxychloroquine, ivermectin, azithromycin, colchicine and interferon β -1a. Conditional recommendations were given for the use of monoclonal antibodies in high-risk outpatients with mild–moderate COVID-19, and remdesivir. There was insufficient evidence to make a recommendation for use of favipiravir and antifungal prophylaxis, and it was recommended that antibiotics should not be routinely prescribed in patients with COVID-19 unless bacterial coinfection or secondary infection is suspected or confirmed. Tocilizumab and corticosteroids were recommended for treatment of severe COVID-19 but not in outpatients with non-severe COVID-19.

* Corresponding author: Michele Bartoletti, Infectious Diseases Unit, Sant'Orsola Malpighi Hospital, Via Massarenti 11, 40138, Bologna, Italy.
E-mail address: m.bartoletti@unibo.it (M. Bartoletti).

Scope: The aim of the present guidance is to provide evidence-based recommendations for management of adults with coronavirus disease 2019 (COVID-19). More specifically, the goal is to aid clinicians managing patients with COVID-19 at various levels of severity including outpatients, hospitalized patients, and those admitted to intensive care unit. Considering the composition of the panel, mostly clinical microbiologists or infectious disease specialists with no pulmonology or intensive care background, we focus only on pharmacological treatment and do not give recommendations on oxygen supplement/support. Similarly, as no paediatricians were included in the panel; the recommendations are only for adult patients with COVID-19. Considering the current literature, no guidance was given for special populations such as the immunocompromised. **Michele Bartoletti, *Clin Microbiol Infect* 2022;28:222**

© 2021 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

Background

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a dramatic impact on healthcare systems, the global economy and social life. The clinical spectrum of COVID-19 induced by SARS-CoV-2 is broad with the majority of infected individuals experiencing only mild or subclinical illness, especially in the early phase of disease [1]. However, 14–30% of hospitalized patients with COVID-19 develop severe respiratory failure requiring intensive care [2–4]. Additionally, as the angiotensin-converting enzyme 2 (ACE2) receptor is widely distributed in human organs and tissues, manifestations of COVID-19 involve many organs including the central nervous system, kidneys, myocardium and gut.

As of 6 July 2021, worldwide more than 184 million people have tested positive for SARS-CoV-2 and nearly 4 million have died of COVID-19. In light of this dramatic situation, the ongoing pandemic generated a historical effort involving many researchers worldwide and prompted an unprecedented number of clinical trials. According to [ClinicalTrials.gov](https://clinicaltrials.gov), as of 10 March 2021, nearly 5000 studies are investigating COVID-19.

Motivations for guideline development

ESCMID did not develop its own recommendations at the start of the pandemic for several reasons: clinical overload of most members, avoid duplication of ongoing efforts, heterogeneity of national recommendations, and lack of appropriate evidence. The latter is particularly relevant, since issuing guidance based on inappropriate evidence-base might do more harm than good. In January 2021, the ESCMID Executive Committee (EC) decided to launch a new initiative to develop ESCMID guidelines on several COVID-19-related issues.

Methods

An ESCMID COVID-19 guidelines task force was established by the ESCMID EC. For each set of guidelines, a small group was established (10–15 panellists). Half were appointed by the chair, in agreement with the EC, and the remaining were selected with an open call carried out on January 2021 and advertised on all ESCMID channels. The ESCMID guidelines subcommittee evaluated the applications and issued a recommendation about inclusion/exclusion of each applicant. As for all ESCMID initiatives, balance in terms of gender, clinical specialty and country was maintained.

Project management

Each panel met virtually once a week. For all decisions, a simple majority vote was used and a decision was made in case of $\geq 80\%$ of agreement.

A long list of clinical questions using the PICO (population, intervention, comparison, outcome) format was developed at the beginning of the process. A maximum number of 15 PICOs was set and selected by vote (the 15 top-rated PICOs were chosen). Criteria for prioritization and vote were general interests by clinicians with clinical microbiology and infectious disease background and availability of evidence, especially for critical outcomes that included mortality or disease progression (intensive care unit (ICU) admission or need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO)). Additional PICOs will be developed at a further stage.

Evidence review

To avoid duplication of efforts, rather than performing a systematic review of the literature for each PICO, each panel reviewed whether evidence for each PICO was already available among the many ongoing initiatives [6–8]. For each PICO and evidence synthesis, ADOLPMENT criteria were used (Table 1). For each PICO, two panel members performed a literature search with a third panellist involved in case of inconsistent results. The results of the searches were presented to the panel during weekly meetings for discussion and voting (quality of evidence, evidence-to-decision criteria, need for update, etc.) based on the GRADE approach.

Definitions

WHO severity criteria for COVID-19 were used [9]. Data from the European Centre for Disease Prevention and Control (ECDC) was used to define risk factors and groups for severe COVID-19 [10].

Questions addressed by guidelines and recommendations

For each PICO question, the motivations for use, patient preferences and additional comments are presented in [Supplementary Appendix 1](#). A summary of all recommendations is presented in [Table 2](#).

What is the effect of hydroxychloroquine treatment on mortality or disease progression in patients with mild COVID-19 compared with no treatment?

Narrative synthesis of evidence

Twenty-three randomized trials in >10 000 patients have assessed the effect of hydroxychloroquine (HCQ) on COVID-19 compared with standard of care (SOC). For the present assessment, 19 trials were included (Table 3). HCQ had no impact on death (risk ratio (RR) 1.06, 95% CI 0.97–1.16) or need for mechanical ventilation (RR 1.08, 95% CI 0.91–1.28). The majority of patients

Table 1
ADOLOPMENT criteria used to determine the suitability of the existing evidence synthesis (need for updating the literature search and for revising the grading of the quality of the evidence)

Criterion	New systematic review (a systematic review that does not qualify as major or minor update)	Major update (first criterion applies and any of the following)	Minor update (all criteria must apply)
Prior review (for question)	No credible available systematic review exists for the question ^a	A credible systematic review exists ^a	A credible systematic review exists ^a
Full text reviewed for the question of interest	N/A	>20	≤20
New studies	N/A	>5	≤5
Evidence profile available	N/A	Not available	Available
Outcomes all addressed	Not all important outcomes addressed	All-important outcomes addressed	All-important outcomes addressed
Type of studies	Search for observational studies		

^a A credible available review is one that has publicly available data, has been conducted in the past 4 months (or a different timescale if deemed appropriate by the drafting group), scores highly on the AMSTAR or another tool, has a reproducible search strategy, meta-analysis (that can be reproduced), existing accessible risk of bias evaluation of individual studies (that can be reproduced).

were included in the RECOVERY and SOLIDARITY trials. RECOVERY is an investigator-initiated platform trial at 176 hospitals in the UK. Within this, 1561 patients were randomized to receive HCQ and 3155 to SOC. No difference in 28-day mortality was observed between HCQ and SOC (RR 1.09; 95% CI 0.97–1.23; *p* 0.15) [11]. In SOLIDARITY, hospitalized patients with COVID-19 were randomized to remdesivir (*n* = 2750), HCQ (*n* = 954), lopinavir (*n* = 1411), interferon β-1a (*n* = 2063) or SOC (*n* = 4088). The primary outcome was 28-day mortality and occurred in 104 of 947 patients receiving HCQ and in 84 of 906 controls (RR 1.19; 95% CI 0.89–1.59; *p* 0.23) [12]. HCQ was not effective in smaller randomized controlled trials (RCTs) in hospitalized patients [13–15], hospitalized patients with severe [16–18] or mild–moderate disease [19–25], or outpatients [26–28]. Lastly, HCQ has not been associated with a faster decline of viral load or higher virological cure compared with SOC in hospitalized patients [19,22,25,28,29].

Safety

Concerns for safety and potential harm have been raised in observational trials and RCTs evaluating patients receiving HCQ. RECOVERY reported that those receiving HCQ experienced longer

in-hospital stay, lower probability of being discharged alive within the 28-day study period (RR 0.92; 95% CI 0.85–0.99) and higher chance to receive mechanical ventilation (30.7% vs. 26.9%; RR 1.14; 95% CI 1.03–1.27). A trend towards greater harm with HCQ was also seen in SOLIDARITY and other RCTs [12].

Recommendation

Strong recommendation against use of HCQ for COVID-19 (quality of evidence (QoE): high for critical outcomes).

What is the effect of bamlanivimab alone or in combination with etesevimab in reducing the risk of disease progression or mortality in patients with mild COVID-19 compared with no treatment?

Narrative synthesis of evidence

Bamlanivimab and etesevimab are recombinant neutralizing human IgG1κ monoclonal antibodies (mAbs) directed against the spike protein of SARS-CoV-2. They were evaluated in BLAZE-1, a randomized, double-blind, placebo-controlled, multipart phase 2/3

Table 2
Summary of recommendations and dosages

Severity of disease/ setting	Treatment recommended	Dosages	European medicine agency authorization ^a	Comments
Mild COVID-19 Outpatient setting	AntiSpike monoclonal antibodies (conditional recommendation)	Bamlanivimab 700 mg + etesevimab 1400 mg Casirivimab 1200 mg + Imdevimab 1200 mg	Rolling review	Only in patients with risk factors for disease progression ^b
Mild COVID-19 Inpatient setting	Casirivimab/imdevimab (conditional recommendation) Remdesivir (conditional recommendation)	Casirivimab 4 g plus imdevimab 4 g 200 mg IV loading dose, followed by 100 mg daily for 5 days	Rolling review Approved	
Severe or Critical COVID-19	Casirivimab/imdevimab (conditional recommendation) Dexamethasone (strong recommendation) Tocilizumab (Strong recommendation)	Casirivimab 4 g plus imdevimab 4 g 6 mg PO or IV daily for 10 days or until discharge 8 mg per kg of actual body weight (up to a maximum of 800 mg), as an intravenous infusion over a period of 1 hour. A second dose may be repeated 12 to 24 hr later	Rolling review Approved Approved	recommended in patients receiving oxygen supplement
	Remdesivir (conditional recommendation)	200 mg IV loading dose, followed by 100 mg daily for 5 days	Approved	Not recommended in patients requiring high-flow oxygen supplementation

Age ≥55 years and at least one of the following: cardiovascular disease; hypertension; chronic obstructive pulmonary disease or other chronic respiratory conditions.

^a <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments>; accessed 20 October 2021.

^b Risk factors for disease progression to consider for mAb treatment in adult patients: Body mass index ≥35, Chronic kidney disease, Diabetes, Immunosuppressive disease, Age ≥65 years.

Table 3
Grade evidence profile PICO1: Hydroxychloroquine for COVID-19

Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without hydroxychloroquine	With hydroxychloroquine			
Hydroxychloroquine for COVID-19 People: Patients with COVID-19 Settings: Inpatients (15 studies) outpatient (5 studies) Intervention: Hydroxychloroquine Comparison: No treatment					
All-cause mortality	168 per 1000	178 per 1000	RR 1.06 (0.97 to 1.16)	19 [12–16,18–21,23,25–28,110–114] (10 382 patients)	⊕⊕⊕⊕ High
	Difference: 10 more per 1000 (95% CI 5 fewer to 27 more)				
Invasive mechanical ventilation or ECMO	85 per 1000	92 per 1000	RR 1.08 (0.91 to 1.28)	8 [14,15,18–20,28,112,114] (5701 patients)	⊕⊕⊕⊕ High
	Difference: 7 more per 1000 (95% CI 8 fewer to 24 more)				
Hospitalization (end of follow-up)	55 per 1000	37 per 1000	RR 0.68 (0.41 to 1.13)	5 [26–28,110,113] (1345 patients)	⊕⊕⊖⊖ Low (serious imprecision and serious risk of bias)
	Difference: 18 fewer per 1000 (95% CI 32 fewer to 7 more)				
Clinical deterioration (within 28 days of treatment begin)	89 per 1000	72 per 1000	RR 0.81 (0.35 to 1.89)	1 [19] (247 patients)	⊕⊕⊖⊖ Low (very serious imprecision)
	Difference: 17 fewer per 1000 (95% CI 58 fewer to 79 more)				
Clinical Improvement (within 28 days of treatment begin)	756 per 1000	794 per 1000	RR 1.05 (0.91 to 1.2)	1 [19] (247 patients)	⊕⊕⊖⊖ Low (very serious imprecision)
	Difference: 38 more per 1000 (95% CI 68 fewer to 151 more)				
Discharge for hospital (within 28 days of treatment begin)	694 per 1000	680 per 1000	RR 0.98 (0.96 to 1.01)	5 [12,19,111,112,114] (7365 patients)	⊕⊕⊕⊕ High
	Difference: 14 fewer per 1000 (95% CI 28 fewer to 7 more)				
Adverse events (end of follow-up)	322 per 1000	538 per 1000	RR 1.67 (1.21 to 2.3)	11 [13,14,19–23,27,28,110,115] (2077 patients)	⊕⊕⊕⊖ Moderate (serious risk of bias)
	Difference: 216 more per 1000 (95% CI 68 more to 419 more)				
Serious adverse events (end of follow-up)	68 per 1000	74 per 1000	RR 1.09 (0.86 to 1.37)	11 [13,19,20,22,23,25,27–29,113,115] (2721 patients)	⊕⊕⊕⊖ Moderate (Serious risk of bias)
	Difference: 6 more per 1000 (95% CI 10 fewer to 25 more)				

References: [12–16,18–29,110–115].

Evidence adopted: Australian National COVID-19 Evidence Taskforce (<https://app.magicapp.org/#/guideline/5446/section/78675>).

Evidence Search date: April 23–June 11.

trial enrolling outpatients with COVID-19. In the first dataset of BLAZE-1, bamlanivimab showed a trend towards decreased viral load vs. placebo with a significant difference for the 2800-mg dose [30]. The second dataset of the BLAZE-1 trial analysed patients randomized to receive a single infusion of bamlanivimab at different dosages, combined bamlanivimab and etesevimab, or placebo. Compared with placebo, a significant decrease in viral load was observed only for combination treatment ($\log -0.57$; 95% CI -1.00 to -0.14 ; p 0.01). The percentages of patients with COVID-19-related hospitalizations or emergency department visits were 5.8% ($n = 9$) for placebo, 1.0% ($n = 1$) for 700 mg, 1.9% ($n = 2$) for 2800 mg, 2.0% ($n = 2$) for 7000 mg and 0.9% ($n = 1$) for combination treatment [31].

On 10 March 2021, via press release, a new analysis on 769 high-risk patients with mild to moderate COVID-19 receiving bamlanivimab plus etesevimab ($n = 511$) or placebo ($n = 258$) was presented. There were four hospitalizations in patients taking bamlanivimab and etesevimab compared with 15 for placebo (risk reduction 87%; $p < 0.0001$) [32].

Overall, in high-risk outpatients bamlanivimab alone (RR 0.26; 95% CI 0.09–0.75; Table 4) or combined with etesevimab (RR 0.30; 95% CI 0.16–0.59; Table 5) is associated with reduced hospitalization. Bamlanivimab plus etesevimab is also associated with reduction in 29-day mortality (RR 0.05; 95% CI 0.00–0.80) in the same population (Table 5).

Bamlanivimab was effective in preventing severe disease among residents and staff of long-term care facilities (BLAZE-2 trial) [33], but not in recovery of hospitalized patients [34].

In vitro studies suggest that bamlanivimab plus etesevimab retains in vitro susceptibility to the B.1.1.7 (Alpha, UK variant), but has markedly reduced activity against the P1 (Gamma, Brazilian) and B.1.351 (Beta, South African) variants. Lastly, the SARS-CoV-2 variant B.1.617 (Delta, Indian) seems to be resistant to bamlanivimab, but its activity may be restored when combined with etesevimab.

Safety

Infusion-related adverse events were reported in 14% of patients in one study. Overall, adverse events were not higher vs. placebo in all studies [30–32].

Recommendation

Weak recommendation against use of bamlanivimab alone (QoE: very low).

Conditional recommendation for use of bamlanivimab plus etesevimab in high-risk outpatients with mild to moderate COVID-19 (QoE: moderate).

Table 4
Grade evidence profile PICO2: Bamlanivimab for COVID-19

People: Patients with COVID-19					
Settings: Outpatients					
Intervention: Bamlanivimab					
Comparison: No treatment					
Outcomes	Absolute effect ^a		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	With bamlanivimab	Without bamlanivimab			
Hospitalization (within 29 days from treatment)	5/309 (1.6%) Difference: 47 fewer per 1000 (95% CI 57 fewer to 16 fewer)	9/143 (6.3%)	RR 0.26 (0.09 to 0.75)	1 [30] (452 patients)	⊕⊕⊕⊖ Low (very serious imprecision)
Serious adverse events (end of follow-up)	0/309 (0%) Difference: 6 fewer per 1000 (95% CI 7 fewer to 19 more)	1/143 (0.7%) per 1000	RR 0.15 (0.01 to 3.78)	1 [30] (452 patient)	⊕⊕⊕⊖ Low (very serious imprecision)

References: [30].

Evidence adopted: Infectious Disease Society of America (IDSA) guidelines available at <https://www.idsociety.org/practice-guideline/COVID-19-guideline-treatment-and-management/>.

Evidence Search date: 23 April–11 June.

Table 5
Grade evidence profile PICO2: Bamlanivimab in combination with etesevimab for COVID-19

People: Patients with COVID-19					
Settings: Outpatients					
Intervention: Bamlanivimab/etesevimab					
Comparison: No treatment					
Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	With bamlanivimab/etesevimab	Without bamlanivimab/etesevimab			
All-cause mortality (within 29 days from treatment)	0/518 (0%) Difference: 19 fewer per 1000 (95% CI 31 fewer to 7 fewer)	10/517 (1.9%)	RR 0.05 (0.00 to 0.80)	1 [116] (1035 patients)	⊕⊕⊕⊖ Low (due to serious imprecision)
Hospitalization (within 29 days from treatment)	11/518 (2.1%) Difference: 49 fewer per 1000 (95% CI 58 fewer to 29 fewer)	36/517 (7.0%)	RR 0.30 (0.16 to 0.59)	1 [116] (1035 patients)	⊕⊕⊕⊖ Low (due to serious imprecision)
Serious adverse events (end of follow-up)	7/518 (1.4%) Difference: 4 more per 1000 (95% CI 5 fewer to 33 more)	5/517 (1%)	RR 1.40 (0.45 to 4.37)	1 [116] (1035 patients)	⊕⊕⊕⊖ Low (serious imprecision)

References: [116].

Evidence adopted: Infectious Disease Society of America (IDSA) guidelines available at <https://www.idsociety.org/practice-guideline/COVID-19-guideline-treatment-and-management/>.

Evidence Search date: 23 April–11 June.

What is the effect of casirivimab combined with imdevimab in reducing the risk of disease progression or mortality in patients with mild COVID-19 compared with no treatment?

Narrative synthesis of evidence

Casirivimab and imdevimab were assessed in a phase 1–3 trial in which patients were randomized to placebo, 2.4 g of combination therapy (casirivimab 1200 mg and imdevimab 1200 mg), or 8.0 g of combination therapy (4.0 g casirivimab and 4.0 g imdevimab). The combination of casirivimab and imdevimab was significantly associated with reduction of viral load [35], COVID-19–related hospitalization, and all-cause death vs. placebo (71.3% reduction; 1.3% vs. 4.6%; $p < 0.0001$) [35]. A significant effect was also seen in patients with baseline positive serum anti-SARS-CoV-2 antibodies [35]. Casirivimab combined with imdevimab was associated with a lower rate of hospitalization (RR 0.27; 95% CI 0.11–0.65; Table 6).

Hospitalized patients

The combination of casirivimab (4.0 g) plus imdevimab (4.0 g) was assessed in RECOVERY and was associated with lower 28-day mortality among anti-SARS-CoV-2 Ab seronegative patients at baseline (RR 0.80; 95% CI 0.70–0.91; $p 0.0010$) [36].

Safety

The rate of adverse events was similar between patients receiving casirivimab plus imdevimab or placebo, while the combination showed fewer serious adverse events [35,36].

Recommendation

Conditional recommendation for use of combination casirivimab plus imdevimab in high-risk outpatients with mild–moderate COVID-19 (QoE: moderate for hospitalization; low for 29-day mortality).

What is the effect of ivermectin in reducing the risk of disease progression or mortality in patients with mild COVID-19 compared with no treatment?

Narrative synthesis of evidence

Ivermectin has been evaluated in 18 RCTs using different dosing regimens and number of doses (1–5). Ten studies primarily had a virological outcome, i.e. virological reduction or clearance [37–46], while most reported secondary clinical outcomes like mechanical ventilation and death. Overall, 11 studies showed a positive effect of

Table 6
Grade evidence profile PICO3: Casirivimab combined with imdevimab for COVID-19

Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	With casirivimab combined with imdevimab	Without casirivimab combined with imdevimab			
People: Patients with COVID-19 Settings: Outpatients Intervention: Casirivimab (1200 mg) combined with imdevimab (1200 mg) Comparison: No treatment					
All-cause mortality (within 29 days from treatment)	1/736 (0.1%) Difference: 0 fewer per 1000 (95% CI 4 fewer to 4 more)	1/748 (0.4%)	RR 1.02 (0.06 to 16.20)	1 [35] (1484 patients)	⊕⊕⊖⊖ Low (due to very serious imprecision)
Hospitalization (within 29 days from treatment)	6/736 (1.9%) Difference: 22 fewer per 1000 (95% CI 27 fewer to 11 fewer)	23/748 (4.3%)	RR 0.27 (0.11 to 0.65)	1 [35] (1484 patients)	⊕⊕⊕⊖ Moderate (Due to serious imprecision)
Serious adverse events (end of follow-up)	50/3688 (1.2%) Difference: 27 fewer per 1000 (95% CI 31 fewer to 21 fewer)	74/1843 (4%)	RR 0.34 (0.24 to 0.48)	1 [35] (5531 patients)	⊕⊕⊕⊖ Moderate (Due to serious imprecision)

95% CI 95% Confidence interval; RR: Risk ratio

References: [35].

Evidence adopted: Infectious Disease Society of America (IDSA) guidelines available at <https://www.idsociety.org/practice-guideline/COVID-19-guideline-treatment-and-management/>.

Evidence Search date: 23 April–11 June.

Table 7
GRADE evidence profile for PICO 4: Ivermectin for COVID-19

Outcomes	Absolute Effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without Ivermectin (Standard Care)	With Ivermectin			
Ivermectin vs. Standard care					
People: Adult patients with COVID-19 Setting: Inpatients (10 studies), Outpatients (7 studies) Intervention: Ivermectin Comparison: Standard Care (15 studies), HCQ (1 study), Lopinavir/ritonavir (1 study)					
All-cause mortality Within 28 days of commencing treatment	53 per 1000 Difference: 31 fewer per 1000 (95% CI 43 fewer to 4 more)	22 per 1000	RR 0.41 (0.19 to 0.92)	6 [17,45,47,117–119] (1079 patients)	⊕⊕⊖⊖ Low (serious risk of bias and serious imprecision)
Mechanical ventilation Within 28 days of commencing treatment	40 per 1000 Difference: 4 fewer per 1000 (95% CI 31 fewer to 57 more)	30 per 1000	RR 0.75 (0.23 to 2.43)	4 [88,117,118] (497 patients)	⊕⊕⊖⊖ Low (very serious imprecision)
Serious adverse events End of treatment	7 per 1000 Difference: 25 more per 1000 (95% CI 19 fewer to 89 more)	8 per 1000	RR 1.12 (0.21 to 5.88)	6 [38,42–44,47,121] (644 patients)	⊕⊕⊖⊖ Low (very serious imprecision)
Adverse events End of treatment	497 per 1000 Difference: 25 fewer per 1000 (95% CI 70 fewer to 25 more)	472 per 1000	RR 0.95 (0.86 to 1.05)	7 [38,42–44,47,121] (805 patients)	⊕⊕⊖⊖ Low (serious imprecision, serious risk of bias)
ICU admission End of follow-up	115 per 1000 Difference: 54 fewer per 1000 (95% CI 102 fewer to 174 more)	61 per 1000	RR 0.53 (0.11 to 2.51)	2 [44,45] (143 patients)	⊕⊕⊖⊖ Low (serious imprecision, serious risk of bias)
Discharge from hospital Within 28 days of commencing treatment	868 per 1000 Difference: 52 more per 1000 (95% CI 9 fewer to 104 more)	920 per 1000	RR 1.06 (0.99 to 1.12)	4 [17,43,118,122] (342 patients)	⊕⊕⊖⊖ Low (serious imprecision, serious risk of bias)

95% CI 95% Confidence interval; RR: Risk ratio

References: [17,39,40,42–47,117–123].

Evidence adopted Australian guidelines for the clinical care of people with COVID-19, Available at: <https://app.magicapp.org/#/guideline/5446/section/78706>

Evidence Search date: 23 April–June 11.

Table 8
Grade evidence profile PICO5: Azithromycin for COVID-19

Azithromycin vs. Standard care					
People: Adult patients with COVID-19 (pregnant patients excluded)					
Setting: hospital (4 studies), outpatients (1 study) [124], 3 Countries (Iran, Brazil, UK)					
Intervention: Azithromycin (500 mg o.d.), 3 to 10 days.					
Comparison: Standard Care					
Patients in both intervention and comparator arms also receiving HCQ in 2 studies [20,50] and HCQ + LPV/r in 1 study [51].					
Outcomes	Absolute Effect ^a		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE) [†]
	Without Azithromycin (Standard Care)	With Azithromycin			
All-cause mortality	172	174	RR 1.01	4 [50,51,124,125]	⊕⊕⊕⊕
Within 28 days of commencing treatment	per 1000	per 1000	(0.92 to 1.10)	(9595 patients)	High
	Difference: 2 more per 1000				
	(95% CI 14 fewer to 17 more)				
Supplemental oxygen	24	20	RR 0.84	1 [124]	⊕⊕⊕⊙
Within 28 days of commencing treatment	per 1000	per 1000	(0.38 to 1.85)	(1122 patients)	Low
	Difference: 4 fewer per 1000				(Very serious imprecision; only data from one study, due to few events)
	(95% CI 15 fewer to 20 more)				
Clinical recovery	658	632	RR 0.96	1 [124]	⊕⊕⊕⊙
Within 28 days of commencing treatment	per 1000	per 1000	(0.88 to 1.05)	(1129 patients)	Low
	Difference: 26 fewer per 1000				(Very serious imprecision; wide confidence intervals, only data from one study)
	(95% CI 79 fewer to 33 more)				
Mechanical ventilation or ECMO	60	56	RR 0.94	2 [124,125]	⊕⊕⊕⊕
Within 28 days of commencing treatment	per 1000	per 1000	(0.79 to 1.14)	(8433 patients)	High
	Difference: 4 fewer per 1000				
	(95% CI 13 fewer to 8 more)				
Serious adverse events	194	219	RR 1.13 (0.90 to 1.42)	2 [20,50] (877 patients)	⊕⊕⊕⊙
End of treatment	per 1000	per 1000			Moderate
	Difference: 25 more per 1000				(serious imprecision; wide confidence intervals)
	(95% CI 19 fewer to 89 more)				
Adverse events	337	394	RR 1.17	1 [20]	⊕⊕⊕⊙
End of treatment	per 1000	per 1000	(0.91 to 1.50)	(438 patients)	Low
	Difference: 57 more per 1000				(very serious imprecision; wide confidence intervals, only data from one study)
	(95% CI 30 fewer to 169 more)				
ICU admission	18 per 1000	9 per 1000	RR 0.48 (0.17 to 1.35)	2 [124] (1231 patients)	⊕⊕⊕⊙
End of follow-up					Low
	Difference: 9 fewer per 1000				(very serious imprecision, due to few events)
	(95% CI 15 fewer to 6 more)				
Discharge from hospital	586	539	RR 0.92	2 [50,125]	⊕⊕⊕⊙
Within 28 days of commencing treatment	per 1000	per 1000	(0.72 to 1.19)	(8162 patients)	Moderate
	Difference: 47 fewer per 1000				(serious imprecision; wide confidence intervals)
	(95% CI 170 fewer to 111 more)				
Duration of hospital stay Mean	Difference: 0.41 lower (MD)		—	2 [20,51]	⊕⊕⊕⊙
	(95% CI 2.42 lower to 1.59 higher)			(442 patients)	Low
					(serious inconsistency and imprecision; wide confidence intervals)
Duration of hospital stay Median	13	12	—	1 [125]	⊕⊕⊕⊙
				(7764 patients)	Moderate
					(serious imprecision; only data from 1 study)

95% CI 95% Confidence interval; RR: Risk ratio

References: [20,50,51,124,125].

Evidence adopted Australian guidelines for the clinical care of people with COVID-19. Available at: <https://app.magicapp.org/#/guideline/5446/section/78706>.

Evidence Search date: 23 April–11 June.

ivermectin while seven did not (Table 7), with the largest reporting no effects [47,48]. The committee was thus uncertain whether ivermectin increased or decreased the chance of need for mechanical ventilation or death.

Safety

While no serious adverse events were recorded (Table 7), there was uncertainty with regards to adverse events and gastrointestinal effects were frequently reported in some studies. Common side effects associated with ivermectin included diarrhoea, nausea, and dizziness.

Recommendation

Strong recommendation against use of ivermectin to treat COVID-19 (QoE: low).

What is the effect of azithromycin on disease progression in patients with COVID-19 compared with no treatment?

Narrative synthesis of evidence

Azithromycin was assessed in four randomized trials (1 in outpatients and 3 in hospitalized patients). In our analysis, it had no

effect on 28-day mortality (RR 1.01; 95% CI 0.92–1.10), risk of disease progression (RR 0.94; 95% CI 0.79–1.14 for mechanical ventilation or ECMO; Table 8), or need for supplemental oxygen (RR 0.84; 95% CI 0.38–1.85). Azithromycin was assessed within the RECOVERY trial which allocated 2582 hospitalized patients to azithromycin and 5181 to SOC; 28-day mortality was similar between groups (RR 0.97, 95% CI 0.87–1.07; *p* 0.50) [49].

COALITION and COALITION II were open-label randomized trials assessing HCQ, HCQ plus azithromycin, azithromycin and SOC [20,50]. The primary endpoint (clinical status at day 15 assessed by a 7-grade ordinal scale) was not affected by any of the study drugs in either trial [20,50]. Azithromycin was not associated with better outcomes in hospitalized patients [51] or outpatients [52].

Safety

Rates of adverse events and severe adverse events were similar in patients receiving azithromycin or SOC [49,50,52]. In the only study that assessed azithromycin and HCQ, adverse events and prolongation of the QTc interval were more frequent in patients receiving HCQ or HCQ plus azithromycin compared with controls [20].

Recommendation

Strong recommendation against use of azithromycin for COVID-19 (QoE: high for 28-day mortality, low for disease progression).

What is the effect of colchicine treatment on mortality or disease progression in patients with mild COVID-19 compared with no treatment?

Narrative synthesis of evidence

More than 30 trials have assessed the role of colchicine in COVID-19. Five were considered to define the current position

statement. Overall, colchicine had no impact on mortality (RR 1.00; 95% CI 0.93–1.07) or need for mechanical ventilation (RR 1.01; 95% CI 0.91–1.13; Table 9).

COLCORONA compared colchicine with placebo in 4488 outpatients with COVID-19. The primary composite endpoint—death or hospitalization for COVID-19—occurred in 4.7% and 5.8% of patients receiving colchicine and placebo, respectively (OR 0.79; 95% CI 0.61–1.03; *p* 0.08). Rates of hospitalization and mechanical ventilation and mortality were similar between two groups [53]. Colchicine showed promising results in small preliminary RCTs [54,55]. However, recent unrefereed results of RECOVERY comparing 28-day mortality in patients receiving colchicine (*n* = 5160) or SOC (*n* = 5730) showed no benefit (RR 1.01; 95% CI 0.93–1.10; *p* 0.77); this finding was similar in all pre-specified subgroups and in those with SARS-CoV-2 infection confirmed by molecular analysis [56].

Safety

Colchicine has known bone marrow toxicity and several dose-dependent gastrointestinal adverse effects [57]. In COLCORONA, the rate of serious adverse events was 4.9% and 6.3% (*p* 0.05) and drug-related adverse events were 24.2% and 15.5% (*p* < 0.0001) in the intervention and placebo groups, respectively. Gastrointestinal adverse events were significantly increased with colchicine (23.9% vs. 14.8%, *p* < 0.0001) as was diarrhoea (13.7% vs. 7.3%, *p* < 0.0001) [53]. In the GRECCO trial, no serious adverse events were reported, while adverse events were similar in the two groups with the exception of diarrhoea, which was mainly seen with colchicine (45.5% vs. 18%; *p* 0.003) [54].

Recommendation

Strong recommendation against use of colchicine for COVID-19 (QoE: high).

Table 9

Grade evidence profile PICO6: Colchicine for COVID-19

People: Adult patients with COVID-19 (pregnant patients excluded)					
Setting: Hospital					
Intervention: Colchicine					
Comparison: Standard care					
Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without colchicine (standard Care)	With colchicine			
All-cause mortality within 21–28 days of treatment administration	149 per 1000 0 fewer per 1000 (CI 95% 10 fewer–10 more)	149 per 1000	RR 1.00 (0.93–1.07)	4 [53–55,126] (15 968 patients)	⊕⊕⊕⊕ High
Disease progression Increase of 2 grades on 7-grade scale; 21 days after commencing treatment	140 per 1000 Difference: 4 122 fewer per 1000 95% CI 187 fewer to 3 more)	18 per 1000	RR 0.13 (0.02–1.02)	1 [54] (105 patients)	⊕⊕⊕⊙ Low (Very serious imprecision; only data from one study, due to few events)
Invasive mechanical ventilation within 21–28 days of treatment administration	80 per 1000 Difference: 1 more per 1000 (CI 95% 7 fewer–10 more)	81 per 1000	RR 1.01 (0.91–1.13)	3 [53,54,126] (15 404 patients)	⊕⊕⊕⊕ High
Serious adverse events End of treatment	61 per 1000 Difference: 13 more per 1000 (95% CI 24 fewer to 0 more)	48 per 1000	RR 0.78 (0.61 to 1.00)	2 [53,54] (4517 patients)	⊕⊕⊕⊙ Moderate(serious imprecision; wide confidence intervals)
Adverse events End of treatment	158 per 1000 Difference: 147 more per 1000 (95% CI 28 more to 341 more)	305 per 1000	RR 1.93 (1.18 to 3.16)	2 [53,54] (4517 patients)	⊕⊕⊕⊙ Moderate (serious imprecision; wide confidence intervals)

References: [53–55,126,127]

Evidence adopted Australian guidelines for the clinical care of people with COVID-19, Available at: <https://app.magicapp.org/#/guideline/5446/section/78673>

Evidence Search date: 23 April–25 May

Table 10
Grade evidence profile of PICO 7: corticosteroids for adult patients with COVID-19 requiring oxygen supplement

Corticosteroids for severe COVID-19 i.e. patients requiring oxygen including mechanically ventilated patients					
People: Patients with COVID-19					
Settings: Inpatients					
Intervention: Corticosteroids					
Comparison: No treatment					
Outcomes	Absolute Effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without Corticosteroids	With Corticosteroids			
All-cause mortality (adults requiring oxygen)	316 per 1000 Difference: 51 fewer per 1000 (95% CI 85 fewer to 6 fewer)	265 per 1000	RR 0.84 (0.73 to 0.98)	9 [58–63,65,66,128,129] (5789 patients)	⊕⊕⊕⊖ Moderate (due to serious inconsistency)
Invasive mechanical ventilation or death (adults requiring oxygen)	320 per 1000 Difference: 38 fewer per 1000 (95% CI 67 fewer to 10 fewer)	282 per 1000	RR 0.88 (0.79 to 0.97)	1 [58] (3883 patients)	⊕⊕⊕⊖ Moderate due to serious inconsistency
Serious adverse events (adults requiring oxygen)	234 per 1000 Difference: 47 more per 1000 (95% CI 110 fewer to 44 more)	187 per 1000	RR 0.80 (0.53 to 1.19)	6 [59,60,62,63,65,128] (696 patients)	⊕⊕⊕⊖ Moderate (due to serious inconsistency)
Superinfection (end of treatment)	186 per 1000 Difference: 2 more per 1000 (95% CI 19 fewer to 24 more)	188 per 1000	RR 1.01 (0.90 to 1.13)	32 [129] (6027 patients)	⊕⊕⊖⊖ Low (due to serious indirectness and imprecision)
Hyperglycaemia (end of treatment)	286 per 1000 Difference: 46 more per 1000 (95% CI 23 more to 72 more)	332 per 1000	RR 1.16 (1.08–1.25)	24 [129]	⊕⊕⊕⊖ Moderate (due to serious indirectness)
Discharge from hospital (within 28 days of treatment begin, adults requiring oxygen)	582 per 1000 Difference: 58 more per 1000 (95% CI 35 more to 87 more)	640 per 1000	RR 1.10 (1.06 to 1.15)	2 [58,66] (4952 patients)	⊕⊕⊕⊖ Moderate (due to serious inconsistency)

References: [58–63,65,66,128,129].

Evidence adopted: Australian guidelines for the clinical care of people with COVID-19, Available at: <https://app.magicapp.org/#/guideline/5477/section/80465>.

Evidence Search date: 23 April–11 May.

Table 11
GRADE evidence profile PICO7: Corticosteroid for COVID-19 in the subgroup of hospitalized patients not requiring supplemental oxygen

Corticosteroids for mild COVID-19 i.e. patients not requiring oxygen					
People: Patients with COVID-19					
Settings: Inpatients					
Intervention: Corticosteroids					
Comparison: No treatment					
Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without Corticosteroids	With Corticosteroids			
All-cause mortality	140 per 1000 Difference: 38 more per 1000 (95% CI 0 more to 85 more)	178 per 1000	RR 1.27 (1.00 to 1.61)	1 [58] (1535 patients)	⊕⊕⊕⊖ Moderate (serious imprecision)
Invasive mechanical ventilation or death	155 per 1000 Difference: 39 more per 1000 (95% CI 0 more to 88 more)	194 per 1000	RR 1.25 (1.0 to 1.57)	1 [58] (1535 patients)	⊕⊕⊕⊖ Moderate (serious imprecision)
Discharge for hospital (within 28 days of treatment begin)	804 per 1000 Difference: 32 fewer per 1000 (95% CI 80 fewer to 8 more)	772 per 1000	RR 0.96 (0.9 to 1.01)	1 [58] (1535 patients)	⊕⊕⊕⊖ Moderate (serious imprecision)

95% CI: 95% Confidence interval; RR: Risk ratio.

References: [58].

Evidence adopted: Australian guidelines for the clinical care of people with COVID-19, Available at: <https://app.magicapp.org/#/guideline/5477/section/80465>.

Evidence Search date: 23 April–11 May.

What is the effect of corticosteroid treatment on mortality in patients with mild COVID-19 compared with no treatment?

Narrative synthesis of evidence

The evidence involved 5789 patients from nine RCTs [58–66]. The RR for mortality was significantly lower in patients who

received corticosteroids compared with SOC (RR 0.83; 95% CI 0.73–0.99). Corticosteroid treatment was also associated with reduced need for mechanical ventilation (RR 0.88; 95% CI 0.79–0.97; Table 10).

The results of meta-analyses are largely influenced by the RECOVERY trial which enrolled 83% of patients [58]. In RECOVERY, corticosteroid (dexamethasone) provided greater mortality

benefits in patients requiring invasive mechanical ventilation (29.3% vs. 41.4%) or oxygen support without invasive mechanical ventilation (23.3% vs. 26.2%) at randomization [58]. Of the remaining seven studies [5–11], despite lower mortality with corticosteroid treatment in several trials, some failed to detect significant differences, and some were terminated early based on the results of RECOVERY. In patients who did not require oxygen, corticosteroids likely increased mortality (RR 1.27; 95% CI 1.00–1.61; 1535 patients in 1 study) and the composite of invasive mechanical ventilation or death [58] (Table 11).

Safety

There was no significant difference between corticosteroid and SOC considering severe adverse events and superinfections. However, corticosteroids are associated with an increase in hyperglycaemia. Indirect evidence of corticosteroid use in patients with similar indications has shown no difference in the incidence of gastrointestinal bleeding, superinfections, neuromuscular weakness, or neuropsychiatric effects (Table 10).

Recommendation

Strong recommendation for systemic corticosteroids for treatment of patients with severe and critical COVID-19 (QoE: moderate).

Strong recommendation against the use corticosteroids to treat patients with non-severe COVID-19 (QoE: moderate).

What is the effect of empirical antibiotic treatment on mortality in patients with severe COVID-19 compared with no treatment?

Narrative synthesis of evidence

Several RCTs have not found any effect of azithromycin compared with SOC [49,50,52]. In the absence of RCTs assessing antibiotic use in patients with COVID-19 complicated with bacterial coinfections or secondary infections, general principles of antimicrobial stewardship should be applied [67]. Given the low rate of bacterial coinfections, only patients with clinical or radiological suspicion of an associated bacterial infection should receive empirical antibiotics when COVID-19 is diagnosed or when hospitalization is needed.

Recommendation

Insufficient evidence to make a proper recommendation. Antibiotics should not be routinely prescribed in patients with COVID-19 unless bacterial coinfection or secondary infection is suspected or confirmed.

What is the effect of convalescent plasma on mortality in patients with severe COVID-19 compared with no treatment?

Narrative synthesis of evidence

Nine RCTs comparing convalescent plasma with SOC in >12 800 patients with COVID-19 were considered [68–76]. Convalescent plasma did not confer a benefit compared with SOC in 28-day mortality (RR 0.93; 95% CI 0.79–1.10), need for mechanical ventilation (RR 0.98; 95% CI 0.89–1.08) or ICU admission (RR 0.75; 95% CI 0.36–1.59; Table 12). Within RECOVERY, 5795 patients received convalescent plasma and 5763 SOC; 28-day mortality was similar

between groups (24% vs. 24%; RR 1.00; 95% CI 0.93–1.07; p 0.95) [68].

PLACID was a multicentre open-label RCT at 39 centres in India enrolling 464 hospitalized adults with moderate–severe COVID-19 [69]. The primary outcome of progression to critical disease or all-cause mortality at 28 days after enrolment was similar between groups (risk difference 0.008; 95% CI –0.062 to 0.078) (RR 1.04; 95% CI 0.71–1.54).

PlasmAr was a double-blind, placebo-controlled, multicentre trial involving 12 sites in Argentina enrolling patients with severe COVID-19 pneumonia randomized to receive convalescent plasma ($n = 228$) or placebo ($n = 105$). The primary outcome (clinical status 30 days after intervention) was similar between groups (OR 0.83; 95% CI 0.52–1.35; p 0.46) [76].

Other smaller RCTs found no significant differences in outcomes in patients with moderate–severe [71] or severe–critical COVID-19 [70,71,75]. Only one study showed a benefit for convalescent plasma administered in older adult patients within 72 hr after onset of mild COVID-19 symptoms. Progression to severe COVID-19 occurred in 13 of 80 (16%) patients receiving plasma and in 25 of 80 (31%) receiving placebo (RR 0.52; 95% CI 0.29–0.94; p 0.03).

Safety

In general, adverse events were not increased compared with controls [68,69,72,74]. Some studies reported higher rates of serious adverse events [76] or a small number of infusion-related adverse events [73,75,76].

Recommendation

Strong recommendation against use of convalescent plasma for COVID-19 (QoE: moderate for mortality, high for mechanical ventilation).

What is the effect of remdesivir on mortality or mechanical ventilation in patients with severe COVID-19 compared with no treatment?

Narrative synthesis of evidence

Our analysis showed that remdesivir probably decreases death slightly in hospitalized patients who do not require ventilation (RR 0.76; 95% CI 0.57–1.02) with uncertain effects on patients undergoing ventilation (RR 1.2; 95% CI 0.98–1.78). Additionally, remdesivir may decrease the need for invasive mechanical ventilation or ECMO (RR 0.57; 95% CI 0.42–0.79; Table 13).

In a double-blind, randomized trial in China enrolling 237 patients with severe COVID-19, time to clinical improvement (hazard ratio (HR) 1.23; 95% CI 0.87–1.75) and mortality rate (14% vs. 13%) were similar with remdesivir and placebo [77]. In SOLIDARITY, 2750 patients were assigned to remdesivir and 2708 to SOC with no difference in 28-day mortality (RR 0.95; 95% CI 0.81–1.11) [12]. ACTT-1 was a multinational, randomized, placebo-controlled trial of remdesivir (given for up to 10 days or until death or discharge) in 1062 patients with confirmed COVID-19. Compared with placebo, remdesivir resulted in faster time to recovery in the overall population (median 10 vs. 15 days; RR for recovery 1.29; 95% CI 1.12–1.49), but not in the subset on mechanical ventilation or ECMO at baseline (RR for recovery 0.98, 95% CI 0.70–1.36) [78]. Among patients on oxygen supplementation but who did not require high-flow oxygen or ventilatory support (non-invasive or invasive), there was a significant mortality benefit (4.0% vs. 12.7%; HR 0.30; 95% CI 0.14–0.64).

Table 12
GRADE evidence profile for PICO 9: convalescent plasma for COVID-19

Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without convalescent plasma (standard care)	With convalescent plasma			
People: Adult patients with COVID-19 (pregnant patients excluded)					
Setting: Hospitalized patients (8 studies), outpatients (1 study)					
Intervention: Convalescent plasma					
Comparison: Standard care					
All-cause mortality	235	219	RR 0.93	9 [69–72,74–76,130,131]	⊕⊕⊕⊖
Within 28 days of commencing treatment	per 1000 Difference: 16 fewer per 1000 (95% CI 49 fewer to 24 more)	per 1000	(0.79 to 1.10)	(12 872 patients)	Moderate (due to serious imprecision)
Invasive mechanical ventilation	124	122	RR 0.98	4 [69,74,76,130]	⊕⊕⊕⊕
Within 28 days of commencing treatment	per 1000 Difference: 2 fewer per 1000 (95% CI 14 fewer to 10 more)	per 1000	(0.89 to 1.08)	(11 898 patients)	High
Serious Adverse events	176	218	RR 1.24	2 [71,76]	⊕⊕⊖⊖
Within 28 days of commencing treatment	per 1000 Difference: 42 more per 1000 (95% CI 33 fewer to 158 more)	per 1000	(0.81 to 1.90)	(414 patients)	Low (Very serious imprecision; wide confidence intervals, only data from one study)
Adverse events	537	789	RR 1.47	2 [70,76]	⊕⊕⊖⊖
Within 28 days of commencing treatment	per 1000 Difference: 252 more per 1000 (95% CI 333 fewer to 2545 more)	per 1000	(0.38 to 5.74)	(370 patients)	Low (risk of bias; serious imprecision; wide confidence intervals, only data from 2 study)
ICU admission	373	280	RR 0.75	2 [74,76]	⊕⊕⊖⊖
End of follow-up	per 1000 Difference: 93 fewer per 1000 (95% CI 239 fewer to 220 more)	per 1000	(0.36 to 1.59)	493 patients)	Low (Risk of bias serious imprecision, due to few events)
Clinical deterioration (progression to severe/critical)	74	53	RR 0.71	2 [69,71]	⊕⊕⊖⊖
Within 28 days of commencing treatment	per 1000 Difference: 21 fewer per 1000 (95% CI 61 fewer to 132 more)	per 1000	(0.18 to 2.78)	(545 patients)	Low (Risk of bias serious imprecision, wide confidence intervals)

95% CI: 95% Confidence interval; RR: Risk ratio.

References: [69–72,74–76,130,131].

Evidence adopted: Australian guidelines for the clinical care of people with COVID-19, Available at: <https://app.magicapp.org/#/guideline/5477/section/80436>.

Evidence Search date: 23 April–11 May.

An open-label trial randomized hospitalized patients with moderate COVID-19 pneumonia to a 10-day ($n = 197$) or 5-day course of remdesivir ($n = 199$) or SOC ($n = 200$). A 5-day course (odds ratio (OR) 1.65; 95% CI, 1.09–2.48; $p 0.02$) of remdesivir, but not a 10-day course ($p 0.18$), was associated with better clinical status at day 11 vs. SOC. No difference in all-cause 28-day mortality was seen [79]. Another open-label randomized trial compared 5-day to 10-day remdesivir in patients with severe COVID-19. The primary outcome was clinical status at day 14 and was similar between groups ($p 0.18$) [80]. A small and likely underpowered RCT in India did not show clinical improvement with remdesivir compared with SOC [81]. Lastly, a large observational trial suggested mortality benefit in patients treated with remdesivir compared with those not treated with remdesivir [82].

Safety

Remdesivir was associated with higher rate of adverse events in two studies, especially when administered for 10 days [79,80]. These included nausea, hypokalaemia, headache and decrease in estimated glomerular filtration rate. However, a lower rate of serious adverse events was observed in one RCT [77].

Recommendation

Conditional recommendation for use of remdesivir for COVID-19 in hospitalized patients not requiring mechanical ventilation or ECMO (QoE: moderate).

What is the effect of favipiravir on mortality or mechanical ventilation in patients with mild–moderate COVID-19 compared with no treatment?

Narrative synthesis of evidence

Favipiravir has shown rapid viral clearance and faster clinical improvement of patients with COVID-19 [83]. Certainty of evidence is very low for all-cause mortality, admission to ICU, and need for mechanical ventilation. In recently published RCTs, it was found that transfer to ICU, adverse events, and mortality in patients with mild–moderate COVID-19 treated with favipiravir was not significantly different compared with SOC [84]. Several ongoing clinical trials will further substantiate the role of favipiravir [84–86].

Recommendation

Insufficient evidence to make a recommendation

Is antifungal prophylaxis associated with a lower incidence of coronavirus-associated pulmonary aspergillosis in mechanically ventilated patients with critical COVID-19 compared with no prophylaxis?

Narrative synthesis of evidence

No antifungal agent is currently approved for prophylaxis in ICU patients. Recently, posaconazole prophylaxis has been evaluated in

Table 13
GRADE evidence profile for PICO 10: remdesivir for severe COVID-19

Remdesivir for COVID-19					
People: Patients with severe COVID-19					
Settings: Inpatients					
Intervention: Remdesivir					
Comparison: No treatment					
Outcomes	Absolute Effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without Remdesivir	With Remdesivir			
All-cause mortality (hospital, no ventilation)	90 per 1000 Difference: 22 fewer per 1000 (95% CI 39 fewer to 2 more)	68 per 1000	RR 0.76 (0.57 to 1.02)	5 [12,77–81] (6400 patients)	⊕⊕⊕⊖ Moderate (due to serious imprecision)
All-cause mortality (ventilation)	248 per 1000 Difference: 50 more per 1000 (95% CI 5 fewer to 117 more)	298 per 1000	RR 1.2 (0.98 to 1.47)	3 [12,77,78] (1004 patients)	⊕⊕⊕⊖ Moderate (due to serious imprecision)
Respiratory failure or ARDS	143 per 1000 Difference: 30 fewer per 1000 (95% CI 93 fewer to 112 more)	113 per 1000	RR 0.79 (0.35 to 1.78)	2 [77,78] (1296 patients)	⊕⊕⊖⊖ Low (due to serious risk of bias and serious inconsistency)
Invasive mechanical ventilation or ECMO (within 28 days of treatment start)	225 per 1000 Difference: 97 fewer per 1000 (95% CI 131 fewer to 47 fewer)	128 per 1000	RR 0.57 (0.42 to 0.79)	1 [78] (766 patients)	⊕⊕⊖⊖ Low (due to serious risk of bias and serious inconsistency)
Patients requiring ventilation (within 28 days of treatment start)	114 per 1000 Difference: 5 more per 1000 (95% CI 13 fewer – 24 more)	119 per 1000	RR 1.04 (0.89 to 1.21)	2 [77,81] (5034 patients)	⊕⊕⊕⊖ Moderate (due to serious imprecision)
Serious adverse events End of follow-up	253 per 1000 Difference: 63 fewer per 1000 (95% CI 94 fewer –28 fewer)	190 per 1000	RR 0.75 (0.63–0.89)	3 [77–79] (1865 patients)	⊕⊕⊕⊖ Moderate (due to serious risk of bias)
Adverse events End of follow-up	548 per 1000 Difference: 22 more per 1000 (95% CI 60 fewer –115 more)	570 per 1000	RR 1.04 (0.89–1.21)	3 [77–79] (1880 patients)	⊕⊕⊖⊖ Low (due to serious risk of bias and inconsistency)

95% CI: 95% Confidence interval; RR: Risk ratio

References: [12,77–81].

Evidence adopted: Australian guidelines for the clinical care of people with COVID-19, Available at: <https://app.magicapp.org/#/guideline/5446/section/78660>

Evidence Search date: 23 April–11 June.

ICU patients with severe influenza to prevent influenza-associated pulmonary aspergillosis (IAPA) [87]. Posaconazole was well tolerated and was discontinued prematurely in 9 of 37 patients for causes unrelated to treatment. No cases of IAPA were observed during posaconazole prophylaxis, but the strategy failed as 71% of cases had IAPA on ICU admission that required immediate antifungal therapy [87]. Although coronavirus-associated pulmonary aspergillosis (CAPA) occurs at a median of 7 days after ICU admission and may thus benefit from prophylaxis, there are currently no studies that support this approach in COVID-19 patients in the ICU. Current guidelines and expert guidance do not recommend antifungal prophylaxis in critically ill COVID-19 patients [88,89].

Recommendation

Insufficient evidence to make a recommendation

What is the effect of tocilizumab on mortality or mechanical ventilation in patients with moderate or severe COVID-19 compared with no treatment?

Narrative synthesis of evidence

Tocilizumab has been assessed in nine RCTs with conflicting results [90–99]. Most of the smaller trials did not show any mortality benefit [90,93–95,100,101]. Conversely, REMAP-CAP and RECOVERY showed small but significant benefit. REMAP-CAP is an

ongoing international, multifactorial, adaptive platform trial including ICU patients randomly assigned to receive tocilizumab, sarilumab or SOC. The primary outcome was respiratory and cardiovascular organ support-free days. Overall, those with tocilizumab had an in-hospital mortality of 27% compared with 36% for controls, and a median of 10 to 11 organ support-free days compared with 0 days for controls [96].

Within RECOVERY, 4116 patients were assigned to tocilizumab or SOC if they had oxygen saturation <92% on ambient air or required oxygen therapy with evidence of systemic inflammation (C-reactive protein ≥75 mg/L). Overall, 29% patients receiving tocilizumab and 33% receiving SOC died within 28 days (RR 0.86; 95% CI 0.77–0.96; p 0.007) [97].

Tocilizumab is associated with reduced mortality (RR 0.89; 95% CI 0.82–0.98) in nine RCTs and a lower need for mechanical ventilation (RR 0.81; 95% CI 0.80–0.93) in four RCTs (Table 14). One possible explanation for the different results among RCTs is that many were conducted in the early stages of the pandemic before corticosteroids were established as SOC. In a recent systematic review, a clear benefit of combination of interleukin-6 blockers and corticosteroids was noted [102].

Safety

Tocilizumab likely has little impact on adverse or serious adverse events, septic shock, or clinical progression. The effect of tocilizumab on other outcomes is uncertain.

Table 14
GRADE evidence profile for PICO 13: Tocilizumab for moderate or severe COVID-19

Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without tocilizumab	With tocilizumab			
People: Patients with COVID-19 Settings: Hospitalized patients Intervention: Tocilizumab Comparison: Standard treatment without tocilizumab					
All-cause mortality Day 21–28 after treatment start	290 per 1000 Difference: 32 fewer per 1000 (CI 95% 52 fewer to 6 fewer)	258 per 1000	RR 0.89 (0.82 — 0.98)	8 [90–99,101] (6481 patients)	Moderate (Due to serious imprecision)
Invasive mechanical ventilation or ECMO End-of-follow-up	159 per 1000 Difference: 30 fewer per 1000 (95% CI 48 fewer to 24 fewer)	129 per 1000	RR 0.81 (0.70 to 0.93)	3 [95,97,101] (4248 patients)	⊕⊕⊕⊕ High
Admission to ICU End-of-follow-up	423 per 1000 Difference: 76 fewer per 1000 (95% CI 195 fewer to 97 more)	347 per 1000	RR 0.82 (0.54–1.23)	4 [90,93,101] (699 patients)	Moderate ⊕⊕⊕⊖ (due to serious imprecision)
Serious adverse events End-of-follow-up	162 Per 1000 Difference: 18 fewer per 1000 (95% CI 41 fewer to 8 more)	144 Per 1000	RR 0.89 (0.75 — 1.05)	7 [90,92,94–96,98,101] (2309 patients)	Moderate ⊕⊕⊕⊖ (due to serious imprecision)
Adverse events End-of-follow-up	466 Per 1000 Difference: 28 more per 1000 (95% CI 65 fewer to 140 more)	494 Per 1000	RR 1.06 (0.86 — 1.3)	6 [90,92,94,95,98,101] (1562 patients)	Moderate ⊕⊕⊕⊖ (due to serious imprecision)

95% CI 95% Confidence interval; RR: Risk ratio

References: [90–99,101].

Evidence adopted: Australian guidelines for the clinical care of people with COVID-19, Available at: <https://app.magicapp.org/#/guideline/5446/section/78668>.

Evidence Search date: 23 April–11 May.

Recommendation

We recommend use of tocilizumab for treatment of severe COVID-19 (QoE: moderate for mortality, high for mechanical ventilation).

Is intermediate dose of low-molecular-weight heparin associated with lower mortality in mechanically ventilated patients with critical COVID-19 compared with prophylactic dose?

Narrative synthesis of evidence

The use of enoxaparin was assessed in one RCT (INSPIRATION) assessing 562 critically ill adult patients with COVID-19 admitted to the ICU and followed for 90 days, and randomly allocated to receive intermediate dose or prophylactic dose anticoagulation for 30 days [103]. The primary outcome was a composite including all-cause mortality, which was similar between groups (HR 1.21; 95% CI 0.95–1.55; *p* 0.11). RR for all-cause mortality was 1.09 (95% CI 0.78–1.53) (Table 15). In addition, another RCT by the investigators from the REMAP-CAP Platform found clinical benefit from therapeutic dosages of enoxaparin among non-critical COVID-19 patients [104]. However, an analysis restricted to critically ill patients found no benefit on the primary outcome (ordinal scale combining in-hospital mortality and days free of organ support to day 21) (adjusted OR 0.87, 95% CI 0.70–1.08) [105].

Safety

The main safety outcome in the RCT was major bleeding. There were seven (2.5%) major bleedings in the intermediate dose group (3 fatal) and four (1.4%) major bleedings in the standard-dose group (0 fatal) (HR 1.82; 95% CI 0.53–6.24) [103].

Recommendation

We recommend against the use of intermediate dose of low-molecular-weight heparin (LMWH) in critically ill patients with COVID-19 (QoE: moderate).

We recommend the use of intermediate or therapeutic doses of LMWH in non-critically ill patients with COVID-19 only in the context of a clinical trial (QoE: moderate).

What is the effect of treatment with interferon β-1a on mortality of critically ill patients with COVID-19 compared with no treatment?

Narrative synthesis of evidence

Interferon β-1a was not associated with lower 28-day mortality (RR 1.07; 95% CI 0.91–1.27; Table 16). Most patients were enrolled in the SOLIDARITY trial. The primary endpoint was 28-mortality and occurred in 243 of 2050 patients receiving interferon and in 216 of 2050 receiving SOC (RR 1.16; 95% CI 0.96–1.39; *p* 0.11) [12]. Consistent results were obtained in the subgroup of patients needing mechanical ventilation (RR 1.40; 95% CI 0.822–4.0). A second smaller open-label, single-center study in Iran showed no benefit of interferon β-1a in addition to SOC [106].

In addition to these two trials, another two RCTs are available [107,108]. Interferon β-1a was not associated with clinical improvement in either trial.

Safety

Some studies documented a higher rate of adverse events in patients treated with interferon β-1a compared with controls [109], whereas others do not [12,106]. Historically, use of interferons in other settings has been associated with several side effects

Table 15
GRADE evidence profile for PICO 14: Low molecular weight heparin for critical COVID-19

Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE) [†]
	Risk with prophylactic dose	Risk with intermediate dose			
All-cause mortality follow up: mean 30 days	409 per 1000	429 per 1000	OR 1.09 (0.78–1.53)	1 [103] (562 patients)	⊕⊕⊕⊖ Moderate (Due to serious imprecision 1 RCT)
Pulmonary embolism	17 per 1000	13 per 1000	OR 0.41 (0.08–2.13)	1 [103] (562 patients)	⊕⊕⊖⊖ Low (serious risk of bias, serious imprecision)
Major Bleeding	14 per 1000	19 per 1000	OR 1.83 (0.53–5.93)	1 [103] (562 patients)	⊕⊖⊖⊖ Very low

95% CI 95% Confidence interval; RR: Risk ratio

Reference: [103].

Evidence adopted: <https://www.hematology.org/-/media/hematology/files/clinicians/guidelines/vte/etd-ash-COVID-19-guideline-recommendation-1a.pdf>.

Evidence Search date: 23 April–11 May.

Table 16
GRADE evidence profile for PICO 15: Interferon β-1a for critical COVID-19

Outcomes	Absolute effect		Relative effect (95% CI)	Number of studies	Certainty of the evidence (GRADE)
	Without interferon β-1a (Standard Care)	With interferon β-1a			
All-cause mortality Within 28 days of commencing treatment	112 per 1000	120 per 1000	RR 1.07 (0.91–1.27)	2 [12,106] (4181 patients)	⊕⊕⊕⊕ High Moderate for critical ill (due to serious indirectness)
Supplemental Ventilation Within 28 days of commencing treatment	116 per 1000	115 per 1000	RR 0.99 (0.83–1.17)	2 [12,106] (3912 patients)	⊕⊕⊖⊖ Low (very serious imprecision; only data from one study, due to few events)
Duration of hospital stay Mean days to discharge	12.3 (mean)	14.8 (mean)		1 [106] (81 patients)	⊕⊖⊖⊖ Very Low (Very serious risk of bias; very serious imprecision and wide confidence intervals, only data from one study)
Serious adverse events End of follow-up	385 per 1000	543 per 1000	RR 1.41 (1.09–1.81)	1 [107] (292 patients)	⊕⊖⊖⊖ Very Low (serious imprecision; serious indirectness)
Adverse events End of follow-up	709 per 1000	815 per 1000	RR 1.15 (1.01–1.30)	1 [107] (438 patients)	⊕⊖⊖⊖ Very Low (serious imprecision; serious indirectness)

95% CI: 95% Confidence interval; RR: Risk ratio.

References: [12,106,107].

Evidence adopted: Australian guidelines for the <https://app.magicapp.org/#/guideline/5446/section/78677>

Evidence Search date: 23 April–11 May.

including thrombotic microangiopathy, hepatic injury, nephrotic syndrome, and depression with suicidal ideation. Interferon β-1a is also associated with immune reactions that can produce flu-like symptoms.

Recommendation

Strong recommendation against use of interferon β-1a in severe COVID-19 patients (QoE: moderate).

Transparency declaration

M.B., O.A., A.B., L.B., O.E., R.K., J.R.-P.P., N.R.P., B.G.S.Z., M.S., T.S., I.Z.S. J.R.-B.: no conflicts to declare. P.E.V.: reports research grants from Gilead Sciences, MSD, Pfizer and F2G; he is a speaker for Gilead Sciences, MundiPharma F2G, and MSD; and is on the advisory boards for Pfizer, MundiPharma, Cidara, MSD, and F2G.

The project received a grant from ESCMID for medical writing assistance.

Author contributions

M.B. chaired the panel, supervised the work, selected and voted for PICO questions and for other relevant decision, performed literature search and drafted and approved the manuscript. O.A., A.B., L.B., O.E., R.K., J.R.P.P., N.P., M.S., B.G.Z., S.T., P.E.V., I.Z. selected and voted for PICO questions and for other relevant decision, performed literature search and drafted and approved the manuscript. J.R.B. supervised the work of the panel, selected and voted for PICO questions and for other relevant decision, performed literature search and drafted and approved the manuscript.

Updating

The panel will meet monthly to assess the need for further update of the present document. Our goal will be an optimization of the guideline development process to allow update of individual recommendations as soon as new evidence becomes available. More specifically, during the monthly meeting the panel will propose new PICOs or revision of prior PICOs. The methodology will be the same as the present document.

Acknowledgements

The medical writing assistance by Patrick Moore and methodology direction and overview by Luigia Scudeller are acknowledged. We also acknowledge the technical assistance by Chiara Speziale. Additionally, we thank the following authors who helped us in the public consultation process sending comments and suggestions: Umang Agrawal (Hinduja Hospital and MRC, India), Manteja Jancovic (University Hospital Centre Zagreb, Croatia), Dmitri Stepanov (Marienkrankenhaus Soest, Germany), Christopher Longshaw (Shionogi, UK), Ricardo Correia de Abreu (Universidade do Porto, Hospital Pedro Hispano, Sra. da Hora, Portugal).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.11.007>.

References

- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323:1239–42.
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;323:2052–9.
- Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. *JAMA* 2020;323:1545–6.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
- Gin. Guidelines international network. Available from: <https://g-i-n.net/COVID-19/COVID-19-evidence-resources>.
- University M. COVID-END. <https://www.mcmasterforum.org/networks/covid-end>.
- Cochrane Library. Coronavirus (COVID-19). Available from: <https://www.cochranelibrary.com/COVID-19#Special%20Collections>.
- LOVE. Living overview of evidence. Available from: <https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d>.
- Who. Clinical management of COVID-19 2020. Available from: [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
- Control ECfDPA. Risk factors and risk groups 2021; updated 26 April 2021. <https://www.ecdc.europa.eu/en/covid-19/latest-evidence/risk-factors-risk-groups>
- Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020;383:2030–40.
- Pan H, Peto R, Heno-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al. Repurposed antiviral drugs for Covid-19 – interim WHO Solidarity trial results. *N Engl J Med* 2021;384:497–511.
- Ader F, Peiffer-Smadja N, Poissy J, Bouscambert-Duchamp M, Belhadi D, Diallo A, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-beta-1a and hydroxychloroquine in hospitalized patients with COVID-19. *Clin Microbiol Infect* 2021;27:1826–37.
- Ulrich RJ, Troxel AB, Carmody E, Eapen J, Backer M, DeHovitz JA, et al. Treating COVID-19 with hydroxychloroquine (TEACH): a multicenter, double-blind randomized controlled trial in hospitalized patients. *Open Forum Infect Dis* 2020;7:ofaa446.
- Abd-El Salam S, Esmail ES, Khalaf M, Abdo EF, Medhat MA, Abd El Ghafar MS, et al. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. *Am J Trop Med Hyg* 2020;103:1635–9.
- Hernandez-Cardenas C, Thirion-Romero I, Rivera-Martinez NE, Meza-Meneses PE, Remigio-Luna A, Perez-Padilla R. Hydroxychloroquine for the treatment of severe respiratory infection by covid-19: a randomized controlled trial. *PLoS One* 2021;16:e0257238.
- Beltran Gonzalez JL, González Gámez M, Mendoza Enciso EA, Esparza Maldonado RJ, Hernández Palacios D, et al. <https://www.medrxiv.org/content/10.1101/2021.02.18.21252037v1>.
- Rea-Neto A, Bernardelli RS, Camara BMD, Reese FB, Queiroga MVO, Oliveira MC. An open-label randomized controlled trial evaluating the efficacy of chloroquine/hydroxychloroquine in severe COVID-19 patients. *Sci Rep* 2021;11:9023.
- Dubee V, Roy PM, Vielle B, Parot-Schinkel E, Blanchet O, Darsonval A, et al. Hydroxychloroquine in mild-to-moderate coronavirus disease 2019: a placebo-controlled double blind trial. *Clin Microbiol Infect* 2021;27:1124–30.
- Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med* 2020;383:2041–52.
- Chen L, Zhang Z, Fu J, Feng Z, Zhang S, Han Q, et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. Available from: <https://www.medrxiv.org/content/10.1101/2020.06.19.20136093v1>.
- Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020;369:m1849.
- Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. [A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19]. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2020;49:215–9.
- Chen CP, Lin YC, Chen TC, Tseng TY, Wong HL, Kuo CY, et al. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). *PLoS One* 2020;15:e0242763.
- Omran AS, Pathan SA, Thomas SA, Harris TRE, Coyle PV, Thomas CE, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. *EClinicalMedicine*; 2020. p. 29100645.
- Johnston C, Brown ER, Stewart J, Karita HCS, Kissinger PJ, Dwyer J, et al. Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: a randomized clinical trial. *EClinicalMedicine* 2021;33:100773.
- Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med* 2020;173:623–31.
- Mitja O, Corbacho-Monne M, Ubals M, Tebe C, Penafiel J, Tobias A, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. *Clin Infect Dis* 2021;73:e4073–81.
- Lyngbakken MN, Berdal JE, Eskesen A, Kvale D, Olsen IC, Rueegg CS, et al. A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. *Nat Commun* 2020;11:5284.
- Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med* 2021;384:229–37.
- Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA* 2021;325:632–44.
- Lilly Eli, Company. Lilly's bamlanivimab and etesevimab together reduced hospitalizations and death in Phase 3 trial for early COVID-19, updated 10 March 2021. Available from: <https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced>.
- Cohen MS, Nirula A, Mulligan M, RLG, Novak R, Marovich M, et al. Bamlanivimab prevents COVID-19 morbidity and mortality in nursing-home setting. Conference on retroviruses and Opportunistic infection (CROI); June 3–November 3, 2021 Virtual. <https://www.croiconference.org/abstract/bamlanivimab-prevents-covid-19-morbidity-and-mortality-in-nursing-home-setting/>
- Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, et al. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. *N Engl J Med* 2021;384:905–14.

- [35] Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med* 2021;384:238–51.
- [36] Group RC. Casirivimab and imdevimab in patients admitted to 3 hospital with COVID-19 (RECOVERY): a randomised, 4 controlled, open-label, platform trial. medRxiv preprint; 2021. <https://doi.org/10.1101/2021.06.15.21258542>.
- [37] Mohan A, Tiwari P, Suri TM, Mittal S, Patel A, Jain A, et al. Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): A single-centre randomized, placebo-controlled trial. *J Infect chemother: Off J Jpn Soc Chemother* 2021;27:1743–9.
- [38] Bukhari KHS, Asghar A, Perveen N, Hayat A, Mangat SA, Butt KR, et al. Efficacy of ivermectin in COVID-19 patients with mild to moderate disease. medRxiv 2021. Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2021.02.02.21250840v1>.
- [39] Biber A, Mandelboim M, Harmelin G. Favorable outcome on viral load and culture viability using ivermectin in early treatment of non-hospitalized patients with mild COVID-19 – a double-blind, randomized placebo-controlled trial. medRxiv 2021. <https://www.medrxiv.org/content/10.1101/2021.05.31.21258081v1>.
- [40] Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis* 2021;103:214–6.
- [41] Babalola OE, Bode CO, Ajayi AA, Alakaloko FM, Akase IE, Otrofanwei E, et al. Ivermectin shows clinical benefits in mild to moderate COVID-19: a randomised controlled double-blind, dose-response study in Lagos. *QJM* 2021. <https://doi.org/10.1093/qjmed/hcab035>.
- [42] Chaccour C, Casellas A, Blanco-Di Matteo A, Pineda I, Fernandez-Montero A, Ruiz-Castillo P, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. *EclinicalMedicine* 2021;3:2100720.
- [43] Krolewiecki A, Lifschitz A, Moragas M, Travacio M, Valentini R, Alonso DF, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: a proof-of-concept randomized trial. *EclinicalMedicine* 2021;3:7100959.
- [44] Pott-Junior H, Bastos Paoiello MM, Miguel AQC, da Cunha AF, de Melo Freire CC, Neves FF, et al. Use of ivermectin in the treatment of Covid-19: a pilot trial. *Toxicol Rep* 2021;8:505–10.
- [45] Ravikirti Roy R, Pattadar C, Raj R, Agarwal N, Biswas B, et al. Evaluation of ivermectin as a potential treatment for mild to moderate COVID-19: a double-blind randomized placebo controlled trial in eastern India. *J Pharm Pharm Sci* 2021;24:343–50.
- [46] Samaha AA, Mouawia H, Fawaz M, Hassan H, Salami A, Bazzal AA, et al. Effects of a single dose of ivermectin on viral and clinical outcomes in asymptomatic SARS-CoV-2 infected subjects: a pilot clinical trial in Lebanon. *Viruses* 2021;13:989.
- [47] Lopez-Medina E, Lopez P, Hurtado IC, Davalos DM, Ramirez O, Martinez E, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. *JAMA* 2021;325:1426–35.
- [48] Vallejos J, Zoni R, Bangher M, Villamandos S, Bobadilla A, Plano F, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. *BMC Infect Dis* 2021;21:635.
- [49] Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:605–12.
- [50] Furtado RHM, Berwanger O, Fonseca HA, Correa TD, Ferraz LR, Lapa MG, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet* 2020;396:959–67.
- [51] Sekhavati E, Jafari F, SeyedAlinaghi S, Jamalimoghaddamsiahkali S, Sadr S, Tabarestani M, et al. Safety and effectiveness of azithromycin in patients with COVID-19: an open-label randomised trial. *Int J Antimicrob Agents* 2020;56:106143.
- [52] Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021;397:1063–74.
- [53] Tardif JC, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multi-centre trial. *Lancet Respir Med* 2021;9:924–32.
- [54] Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical Trial. *JAMA Netw Open* 2020;3:e2013136.
- [55] Lopes MI, Bonjorno LP, Giannini MC, Amaral NB, Menezes PI, Dib SM, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. *RMD Open* 2021;7:e001455.
- [56] RECOVERY Collaborative Group, Horby PW, Campbell M, Spata E, Emberson JR, Staplin N, Pessoa-Amorim G, et al. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. 2021.
- [57] Alabed S, Cabello JB, Irving GJ, Qintar M, Burls A. Colchicine for pericarditis. *Cochrane Database Syst Rev*; 2014CD010652.
- [58] Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
- [59] Dequin PF, Heming N, Meziani F, Planteveve G, Voiriot G, Badie J, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA* 2020;324:1298–306.
- [60] Du B, Weng LI. Glucocorticoid therapy for COVID-19 critically ill patients with severe acute respiratory failure 2021. Available from: <https://www.clinicaltrials.gov/ct2/show/study/NCT04244591>.
- [61] Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis* 2021;72:e373–81.
- [62] Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324:1317–29.
- [63] Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of Dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020;324:1307–16.
- [64] Munch MW, Meyhoff TS, Helleberg M, Kjaer MN, Granholm A, Hjortso CJS, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: the COVID STEROID randomised, placebo-controlled trial. *Acta Anaesthesiol Scand* 2021;65:1421–30.
- [65] Villar J, Ferrando C, Martinez D, Ambros A, Munoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multi-centre, randomised controlled trial. *Lancet Respir Med* 2020;8:267–76.
- [66] Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur Respir J* 2020;56:2002808.
- [67] Huttner BD, Catho G, Pano-Pardo JR, Pulcini C, Schouten J. COVID-19: don't neglect antimicrobial stewardship principles. *Clin Microbiol Infect* 2020;26:808–10.
- [68] Cadeгами FA, Goren A, Wambier CG, McCoy J. Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly improved COVID-19 outcomes compared to known outcomes in untreated patients. *New Microbe. New Infect* 2021;43:100915.
- [69] Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID trial). *BMJ* 2020;371:m3939.
- [70] AlQahtani M, Abdulrahman A, Almadani A, Alali SY, Al Zamrooni AM, Hejab AH, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. *Sci Rep* 2021;11:9927.
- [71] Avendaño-Solà C, Ramos-Martínez A, Muñoz-Rubio E, Ruiz-Antorán B, Malo de Molina R, Torres F, et al. Convalescent Plasma for COVID-19: a multicenter, randomized clinical trial 2020. Available from: <https://www.medrxiv.org/content/10.1101/2020.08.26.20182444v3>; 2020.
- [72] Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. *Nat Commun* 2021;12:3189.
- [73] Wang D, Ju XL, Xie F, Lu Y, Li FY, Huang HH, et al. [Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China]. *Zhonghua Er Ke Za Zhi* 2020;58:E011.
- [74] Libster R, Perez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med* 2021;384:610–8.
- [75] Rasheed AM, Fatak DF, Hashim HA, Maulood MF, Kabah KK, Almusawi YA, et al. The therapeutic utility of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. *Infez Med* 2020;28:357–66.
- [76] Simonovich VA, Burgos Pratz LD, Scibona P, Beruto MV, Vallone MG, Vazquez C, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med* 2021;384:619–29.
- [77] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multi-centre trial. *Lancet* 2020;395:1569–78.
- [78] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 – final report. *N Engl J Med* 2020;383:1813–26.
- [79] Spinner CD, Gottlieb RL, Criner GJ, Arribas Lopez JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA* 2020;324:1048–57.
- [80] Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med* 2020;383:1827–37.
- [81] Mahajan L, Singh AP, Gifty. Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: a prospective randomised study. *Indian J Anaesth* 2021;65:S41–6.
- [82] Mozaffari E, Chandak A, Zhang Z, Liang S, Thrun M, Gottlieb RL, et al. Remdesivir treatment in hospitalized patients with COVID-19: a comparative analysis of in-hospital all-cause mortality in a large multi-center observational cohort. *Clin Infect Dis* 2021;ciab875. <https://doi.org/10.1093/cid/ciab875>.

- [83] Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic? *J Virus Erad* 2020;6:45–51.
- [84] Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials. *Sci Rep* 2021;11:11022.
- [85] Udwardia ZF, Barkate H, Patil S, Rangwala S, Wu W, Caracta CF, et al. Response to the comments received on article "Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: a randomized, comparative, open-label, multicenter, phase 3 clinical trial" by Udwardia et al. *Int J Infect Dis* 2021;105:686–7.
- [86] Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. AVIFAVIR for treatment of patients with moderate COVID-19: interim results of a phase III/II multicenter randomized clinical trial. *Clin Infect Dis* 2021;73:531–4.
- [87] Vanderbeke L, Janssen NAF, Bergmans D, Bourgeois M, Buil JB, Debaveye Y, et al. Posaconazole for prevention of invasive pulmonary aspergillosis in critically ill influenza patients (POSA-FLU): a randomised, open-label, proof-of-concept trial. *Intensive Care Med* 2021;47:674–86.
- [88] Recommendations for the diagnosis and management of COVID-19 associated pulmonary aspergillosis (CAPA). Available from: <https://swab.nl/nl/article/nieuws/539/addendum-recommendations-for-the-diagnosis-and-management-of-covid-19-associated-pulmonary-aspergillosis-capagepubliceerd>.
- [89] Verweij PE, Bruggemann RJM, Azoulay E, Bassetti M, Blot S, Buil JB, et al. Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis. *Intensive Care Med* 2021;47:819–34.
- [90] Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021;181:32–40.
- [91] Horby P, Pessoa-Amorim G, Peto L, Brightling C, Sarkar R, Thomas K, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial 2021. Available from: <https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1.full.pdf>.
- [92] Salama C, Mohan SV. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *Reply N Engl J Med* 2021;384:1473–4.
- [93] Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021;181:24–31.
- [94] Veiga VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ* 2021;372:n84.
- [95] Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med* 2020;383:2333–44.
- [96] Investigators R-C, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021;384:1491–502.
- [97] Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637–45.
- [98] Wang D, Fu B, Peng Z, Yang D, Han M, Li M, et al. Tocilizumab in patients with moderate or severe COVID-19: a randomized, controlled, open-label, multicenter trial. *Front Med* 2021;15:486–94.
- [99] Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COV-INTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. *Lancet Respir Med* 2021;9:511–21.
- [100] FH-LR Ltd. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe associated pneumonia. <https://www.roche.com/media/releases/med-cor-2020-07-29.htm>.
- [101] Rosas IO, Brau N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. *N Engl J Med* 2021;384:1503–6.
- [102] Group WHOREAfC-TW, Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, et al. Association between administration of il-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. *JAMA* 2021;326:499–518.
- [103] Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, Farrokhpour M, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA* 2021;325:1620–30.
- [104] Investigators Atacc, et al. Therapeutic anticoagulation with heparin in non-critically ill patients with Covid-19. *N Engl J Med* 2021;385:790–802.
- [105] Remap-Cap Investigators R-C, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. *N Engl J Med* 2021;385:777–89.
- [106] Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, et al. A randomized clinical trial of the efficacy and safety of interferon beta-1a in treatment of severe COVID-19. *Antimicrob Agents Chemother* 2020;64. e01061–20.
- [107] Ader F, Peiffer-Smadja N, Poissy J, Bouscambert-Duchamp M, Belhadi D, Diallo A, et al. Antiviral drugs in hospitalized patients with COVID-19 – the DisCoVeReY trial. *medRxiv* 2021:20248149.
- [108] Alavi Darazam I, Shokouhi S, Pourhoseingholi MA, Naghibi Irvani SS, Mokhtari M, Shabani M, et al. Role of interferon therapy in severe COVID-19: the COVIFERON randomized controlled trial. *Sci Rep* 2021;11:8059.
- [109] Ader F, Peiffer-Smadja N, Poissy J, Bouscambert-Duchamp M, Belhadi D, Diallo A, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-beta-1a and hydroxychloroquine in hospitalized patients with COVID-19. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2021;27:1826–37.
- [110] Amaravadi RK, Giles L, Carberry M, Hyman MC, Frank I, Nasta SD, et al. Hydroxychloroquine for SARS-CoV-2 positive patients quarantined at home: the first interim analysis of a remotely conducted randomized clinical trial. *medRxiv* 2021. 2022.21252228. <https://www.medrxiv.org/content/10.1101/2021.02.22.21252228v1>.
- [111] Gonzalez JLB, González Gámez M, Enciso EAM, Maldonado RJE, Hernández Palacios D, Duenas Campos S, et al. Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. *medRxiv* 2021:21252037. <https://www.medrxiv.org/content/10.1101/2021.02.18.21252037v1>.
- [112] Group RC, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020;383:2030–40.
- [113] Reis G, Moreira Silva E, Medeiros Silva DC, Thabane L, Singh G, Park JH, et al. Effect of early treatment with hydroxychloroquine or lopinavir and ritonavir on risk of hospitalization among patients with COVID-19: the TOGETHER randomized clinical trial. *JAMA Netw Open* 2021;4:e216468.
- [114] Self WH, Semler MW, Leather LM, Casey JD, Angus DC, Brower RG, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. *JAMA* 2020;324:2165–76.
- [115] Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv* 2020. 2022.20040758. <https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v3>.
- [116] Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. *N Engl J Med* 2021;385:1382–92.
- [117] Abd-Elsalam S, Noor RA, Badawi R, Khalaf M, Esmail ES, Soliman S, et al. Clinical study evaluating the efficacy of ivermectin in COVID-19 treatment: a randomized controlled study. *J Med Virol* 2021;93:5833–8.
- [118] Mohan A, Tiwari P, Suri T. Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial. PREPRINT (Version 1), available at: Research Square, <https://doi.org/10.21203/rs.3.rs-191648/v1>. 2021; 2021.
- [119] Niaee MS, Gheibi N, Pea Namdar. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial, 24 November 2020, PREPRINT (Version 1); available at: Research Square, <https://doi.org/10.21203/rs.3.rs-109670/v1>. 2020; 2021.
- [121] Shahbaznejad L, Davoudi A, Eslami G, Markowitz JS, Navaeifar MR, Hossainzadeh F, et al. Effects of ivermectin in patients with COVID-19: a multicenter, double-blind, randomized, controlled clinical trial. *Clin Ther* 2021;43:1007–19.
- [122] Kishoria N, Mathur SL, Parmar V. Ivermectin as adjuvant to hydroxychloroquine in patients resistant to standard treatment for SARS-CoV-2: results of an open-label randomized clinical study. *Indian J Res* 2020;9:1–4.
- [123] Podder CS, Chowdhury N, Sina MI, Haque WMMU. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. *IMC J Med Sci* 2021;14:11–8.
- [124] Group PTC. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021;397:1063–74.
- [125] Group RC. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:605–12.
- [126] Group RC. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Resp Med* 2021;9:1419–26.
- [127] Salehzadeh F, Pourfarzi F, Ataei Sea. The impact of colchicine on the COVID-19 patients; A clinical trial study, 21 september 2020. PREPRINT (Version 1); available at: Research Square, <https://doi.org/10.21203/rs.3.rs-69374/v1>; 2021.
- [128] Petersen MW, Meyhoff TS, Helleberg M, Kjaer MN, Granholm A, Hjortso CJS, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial-Protocol and statistical analysis plan. *Acta Anaesthesiol Scand* 2020;64:1365–75.
- [129] World Health Organization. Corticosteroids for COVID-19, living guidance. 2020. Available at: <https://apps.who.int/iris/handle/10665/334125>.
- [130] Group RC. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet* 2021;397:2049–59.
- [131] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA* 2020;324:460–70.