Therapeutic interventions for COVID-19: a living overview of reviews

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Malahat Khalili, Maryam Chegeni, Sara Javadi, Mehrdad Farokhnia, Hamid Sharifi and Mohammad Karamouzian

Abstract

Background: Coronavirus disease 2019 (COVID-19) has rapidly spread worldwide, but safe and effective treatment options remain unavailable. Numerous systematic reviews of varying qualities have tried to summarize the evidence on the available therapeutic interventions for COVID-19. This overview of reviews aims to provide a succinct summary of the findings of systematic reviews on different pharmacological and non-pharmacological therapeutic interventions for COVID-19.

Methods: We searched PubMed, Embase, Google Scholar, Cochrane Database of Systematic Reviews, and WHO database of publications on COVID-19 from 1 December 2019 through to 11 June 2020 for peer-reviewed systematic review studies that reported on potential pharmacological or non-pharmacological therapies for COVID-19. Quality assessment was completed using A MeaSurement Tool to Assess systematic Reviews-2 (AMSTAR-2) measure.

Results: Out of 816 non-duplicate studies, 45 were included in the overview. Antiviral and antibiotic agents, corticosteroids, and anti-malarial agents were the most common drug classes used to treat COVID-19; however, there was no direct or strong evidence to support their efficacy. Oxygen therapy and ventilatory support was the most common non-pharmacological supportive care. The quality of most of the included reviews was rated as low or critically low.

Conclusion: This overview of reviews demonstrates that although some therapeutic interventions may be beneficial to specific subgroups of COVID-19 patients, the available data are insufficient to strongly recommend any particular treatment option to be used at a population level. Future systematic reviews on COVID-19 treatments should adhere to the recommended systematic review methodologies and ensure that promptness and comprehensiveness are balanced.

The reviews of this paper are available via the supplemental material section.

Keywords: COVID-19, pandemic, review, therapeutics

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Correspondence to:
Mohammad Karamouzian
School of Population and Public Health, University of British Columbia, 2206 E Mall, Vancouver, BC V6T 1Z3, Canada
Karamouzian.m@alumni.ubc.ca

Malahat Khalili
Maryam Chegeni
Sara Javadi
Hamid Sharifi
HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

Mehrdad Farokhnia
Department of Internal Medicine, Faculty of Medicine, Afzalipour Hospital, Kerman University of Medical School, Kerman, Iran

Introduction

Severe acute respiratory coronavirus 2 (SARS-CoV-2) was first detected in patients linked with Wuhan's wet markets, but soon grew out of China and the coronavirus disease 2019 (COVID-19) was declared a pandemic on 11 March 2020.[1] Healthcare systems worldwide have been overwhelmed and continue to struggle with the soaring number of patients, limited supplies of personal protective equipment (PPE), and ventilators. Based on the existing evidence, the risk is relatively low for the general population, although elderly populations, immunocompromised people, and those with pre-existing medical conditions are at an increased risk of adverse outcomes.[2,3] As of 5 October 2020, 35,330,119 COVID-19 patients have been detected, 1,038,958 of whom have died and 24,564,100 have recovered;[4] figures that are most likely underestimated due to the limited number of SARS-CoV-2 tests completed, inadequate confidence in the sensitivity and specificity of diagnostic testing, and various systems of case reporting and recovery definitions across the world.[5]

The current evidence suggests that most COVID-19 patients may remain asymptomatic or experience mild clinical symptoms that require no specific treatments. Severe cases, however, suffer from a range of life-threatening conditions such as pneumonia, acute respiratory distress syndrome (ARDS),[6] and respiratory failure.[3,7] To date, highly effective treatments for COVID-19 are unavailable;[8] however, numerous trials and studies have been conducted and are ongoing to develop and assess various pharmacological and non-pharmacological therapeutic options for the treatment and prevention of COVID-19.[9,10] As of 5 October 2020, 3507 clinical trials have been registered on ClinicalTrials.gov[11] and the effectiveness of several classes of drugs such as antiviral, antibiotic, antimalarial agents, and corticosteroids are being investigated.[11]

Given the urgency of the issue and the novelty of the disease, numerous systematic reviews of varying qualities and scope have tried to summarize the evidence on available therapeutic interventions for COVID-19; papers that have been published in several journals over a very short time. While these review papers are helpful, the overwhelming amount of information and the unprecedented number of COVID-19-related evidence syntheses of unclear quality, create challenges for policymakers and healthcare providers to sift through relevant and reliable research findings. This living overview of reviews aims to provide a succinct summary of the findings of peer-reviewed systematic reviews on different pharmacological and non-pharmacological therapeutic options for COVID-19, and assess the methodological and reporting quality of the existing systematic reviews.

Methods

The living overview of systematic reviews was guided by the methodological guidance on the conduct of overviews of reviews published by the Cochrane collaboration[12] and other recently developed guidelines.[13,14] Inclusion criteria and analytical approaches were designed a priori and are documented in a protocol published in the Open Science Framework (https://osf.io/sby9u/).

Databases and search strategy

Following the peer review of electronic search strategies guidelines,[15] we searched PubMed, Embase, Google Scholar, Cochrane Database of Systematic Reviews, and WHO database of publications on COVID-19 from 1 December 2019 through to 11 June 2020, for peer-reviewed review studies that synthesized and reported on potential pharmacological or non-pharmacological therapies for COVID-19. Search terms were combined using appropriate Boolean operators, and included subject heading terms and keywords relevant to COVID-19 and different treatment approaches. We also screened the reference lists of the included articles. Preprint papers that had not gone through peer review were excluded, given their potential for misinforming our conclusions. The live nature of our overview allows for relevant publications to be added to our body of evidence as they become visible in peer-reviewed journals. A detailed overview of the search strategy is provided in Supplemental Table 1.

Inclusion criteria

Systematic reviews, scoping reviews, and rapid reviews that summarized and synthesized primary studies about the effectiveness of pharmacological and non-pharmacological treatments for people with a confirmed diagnosis of COVID-19 using real-time reverse transcription polymerase chain reaction (RT-PCR), nasal/pharyngeal swabs, or other prespecified diagnostic approaches such as clinical or radiological findings were included in this overview. Studies on children or pregnant women were not excluded. Interventions could be of any duration, delivery, frequency, and intensity. Reviews were eligible if they provided an explicit description of inclusion criteria and included a systematic search of at least one electronic database. Letters, commentaries, expert opinion, theoretical and unstructured reviews as well as narrative reviews not meeting the above-mentioned eligibility criteria were excluded. Studies were not excluded based on language, and records published in languages other than English were assessed for eligibility using Google Translate (https://translate.google.com/).

Study selection

Two authors (MKH and MC) completed the title and abstract screening, independently. Citations that met our eligibility criteria or were unclear, were screened at full text by two independent reviewers (MKH and MC). Disagreements over the inclusion of studies were resolved through discussion or arbitration with the senior author (MK). Duplicate records were excluded.

Table 1. Characteristics of the included studies in the overview of reviews.

Author	Publication date	Journal and impact factor	Study design	Information sources	Search date	No. studies screened	No. included primary studies	Sample size	Age (years)	Sex (male %)	Study design of included studies
Liu *et al.*[20]	3 June 2020	Canadian Medical Association Journal JIF = 7.7 *Authors should follow PRISMA guidelines.*	SR & MA	MEDLINE, Embase, CENTRAL, Clinical-Trials.gov, PubMed, CNKI, Wanfang Data, SinoMed, Chongqing VIP Information, medRxiv, and Chinaxiv.	19 April 2020	8355	19 (12 on COVID-19)	4127 (Including 1931 for COVID-19)	Mean: 41.0	59.3%	7 RCTs, 11 Cohort, 1 Case control
Qu *et al.*[21]	29 May 2020	Stem Cells Translational Medicine JIF = 5.980	SR	MEDLINE, Embase, CENTRAL, Clinical-Trials.gov, Cochrane Database of Systematic Reviews, and Scopus.	31 March 2020	2691	9 (1 on COVID-19)	200 (Including 10 for COVID-19)	Mean: 59.4	NR	1 Phase I clinical trial
Das *et al.*[22]	28 May 2020	Clinical Drug Investigation JIF = 2.158 *Authors should follow PRISMA guidelines.*	SR	PubMed, Embase, ClinicalTrials.gov, ICTRP, Cochrane Library, medRxiv, and Research Square.	10 May 2020	663	12	3543	Mean: 44.0	58.1%	4 Prospective observational studies, 4 Retrospective observational studies, 4 RCTs
Fajgenbaum *et al.*[23]	27 May 2020	Infectious Diseases and Therapy JIF = 0 *Authors should follow PRISMA guidelines.*	SR	PubMed, bioRxiv, medRxiv, and ChinaXiv.	27 March 2020	2711	156	9152	Mean: 44.4	54.6%	84 Case reports, 72 Case series
Ye *et al.*[24]	27 May 2020	Canadian Medical Association Journal JIF = 7.7 *Authors should follow PRISMA guidelines.*	SR & MA	MEDLINE, Embase, PubMed, CENTRAL, ClinicalTrials.gov, medRxiv, CNKI, Wanfang Data, Chongqing VIP Information, and ChinaXiv.	19 April 2020	5120	11 (6 on COVID-19)	8473 (Including 763 for COVID-19)	NR	NR	10 Cohort, 1 RCT
Hernandez *et al.*[25]	27 May 2020	Annals of Internal Medicine JIF = 19.315 *Authors should follow PRISMA guidelines.*	SR	PubMed, Embase, Scopus, Web of Science, Cochrane Library, bioRxiv, Preprints, Clinical Trials.gov, ICTRP, and Chinese Clinical Trials Registry.	8 May 2020	838	23	5499	Range of mean: 44–69	Range: 42–100%	4 RCTs, 10 Cohort studies, 9 Case series

(Continued)

Table 1. (Continued)

Author	Publication date	Journal and impact factor	Study design	Information sources	Search date	No. studies screened	No. included primary studies	Sample size	Age (years)	Sex (male %)	Study design of included studies
Rodrigo *et al.*[26]	26 May 2020	Clinical Microbiology and Infection JIF = 6.425 *Authors should follow PRISMA guidelines.*	SR	PubMed, Embase, Scopus, Web of Science, CENTRAL, Chinese Clinical Trials Registry, and medRxiv.	3 April 2020	2267	19 (6 on COVID-19)	NR.	NR	NR	17 RCTs, 2 Prospective studies
Jorgensen *et al.*[27]	23 May 2020	Pharmacotherapy JIF = 3.196 *Authors should follow PRISMA guidelines.*	SR	PubMed.	5 May 2020	NR	6	71	NR	NR	1 Case series, 5 Case report
Ang *et al.*[28]	23 May 2020	Journal of Clinical Medicine JIF = 5.688 *Authors should follow PRISMA guidelines.*	SR & MA	PubMed, Embase, Allied and Complementary Medicine Database, CENTRAL, Chinese National Knowledge Infrastructure Database, Chinese Science and Technique Journals Database, CBM, Wanfang Data, Korean Association of Medical Journal database, Korean Medical database, Research Information Service System, and OASIS database.	12 May 2020	2027	7	855	Mean: 51.1	55.2%	7 RCTs
Schunemann *et al.*[29]	22 May 2020	Annals of Internal Medicine JIF = 19.315 *Authors should follow PRISMA guidelines.*	SR & MA	MEDLINE, PubMed, Embase, CINAHL, Cochrane Library, COVID-19 Open Research Dataset, COVID-19 Research Database maintained, Epistemonikos, ClinicalTrials.gov, U.S. National Library of Medicine's register of clinical trials, and ICTRP.	1 May 2020	38942	123 (45 on COVID-19)	NR	NR	NR	57 Case series, 24 Cohort, 2 Case control, 2 Case studies, 1 Cost study, 9 Retrospective studies, 1 RCT

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Table 1. (Continued)

Author	Publication date	Journal and impact factor	Study design	Information sources	Search date	No. studies screened	No. included primary studies	Sample size	Age (years)	Sex (male %)	Study design of included studies
Antwi-Amoabeng *et al.*[30]	21 May 2020	Journal of Medical Virology JIF = 2.049 *Invited reviews only.*	SR	PubMed, Embase, and MEDLINE.	27 April	352	11	29	Mean: 63	82.8%	4 Case series, 7 Case reports
Tahvildari *et al.*[31]	15 May 2020	Frontiers in MEDICINE JIF = 3.113 *Authors should follow PRISMA guidelines.*	SR	PubMed, Embase, Web of Science, and Cochrane Library.	24 April 2020	1102	34	99	Mean: 46.2	47.7%	23 Case reports, 11 Case series
Valk *et al.*[32]	14 May 2020	Cochrane database of systematic reviews JIF = 7.755 *Cochrane Reviews are prepared by author teams who work with Cochrane Review Group.*	RR	WHO COVID-19 Global Research Database, MEDLINE, Embase, PubMed, Center for Disease Control and Prevention COVID-19 Research Article Database, Cochrane COVID-19 Study Register, ClinicalTrials.gov, and ICTRP.	23 April 2020	1267	8	32	NR	NR	7 Case series, 1 Clinical trial
Zhang *et al.*[33]	14 May 2020	Clinical Infectious Diseases JIF = 9.117	SR & MA	MEDLINE, Embase, CENTRAL, and PubMed.	15 March 2020	1481	45	4203	Mean: 45	66.5%	Non-randomized, Retrospective observational studies
Liu *et al.*[34]	12 May 2020	Pharmacological Research JIF = 5.574 *Review articles and MAs are welcome but should be topical and not just an overview of the literature.*	SR & MA	PubMed, Embase, Cochrane Library, CNKI, Wanfang Data, and CBM.	24 March 2020	1212	11	982	NR	58.5%	4 RCTs, 7 Case-Control Studies
Singh *et al.*[35]	12 May 2020	Diabetes & Metabolic Syndrome JIF = 0	SR	PubMed, ClinicalTrial.org, and medRxiv.	5 May 2020	NR	11	1778	NR	NR	3 Case studies, 4 Clinical trials, 4 Ongoing RCTs

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Table 1. (Continued)

Author	Publication date	Journal and impact factor	Study design	Information sources	Search date	No. studies screened	No. included primary studies	Sample size	Age (years)	Sex (male %)	Study design of included studies
Gbinigie and Frie[10]	12 May 2020	BJGP Open JIF = 0 *Invited reviews only; Authors should follow PRISMA guidelines.*	RR	PubMed, TRIP Database, EPPI COVID Living Map, medRxiv, Google Scholar, and Google.	16 April 2020	230	3	36	45.0	NR	2 *in vitro*; 1 RCT
Singh *et al.*[36]	12 May 2020	Diabetes & Metabolic Syndrome JIF = 0	SR & MA	PubMed, Scopus, Cochrane Library, and medRxiv.	30 April 2020	211	10	2042	Mean: 50.1	NR	3 RCTs, 1 nRCT, 1 qRCT, 2 Retrospective studies, 3 Prospective studies
Li *et al.*[37]	6 May 2020	Drug discoveries & therapeutics JIF = 1.11	RR	PubMed and MEDLINE.	NR	NR	12 (10 on COVID-19)	NR	NR	NR	7 Ongoing RCTs, 3 Experimental studies, 1 Case report, 1 Cross-sectional study
Li *et al.*[38]	5 May 2020	Leukemia JIF = 12.104	SR & MA	PubMed, Web of Science, MEDLINE, Wanfang Data, and ZhiWang Database.	20 March 2020	8788	11 (4 on COVID-19)	5249 (Including 1426 for COVID-19)	Mean = 51.9	NR	1 RCT, 10 Observational
Xu *et al.*[39]	5 May 2020	Military Medical Research JIF = 1.73	SR	PubMed and Cochrane Library.	NR	1325	30	1949	NR	NR	2 Prospective cohort studies, 5 RCTs, 4 Retrospective cohort studies, 8 Case series, 7 Cohort studies, 4 Case report, 1 MA, 1 Case control studies
Alijotas-Reig *et al.*[40]	3 May 2020	Autoimmunity Reviews JIF = 7.716	SR	MEDLINE, PubMed, and Cochrane Library.	30 March 2020	NR	NR	NR	NR	NR	NR
Rawson *et al.*[41]	2 May 2020	Clinical Infectious Diseases JIF = 9.117	RR	MEDLINE and Embase.	18 April 2020	1007	18 (9 on COVID-19)	7033 (Including 2010 for COVID-19)	NR	NR	NR
Chowdhury *et al.*[42]	2 May 2020	Academic Emergency Medicine JIF = 2.963 *Authors should follow PRISMA guidelines.*	RR	Cochrane Library, MEDLINE, Embase, medRxiv, and ClinicalTrials.gov.	26 April 2020	59	36 (29 ongoing RCTs)	486	NR	NR	6 Clinical trials, 1 letter

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Table 1. (Continued)

Author	Publication date	Journal and impact factor	Study design	Information sources	Search date	No. studies screened	No. included primary studies	Sample size	Age (years)	Sex (male %)	Study design of included studies
Zhang *et al.*[43]	1 May 2020	Annals of translational medicine JIF = 3.689 *Authors should follow PRISMA guidelines.*	RR	Cochrane library, MEDLINE, Embase, Web of Science, China Biology Medicine disc, CNKI, Wanfang Data, ICTRP, ISRCTN Registry, ClinicalTrials.gov, Google Scholar, medRxiv, bioRxiv, and SSRN.	31 March 2020	1519	6 (2 on COVID-19)	112 for COVID-19	Mean in case series: 55 Range in case report: 34–56	57.1%	4 Case series, 1 Case report, 1 RCT
Rajendran *et al.*[44]	1 May 2020	Journal of Medical Virology JIF = 2.049 *Invited reviews only.*	SR	PubMed, Embase, and MEDLINE.	NR	110	5	27	Range: 28–73	56%	3 Case report, 2 Case series
Lu *et al.*[45]	1 May 2020	Annals of translational medicine JIF = 3.689 *Authors should follow PRISMA guidelines.*	SR & MA	Cochrane library, MEDLINE, Embase, Web of Science, China Biology Medicine, CNKI, Wanfang Data, ICTRP, ISRCTN Registry, ClinicalTrials, Google Scholar, medRxiv, bioRxiv, and SSRN.	31 March 2020	2509	23 (5 on COVID-19)	13815 (Including 926 for COVID-19)	Mean: 51.28	55.2%	1 RCT, 22 Cohort studies
Shi *et al.*[46]	May 2020	Annals of translational medicine JIF = 3.689 *Authors should follow PRISMA guidelines.*	RR	PubMed, Embase, Web of Science, Cochrane Library, China Biology Medicine, CNKI, Wanfang Data, ICTRP, US National Institutes of Health Trials Register, International Standard Randomized Controlled Trial Number Register, Google Scholar, Official websites of WHO and Centers for Disease Control, bioRxiv, medRxiv, and SSRN.	31 March 2020	4101	23 (7 on COVID-19, 13 on SARS, 3 on MERS)	6008	Range: 26.7 to 67.4	43%	6 RCTs, 17 Cohort studies

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Table 1. (Continued)

Author	Publication date	Journal and impact factor	Study design	Information sources	Search date	No. studies screened	No. included primary studies	Sample size	Age (years)	Sex (male %)	Study design of included studies
Wang *et al.*[47]	May 2020	Annals of translational medicine JIF = 3.689 *Authors should follow PRISMA guidelines.*	RR	Cochrane library, PubMed, Embase, Web of Science, China Biology Medicine disc, CNKI, Wanfang, Data, ICTRP, US National Institutes of Health Trials Register, ISRCTN Registry, and Google Scholar.	31 March 2020	2183	33 (including 4 on children only)	3203 (including 48 children)	Mean: 37.3	NR	10 Case reports, 20 Case series, 1 Cohort, 1 Descriptive, 1 Cross-sectional study
Alzghari and Acuña[48]	30 April 2020	Journal of Clinical Virology JIF = 3.02	SR	PubMed, Embase, Scopus, and Web of Science.	NR	63	6	40	Mean: 62.7	82.7%	2 Retrospective analyses, 4 case reports
Zhong *et al.*[49]	30 April 2020	Pharmacological Research JIF = 5.574 *Authors should follow PRISMA guidelines.*	SR & MA	Embase, Cochrane Library, CNKI, China Science and Technology Journal Database, Wanfang Data, medRxiv, and bioRxiv.	20 April 2020	5570	18 (7 on COVID-19)	5002 (Including 644 for COVID-19)	Mean: 50.23	54.8%	5 RCTs, 13 Controlled cohort
Pascarella *et al.*[50]	29 April 2020	Journal of Internal Medicine JIF = 6.051	SR	PubMed, Google Scholar, MEDLINE, UpToDate, Embase, and Web of Science.	3 April 2020	NR	NR	NR	NR	NR	NR
Veronese *et al.*[51]	24 April 2020	Frontiers in MEDICINE JIF =3.113 *Authors should follow PRISMA guidelines.*	SR	Embase, PubMed, Web of Science, CNKI, MEDLINE, CINAHL, Toxline, Scopus, and Wanfang Data.	15 March 2020	31	4	542	Mean: 52.4	55%	4 Retrospective cohort studies
Sarma *et al.*[52]	16 April 2020	Journal of Medical Virology JIF = 2.049 *Invited reviews only.*	SR & MA	PubMed, CINAHL, Scopus, Wiley online library, Web of Science, CENTRAL, Embase, medRxiv, bioRxiv, TRIP Database, Nature, Epistemonikos, Science Direct, Virtual Health Library, Pan American Health Organization, CNKI, and Mediterranee-infection.com/pre-prints-ihu.	8 April 2020	408	7	1358	NR	NR	NR

(Continued)

Table 1. (Continued)

Author	Publication date	Journal and impact factor	Study design	Information sources	Search date	No. studies screened	No. included primary studies	Sample size	Age (years)	Sex (male %)	Study design of included studies
Ford *et al.*[53]	15 April 2020	Journal of the International AIDS Society JIF = 5.192 *Authors should follow PRISMA guidelines.*	SR	PubMed, Embase, Cochrane Library, WHO database of publications on COVID-19, Clinicaitrials.gov, and Chictr.org.cn.	30 March 2020	433	26 (Including 17 on COVID-19)	2260 (Including 662 for COVID-19)	NR	NR	2 RCTs and 24 Observational; For COVID-19: 2 RCTs, 3 Case reports, 1 Case series, 7 Retrospective cohorts, 1 Comparative cohort.
Fu *et al.*[7]	10 April 2020	Journal of Infection JIF = 5.099 *Authors should follow PRISMA guidelines.*	SR & MA	PubMed, Embase, Web of Science, and CNKI.	2 March 2020	2247	43	3600	Median: 41	56.5% Median (29–77%)	40 Retrospective case series, 1 Cross-sectional, 2 Prospective studies
Yang *et al.*[54]	10 April 20	Journal of Infection JIF = 5.099 *Authors should follow PRISMA guidelines.*	SR & MA	PubMed, Embase, Cochrane library, and CNKI.	15 March 2020	1685	15 (Including 2 on COVID-19)	5270 (Including 179 on COVID-19)	NR	NR	15 Retrospective studies
Gbinigie and Frie[55]	7 April 2020	BJGP Open JIF = 0 *Inviting reviews only; Authors should follow PRISMA guidelines.*	RR	PubMed, Google Scholar, and Google.	NR	NR	6	66	Mean: 51 Intervention group, 42 Control group	NR	3 *in vitro*, 1 Open-label randomized trial, 1 Open-label non-randomized trial, 1 Letter
Yousefifard *et al.*[56]	6 April 2020	Archives of Academic Emergency Medicine JIF = 0 *Authors should follow PRISMA guidelines.*	SR	PubMed, Embase, Scopus, CENTRAL, Web of Science, Google, and Google Scholar.	15 March 2020	4997	22	2856	Mean: 43.9	47.3%	1 Clinical trial, 16 Case-series, 5 Case-reports
Tobaiqy *et al.*[57]	6 April 2020	Infection Prevention in Practice JIF = 0 *Inviting reviews only; Authors should follow PRISMA guidelines.*	SR	Embase, MEDLINE, and Google Scholar.	26 March 2020	449	41	8806	Mean: 50.8	24% Male, 34% Other, 0.3% Unspecified	3 Clinical trials, 7 Case reports, 10 Case series, 11 Retrospective, 10 Prospective studies

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Table 1. (Continued)

Author	Publication date	Journal and impact factor	Study design	Information sources	Search date	No. studies screened	No. included primary studies	Sample size	Age (years)	Sex (male %)	Study design of included studies
Insiat Islam[58]	4 April 2020	Journal of Pharmacy and Pharmaceutical Sciences JIF = 2.042	SR	PubMed, Google Scholar, and Science Direct databases.	25 March 2020	1153	22	NR	NR	NR	8 Case reports, 4 Laboratory tests, 1 Animal trial, 9 Recommendations other viral infection (i.e. malaria, Ebola, SARS, MERS)
Guida[18]	2 April 2020	Inter American Journal of Medicine and Health JIF = 0	SR	PubMed, Scielo, Brazilian Registry of Clinical Trials, and ClinicalTrials.gov.	30 March 2020	41	1	36	51.2 Intervention group, 37.3 Control group	NR	1 Open-label non-randomized clinical trial, 3 Ongoing clinical trials
Pacheco and Riera[9]	31 March 2020	Journal of Evidence-Based Healthcare JIF = 0	RR	Cochrane Library, Embase, Literatura Latino-Americana e do Caribeem, Ciências da Saúde, PubMed, Opengrey, ClinicalTrials. gov, ICTRP, and Chinese Clinical Trial Registry.	26 March 2020	223	30	In 2 clinical trials: 66	Mean:51 Intervention group, 42 Control group	NR	1 Open-label randomized trial, 1 Open-label non-randomized trial, 28 Ongoing clinical studies[a]
Borges do Nascimento *et al.*[19]	30 March 2020	Journal of Clinical Medicine JIF = 5.688 *Authors should follow PRISMA guidelines.*	SR & MA	MEDLINE, CENTRAL, Embase, Scopus, and LILACS.	24 February 2020	2701	60 (Only 26 were about pharmacological and/or supportive interventions)	59254, (1876 about pharmacological and/or supportive interventions)	Range: 3 months to 99 years	54%	20 Case reports, 37 Case series, 3 Epidemiological reports
Singh *et al.*[59]	26 March 2020	Diabetes & Metabolic Syndrome JIF = 0	SR	PubMed and ClinicalTrials.gov.	21 March 2020	NR	11	> 136	Mean: In one study: 51.2 Intervention group, 37.3 Control group	NR	9 *in vitro* studies, 1 Open-label non-randomized trial, 1 Letter

Studies are listed on the chronological order of their publication dates.
CBM, Chinese Biomedical Database; CNKI, China National Knowledge Infrastructure; CENTRAL, Cochrane Central Register of Controlled Trials; ICTRP, WHO International Clinical Trials Registry Platform; JIF, Journal Impact Factor; ISRCTN, International Standard Randomized Controlled Trial Number; MA, Meta-Aanalysis; MERS, Middle East Respiratory Syndrome; NR, Not Rreported; nRCT, non-Randomized Controlled Trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Anlyses; qRCT, quasi-Randomized Controlled Trial; RCTs, Randomized Controlled Trials; RR, Rapid Review; SARS: Severe Acute Respiratory Syndrome; SR, Systematic Review; SSRN, Social Science Research Network; WHO, World Health Organization.

Data extraction

A data extraction sheet was designed and piloted by two independent authors (MKH and MC). Data were extracted independently by the two authors (MKH and MC), and discrepancies were resolved through discussion or arbitration with the senior author (MK). Data were extracted on study type (e.g. systematic review, rapid review), publication date, information sources (e.g. MEDLINE, Embase), search date, number of included studies in each review, total sample size, age and sex of the participants, study design of included studies in the review, description of the pharmacological (e.g. antivirals, antibiotics, antimalarial) and non-pharmacological (e.g. oxygen therapy, invasive or non-invasive mechanical ventilation) treatments, and main findings.

Quality and overlap assessment of individual reviews

Two reviewers (MKH and MK) independently evaluated the methodological quality of included reviews using A MeaSurement Tool to Assess systematic Reviews-2 (AMSTAR-2).[16] This tool contains 16 items to appraise the methodological aspects of the systematic reviews that include randomized or non-randomized primary studies. The methodological quality for each review was rated as critically low (i.e. more than one critical flaw with or without non-critical weaknesses), low (i.e. one critical flaw with or without non-critical weaknesses), moderate (i.e. more than one non-critical weakness), and high (i.e. no or one non-critical weakness). Scores on the AMSTAR-2 tool range from 0 to 16 and higher scores correspond to higher quality of systematic reviews.[16] We also assessed the degree of overlap within the systematic reviews by calculating the recently developed metric of corrected covered area (CCA) based on the following recommended cut-offs (i.e. slight overlap: CCA of 0–5%; moderate overlap: 6–10%; high overlap: 11–15%; and very high overlap: >15%).[17]

Data synthesis

Studies were summarized in a narrative fashion, and an overview of their methods and main findings were presented. Data synthesis was based on the pharmacological and non-pharmacological nature of the treatments.

Living overview of reviews

Given the rapidly increasing number of systematic reviews on COVID-19 treatment options, we will screen the online databases listed above on a bimonthly basis through December 2020 for new relevant evidence. If resources are available, we plan to update the overview of reviews when new peer-reviewed evidence that significantly alters the direction or strength of our original conclusions emerges.

Results

Literature search

The online database and reference search retrieved 992 studies, 176 of which were duplicate records and were excluded. A total of 686 records were excluded after the title and abstract screening. Of the remaining 130 articles that were assessed in the full-text screening phase, 45 were included in the overview (Figure 1). No additional systematic reviews were found through reference list screening.

Characteristics of the included reviews

Table 1 summarizes the overall characteristics of the 45 included reviews. All reviews were published between April and June 2020 and search dates were as early as 2 March 2020.[7] Reviews were published in 30 different journals, most of which had specific submission requirements for systematic reviews. The journal impact factor (JIF) of journals that published the systematic reviews ranged from 0 to 19.315 (median JIF = 3.689). All included reviews were published in English. The number of included primary studies in the reviews varied greatly from one[18] to 60[19] (median number of primary studies = 11). The majority (n = 30; 67%) of the reviews did not include a meta-analysis in their statistical analysis. Most reviews investigated pharmacological treatments for COVID-19.

A range of study designs was included across different systematic reviews; most of which included retrospective/prospective observational studies and case series/case reports. The target population was confirmed cases of COVID-19 patients and included children in three reviews[43,46,47] and adult patients in the remaining studies. None of the included reviews reported on pregnant women.

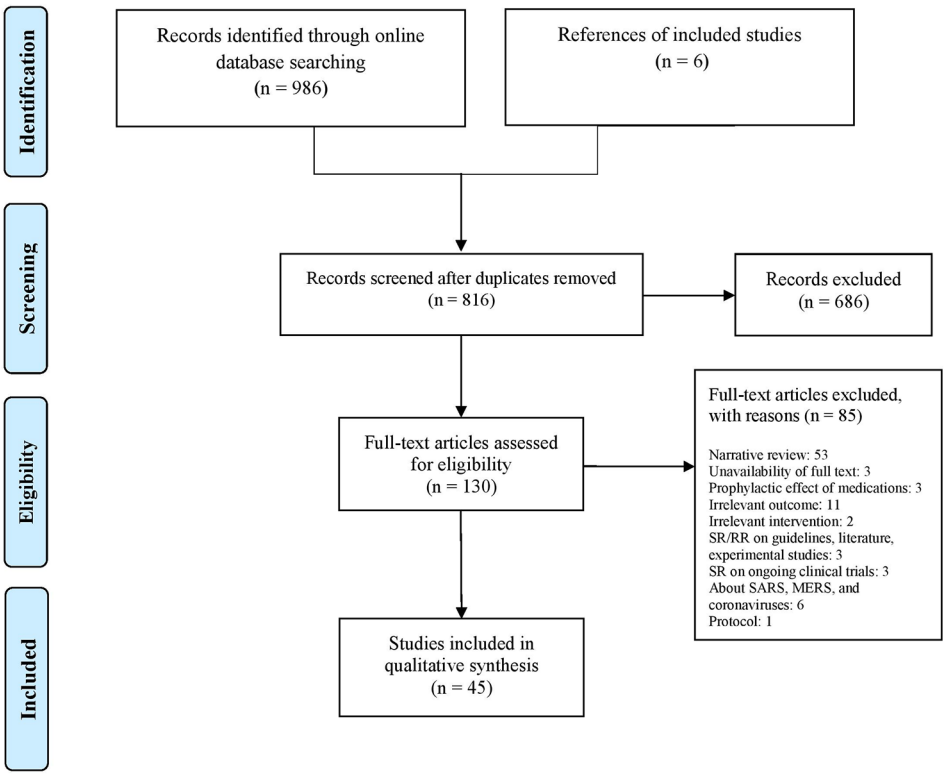

Figure 1. Flowchart of screened and included studies in the overview of reviews on therapeutic interventions for COVID-19.

Quality of included reviews

Supplemental Table 2 shows the details of AMSTAR-2 scores for each systematic review. The AMSTAR-2 score had a mean of 6.0 (range 0–13) and methodological drawbacks were frequent. According to AMSTAR-2, 29 systematic reviews were of critically low quality, nine were of low quality, and seven were of moderate quality. Seventeen reviews had pre-specified their clinical research question and inclusion criteria according to the components of population, intervention, comparators, and outcomes (PICO). Study selection and data extraction were performed in duplicate in 31 and 22 reviews, respectively. Only three reviews conducted a comprehensive literature search, and 13 reviews provided a list of excluded studies. Twenty-seven reviews described the characteristics of included studies in adequate detail and, 13 reviews assessed the risk of bias. In 15 reviews, appropriate meta-analysis methods were used for the statistical combination of results. Seven reviews provided sufficient explanation for any heterogeneity observed in the results, and eight studies carried out an adequate investigation of publication bias. Only in two reviews, the authors assessed the potential impact of risk of bias in individual studies on the results of the meta-analysis.[24,28] Only three reviews accounted for the risk of bias when discussing the results.[24,26,32] The value of the CCA was approximately 1.7, which corresponded to a slight overlap.

Therapeutic interventions for COVID-19

Details of the pharmacological and non-pharmacological therapeutic interventions and the main findings of each systematic review are summarized in Table 2. Most systematic reviews were conducted on observational studies without having suitable control groups for comparison. Moreover, systematic reviews reported on a range of different outcomes (e.g. viral clearance, viral load, improvement in radiology findings, time to a clinically meaningful response, mortality, intensive care unit [ICU] admission or duration, need for mechanical ventilation, disease progression, time to recovery, C-reactive protein level, white

Table 2. Overview of therapeutic interventions for COVID-19 patients included in the study.

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Liu *et al.*[20]	To address the benefits and harms of antiviral treatments for COVID-19.	Antivirals: Favipiravir (1600 mg, 12/h, on day 1 and 600 mg, 12/h on days 2–14) in 2 studies, Lopinavir (200–400 mg, 12/h)/Ritonavir (50–100 mg, 12/h) 1–14 days in 5 studies, Arbidol (200 mg, 8/h, 7–10 days) in 5 studies, Interferon-α by aerosol inhalation (60 μg/5 mIU, 12/h) in 3 studies.	NR.	Lopinavir/Ritonavir: RR = 0.99 viral clearance at day 14, RD = 5 length of stay in ICU; Reported only very low-quality evidence with little or no suggestion of benefit for most treatments.	11
		Antimalarial: HCQ (400–800 mg/day, 5–21 days) in 5 studies.		HCQ: RR = 0.98 viral clearance at day 14; RR = 0.96 progressing from non-severe to severe; RR = 1.48 mortality.	
Qu *et al.*[21]	To determine the potential value of mesenchymal stromal cells therapy for treating COVID-19 patients with ARDS.	NR.	Mesenchymal stromal cells in 1 study.	All symptoms disappeared in all patients, oxygen saturations rose to ⩾95% at rest, with or without oxygen uptake at 2–4 d after transplantation; Signs of pneumonia and ground-glass opacity on CT improvement on day 9.	10
Das *et al.*[22]	To systematically review the therapeutic role of HCQ in COVID-19.	Intervention groups: Antimalarial: HCQ (600 mg, daily, 10 days) alone or with Azithromycin (500 mg on day 1, 250 mg on days 2–5) in 7 studies; (400–600 mg, daily) in 3 studies; HCQ (1200 mg, daily, 3 days, then 800 mg, daily, 2–3 weeks) in 1 study; HCQ (1200 mg, daily, 1 day, then 400 mg, 4 days), daily for 4 days; optional Azithromycin (500 mg on day 1, 250 mg on days 2–5) in 1 study. Control groups: Standard treatment in 6 studies.	NR.	In 5 studies: Good virological and clinical outcomes with HCQ therapy alone or in combination with azithromycin; In 5 studies: Negative or equivocal results along with the risk of adverse reactions; In 1 study: No significant effect of HCQ on intubation or death in COVID-19 patients.	2
Fajgenbaum *et al.*[23]	To review all treatments that have been reported through any study design to be given to COVID-19 patients.	Antivirals in 71.5% of patients: Lopinavir/Ritonavir in 21.9% of patients, Interferon-α/b in 19.3% of patients, Arbidol in 10.6% of patients, Oseltamivir in 10.2% of patients, Ganciclovir in 2.3% of patients, Ribavirin in 1.7% of patients, Favipiravir in 1.6% of patients.	NR.	Mean of time to clinically meaningful response: 19.8 days Oseltamivir (longest average), 9.9 days Interferon-a/b (shortest time), 11.7 days Lopinavir/Ritonavir (most frequently administered), 10.9 days Umifenovir.	4
		Antibiotics in 46.6% of patients: Moxifloxacin in 6.5% of patients, Azithromycin in 1.4% of patients.		Mean of time to clinically meaningful response: 16.2 days Moxifloxacin.	
		Corticosteroids in 26.1% of patients: 4.6% Methylprednisolone.		Mean of time to clinically meaningful response: 14.2 days Methylprednisolone.	
		Immunostimulants in 20.3% of patients; Immunoglobulins: Immunoglobulin human normal in 11.5% of patients; Herbal Medicine in 7.6% of patients; Pituitary/Hypothalamic in 1.6% of patients; Antimycotics in 1.6% of patients; Antithrombotics in 1.5% of patients: Heparin in 1.4% of patients; Antimalarial: HCQ/CQ in 1.2% of patients; Blood substitutes in 1.2% of patients; Other category in 4.2% of patients: Thymosin-a1 in 1.7% of patients.		Effects of medications were not reported.	

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Ye *et al.*[24]	To examine the impact of corticosteroids in COVID-19 and related severe acute respiratory illnesses.	Corticosteroids in 6 studies.	NR.	In patients with COVID-19 and ARDS: HR = 0.41 mortality; In patients with COVID-19 but without ARDS: HR = 2.3 mortality; increase in the composite outcome of mortality or ICU admission; prolonged viral shedding.	12
Hernandez *et al.*[25]	To summarize the evidence about the benefits and harms of HCQ or CQ for the treatment or prophylaxis of COVID-19.	Intervention groups: Antimalarial: HCQ (400–600 mg, daily) in 8 studies, HCQ + Azithromycin (400–800 mg, daily + 500 mg on day 1 and 250 mg, 2–5 days) in 12 studies; CQ (300–600 mg, daily) in 4 studies.	Oxygen therapy in 3 studies.	CQ: RD = 0.0%, 24% all-cause mortality, RD = 9.5% need for mechanical ventilation, RD = 0.0%, 40.9% ICU admission, MD = −0.7 symptom resolution, upper respiratory viral clearance (RD = −8.3%, 16.4%, 34%); HCQ: RD = −26.9%, 6.1%, 16.4% and RD: −0.6% to 9.8% all-cause mortality, RD = 17.4% composite of intubation or death, RD = −0.8%, 0.0%, 14.4% need for mechanical ventilation, RD = −12.9%, 6.7%, 4.4%, MD = 0.47 severe disease progression, MD = −1.1, 0.0 symptom resolution, RD = −22.6, −13.3% progression of pulmonary lesions on CT, RD = 25.8% improvement in pulmonary lesions on CT, RD = −43.1%, 57.6%, −0.4% upper respiratory virologic clearance.	4
		Antivirals: Lopinavir/Ritonavir and/or Interferon beta in 1 study; Antibiotics: Ceftriaxone in 1 study; IL-6 blockade: Tocilizumab in 1 study; Steroids in 1 study; Control groups: Low-dosage CQ (450 mg, 3 days + 150 mg), and placebo (1 tablet, 12/h, daily on day 0, 3) in 1 study; Standard care in 13 studies.		Effect of medications were not reported.	
Rodrigo *et al.*[26]	To summarize evidence from human clinical studies for using HCQ or CQ as antivirals for any viral infection.	Intervention groups: Antimalarial: HCQ (400 mg–600 mg, daily, 5–10 days) in 3 studies; HCQ (200 mg, daily, 3 days, then 800 mg, daily, 14–21 days) in 1 study; CQ (600–1200 mg, daily 10 days) in 2 studies; Control groups: Standard/supportive treatment in 4 studies, Lopinavir/Ritonavir (400/100 mg, 12/h, 10 days) in 1 study, CQ (900 mg, day 1 and 450 mg, daily, 4 days) in 1 study.	NR.	In 2 studies no statistically significant difference between HCQ and Standard treatment: in the clearance of viremia by day 7 and 28, symptom resolution by day 28, fever clearance time, total duration of hospitalization; In 1 study rate of clearance of viremia by day 6 of illness: 70% HCQ *versus* 12.5% placebo In 1 study faster fever recovery and cough relief in HCQ group. CQ: No statistically significant difference in viraemia clearance; Faster radiological resolution and reduced hospital stay than Lopinavir/Ritonavir; Significantly higher mortality in high dose (1200 mg *versus* 900 mg).	6

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Jorgensen *et al.*[27]	To critically review the data on Remdesivir with an emphasis on biochemistry, pharmacology, pharmacokinetics and in vitro activity against coronaviruses, and clinical experience in COVID-19 clinical trials.	Antivirals: Remdesivir (200 mg, on day 1, then 100 mg, on days 2–5) in 6 studies.	NR.	67.9% improvement in oxygen support category at median 18 days after Remdesivir initiation; 13.2% died in hospital after median 15 days; 5/6 symptoms resolved; 4/6 discharged; 2 case report extubated and stable in hospital.	4
Ang *et al.*[28]	To evaluate the effectiveness and adverse events of herbal medicines for the treatment of COVID-19.	Intervention groups: Herbal medicines: Lianhua Qingke granules (1 packet, 2–3 times daily, 7–14 days) in 2 studies, Shufeng Jiedu capsule (4 capsules, 3 times daily, 2 weeks) in 1 study, Jinhua Qinggan granules (2 packets, 3 times daily, 5 days) in 1 study, Toujie Quwen granules (1 packet per time, 2 times daily, 10–15 days) in 2 studies, Herbal decoction (2 times daily, 7 days) in 1 study.	NR.	Herbal medicine + Western medicine *versus* Western medicine: RR = 1.23 total effective rate, RR = 1.42 discharge rate, RR = 1.35, Symptom disappearance rate: RR = 1.45 cough, RR = 1.73 sputum production, RR = 1.51 fever, Mean difference = −6.32 C-reactive protein level, Mean difference = 3.83 lymphocyte percentage, Mean difference = 0.41 white blood cell counts.	13
		Intervention and control groups: Antivirals: Lopinavir/Ritonavir (200 mg, 12/h, 14 days) in 3 studies, 5 Arbidol (200–500 mg, 8/h) in 3 studies, Ribavirin (dosage not reported, 12/h) in 1 study, Alpha interferon (dosage not reported,12/h) in 2 studies; Secretolytics: Ambroxol (30 mg, 8/h, 3 days) in 3 studies; Antimalarial: CQ (500 mg) in 1 study; Antibiotics: Moxifloxacin in 2 studies.		Effect of medications were not reported.	
Schunemann *et al.*[29]	To review multiple streams of evidence on the benefits and harms of ventilation techniques for coronavirus infections, including COVID-19.	NR.	Oxygen therapy, NIV, IMV, and HFNC	HR = 1.61 mortality with NIV *versus* IMV; Higher death rate in patients receiving helmet CPAP or other NIV compared with IMV; A large reduction in mortality with NIV compared with conventional oxygen therapy; Indirect and low-certainty evidence suggests that use of NIV, similar to IMV, probably reduces mortality.	8
Antwi-Amoabeng *et al.*[30]	To summarize the baseline characteristics of COVID-19 patients who received tocilizumab.	IL-6 blockade: Tocilizumab in 100% of patients.	NR.	20.7% Death; Higher IL-6 level after the initiation of Tocilizumab (376.6 pg/mL) *versus* baseline of (71.1 pg/mL); C-reactive protein level was significantly lower after the initiation of Tocilizumab.	4
		Corticosteroids in 34.5% of patients; Antimalarial: HCQ in 24.1% of patients; Antivirals: Lopinavir/Ritonavir in 20.7% of patients, Ribavarin in 3.4% of patients, Arbidol in 3.4% of patients.		Effect of medications were not reported.	

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Tahvildari *et al.*[31]	To characterize the clinical, diagnostic, and treatment characteristics of patients presenting with COVID-19.	Antivirals: Lopinavir in 9% of patients, Arbidol in 6% of patients, Oseltamivir in 5% of patients, Veletonavir in 1% of patients, Remdesivir in 1% of patients, Ribavirin in 1% of patients, Ritonavir in 1% of patients, Gancyclovir in 1% of patients, Interferon alpha-2b in 2% of patients; Antibiotics: Moxifloxacin in 5% of patients, Vancomycin in 1% of patients, Cefepime in 1% of patients, Meropenem in 2% of patients, Piperacillin tazobactam in 2% of patients, Cefoselis in 1% of patients, Linezolid in 1% of patients, Levofloxacin in 1% of patients; Corticosteroids: Methylprednisolone in 6% of patients; Immunoglobulin in 4% of patients; Herbal Medicine in 3% of patients.	Non-invasive ventilation in 10% of patients.	2% death, 32% hospitalization, 12% discharged, 2% ARDS. A wide range of therapeutic modalities was tried across studies, with antiviral treatments being the most used; There is currently not a well-established gold standard therapy for the treatment of diagnosed COVID-19.	5
Valk *et al.*[32]	To assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19.		Convalescent plasma therapy or Hyper-immune immunoglobulin transfusion in 8 studies.	Convalescent plasma or Hyper-immune immunoglobulin transfusion: 15 participants discharged, 6 still hospitalized, 11 unclear; **In all studies:** Improvement of clinical symptoms; 4–35 days, time to discharge from hospital after convalescent plasma therapy; **In 6 studies:** A decrease in ICU duration or required mechanical ventilation. In 2 critically ill patients requiring intubation and mechanical ventilation, both received a tracheotomy and one extubated by day 18; 40% Decreasing respiratory support within 3 days.	11
		Antivirals, Antifungals or Antibiotics, Corticosteroids, Antimalarials: HCQ.	Respiratory support in 87.5% of patients: Mechanical ventilation in 5 studies, HFNC in 2 studies, ECMO in 2 studies, Nasal cannula in 2 studies.	Effect of medications and interventions were not reported.	
Zhang *et al.*[33]	To investigate the predictive value of laboratory investigations for severe disease and adverse outcomes, and evaluate the efficacy of antivirals and corticosteroids for COVID-19.	**Corticosteroids** in 57.3% of patients.	NR.	**Corticosteroids:** 7.2% mortality rate; 22.7% ARSD rate.	4

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
		Antivirals: Lopinavir/Ritonavir in 15.1% of patients, Oseltamivir, Ganciclovir, Ribavirin, Arbidol.		**Lopinavir-Ritonavir:** 6.2% mortality rate, 15.6% ARDS **Other/non-specified antivirals:** 5.5% mortality rate, 24.2% ARDS.	
		Antibiotics: Moxifloxacin, Ceftriaxone, Azithromycin.		Effect of medications were not reported.	
Liu *et al.*[34]	To assess the efficacy and safety of Integrated Traditional Chinese and Western Medicine to COVID-19.	Intervention groups: Traditional Chinese Medicine in 11 study: Diammonium glycyrrhizinate enteric-coated capsules (150 mg, 8/h) in 1 study, Qingfeitouxie fuzhengfang (150 ml, 12/h) in 1 study, Shufeng Jiedu Capsule (2.08 g,tid) in 2 studies, Lianhua Qingwen granules (6 g, 8/h) in 2 studies, Reyanning mixture (10–20 ml,12/h) in 1 study, Tongjiequwen granule (150 ml, 12/h) in 1 study, Jinhua Qinggan granules (10 g, 8/h) in 1 study.	NR.	Traditional Chinese Medicine versus Western Medicine alone: RR = 1.23 overall response rate; RR = 1.60 cure rate; RR = 0.35 severity of illness; WMD = −1.991 hospital stay; RR = 1.32 Fever disappearance rate; Better improve the symptoms disappearance rate and reduced the symptoms disappearance time; Significantly increased disappearance rate of fever, cough, expectoration, fatigue, chest tightness and anorexia in patients and reduced patients' fever, and fatigue time.	12
		Intervention and control groups: Western Medicine in 11 study: Lopinavir (100–500 mg, 12/h) in 2 studies, Interferon-α (5 mU, 12/h) in 2 studies, Ribavirin (500 mg, 12/h) in 2 studies, Arbidol (200 mg, 8/h) in 3 studies.		Effect of medications were not reported.	
Singh *et al.*[35]	To understand the pharmacology and clinical effects of Remdesivir in patients with COVID-19.	Intervention groups: Remdesivir (200 mg then 100 mg, OD, 2–10 days) in 7 studies; Control groups: Placebo or standard care.	NR.	Initial compassionate use of Remdesivir has shown a fairly good result (clinical improvement); Very first RCT conducted in Wuhan, did not find any significant benefit compared to the control; The preliminary result of another similar multi-country trial has shown a significant faster time to recovery (%31) but without any difference in mortality.	2
Gbinigie and Frie[10]	To review the evidence for the effectiveness and safety of azithromycin in treating COVID-19.	Antimalarial & Antibiotics: HCQ + Azithromycin in 3 studies.	NR.	6 patients who received Azithromycin combined with HCQ were significantly more likely to test negative for SARS-CoV- 2 on Days 3, 4, 5, and 6. On Day 6, 57.1% of the HCQ group, compared to 100% of the combined HCQ and azithromycin group, were virologically cured. *In vivo*: Azithromycin + HCQ inhibited viral replication.	6

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Singh *et al.*[36]	To study the efficacy of HCQ compared to the control in COVID-19 subjects.	Antimalarial & Antibiotics: HCQ: 2 (400 mg, daily, 5 days), 2 (600 mg, daily, 7–10 days), 1 (1200 mg, daily, 3 days, followed by 800 mg, daily, 2 weeks (mild/moderate cases) or 3 weeks (severe cases)), 1 (800 mg, daily, 1–2 days, followed by 200–400 mg, OD, 3–4 days); HCQ + Azithromycin: 3 (600 mg, daily, 10 days + 500 mg on day 1 and 250 mg, 2–5 days).	NR.	RR = 0.744 RT-PCR negativity, RR = 2.17 death.	5
Li *et al.*[37]	To critically assess the potential anti-coronavirus effect of Remdesivir on COVID-19 and other coronaviruses.	Antivirals: Remdesivir in 10 studies.	NR.	In experimental study: Remdesivir therapeutically inhibited SARS-CoV-2 replication, while no prophylactic effect was found. Remdesivir could inhibit SARS-CoV-2 infection in human liver cancer Huh-7 cells; In human studies: Recovery of a patient; Clinical improvement in 68% of the 53 recruited patients who had severe COVID-19.	0
Li *et al.*[38]	To determine safety and efficacy of corticosteroids in SARS-CoV-2, SARS-CoV, and MERS-CoV infections.	Corticosteroids in 4 studies.	NR.	RR = 1.07 mortality Corticosteroid use in subjects with SARS-CoV-2, SARS-CoV, and MERS-CoV infections delayed virus clearing and did not convincingly improve survival, reduce hospitalization duration or ICU admission rate and/or use of mechanical ventilation.	6
Xu *et al.*[39]	To summarize the clinical evidence of investigational adjunctive treatments used in COVID-19 patients.	Antimalarial: CQ or HCQ in 7 studies.		Limited benefit from CQ/HCQ in general.	3
		Antivirals: Lopinavir/Ritonavir in 5 studies, Arbidol in 2 studies, Remdesivir in 4 studies.		The equivocal benefit of Lopinavir/Ritonavir on clinical improvement and viral clearance; Higher discharge and survive in Arbidol groups; Possibility of decreasing the viral load of COVID-19 and delaying the progression of lung lesions with combination of Lopinavir/Ritonavir and Arbidol; No conclusions can be drawn about efficacy or safety of Remdesivir.	
		Corticosteroids in 2 studies.		No routine use of corticosteroids in critically ill patients; No survival advantage; Associated with longer hospital stay	
		Anticoagulants: Heparin in 2 studies.		Heparin may improve 28-day mortality in severe COVID-19 patients meeting sepsis-induced coagulopathy criteria or markedly elevated Ddimer	
		IL-6 blockade: Tocilizumab in 2 studies.		Tocilizumab could improve clinical status in severe to critically ill patients	

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
			Convalescent plasma in 3 studies; Mesenchymal stem cell in 2 studies.	Convalescent plasma could improve clinical status in critically ill patients with ARDS; Symptoms, pulmonary function biochemistry apparently may be improved after mesenchymal stem cell transplantation.	
Alijotas-Reig *et al.*[40]	To study immunomodulatory therapy for the management of severe COVID-19.	Immunoglobulins: IVIG/Hyperimmune immunoglobulin; IL-6 blockade: Tocilizumab, Sarilumab; IL-1 blockade: Anakinra; IL-2 inhibition: Cyclosporin A, Tacrolimus; Janus kinase pathway inhibition: Ruxolitinib; Anticoagulants: Heparin, Fondaparinux; Glucocorticoids; ACE agonists; Statins; Antimalarials: CQ, HCQ.	Convalescent plasma therapy.	In severe and life-threating subsets a high intensity anti-inflammatory and immunomodulatory therapy could be a therapeutic option. However, data on the effectiveness of different immunomodulating drugs are scarce.	3
Rawson *et al.*[41]	To explore the current literature surrounding bacterial/fungal co- infection in patients with coronavirus infection.	Antibacterial in 72% of patients: Quinolone in 3 studies, Cephalosporins in 3 studies, Carbapenems in 2 studies, Linezolid in 2 studies, Moxifloxacin in 3 studies; Antifungals in 4 studies.	NR.	Despite low rates of bacterial/fungal co-infection reported in patients with COVID-19, high rates of antimicrobial prescribing are reported.	4
Chowdhury *et al.*[42]	To review the literature regarding the clinical use of CQ and HCQ as treatment in COVID-19 patients.	Intervention groups: Antimalarial: HCQ (600 mg, 1–10 days) + Azithromycin (500 mg first day, 250 mg 2–5 days) in 2 studies; HCQ (400 mg D,1–5 days) in 2 studies; HCQ (1200 mg 1–3 days, then 800 mg, 4–21 days) in 1 study; CQ (500 mg, 12/h, 1–10 days) in 1 study; CQ (500 mg, 12/h, 1–10 days) + Lopinavir/Ritonavir (400 mg/100 mg, 12/h, 1–10 days) in 1 study; Control groups: Standard care in 4 studies; Lopinavir/ritonavir (400 mg/100 mg, 1–10 days) in 1 study.	NR.	Optimized the time to clinical recovery and radiologic improvement *versus* supportive care; HR = 8.83 alleviation of clinical symptoms; Controlling inflammation and preventing disease progression (6.98 *versus* 2.72 in standard of care). In one study: No difference in clinical improvement, imaging findings, and duration of disease course *versus* supportive care.	5
Zhang *et al.*[43]	To explore the clinical effectiveness and safety of IVIG in the treatment of children with severe COVID-19.	Immunoglobulins in 2 studies: IVIG (25 g, daily, 5 days) in 50% of patients.		In 1 case series: The risk of death was not associated with the use of IVIG in the patients with ARDS; In 1 case report: A high dose IVIG administered at the appropriate point could successfully block the progression of disease cascade, and finally improve the outcome of COVID-19.	8
		In 2 studies: Antibiotics; Glucocorticoids; Interferons; Antivirals.	Oxygen therapy in 1 study.	Effects of the medications and interventions were not reported.	

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Rajendran *et al.*[44]	To evaluate the effectiveness of convalescent plasma transfusion therapy in COVID-19 patients.		Convalescent plasma in 5 studies.	55.6% discharge from hospital; may reduce mortality in critically ill patients, reducing viral load and increasing level of neutralizing antibody over time in all studies; improvements of clinical symptoms.	4
		Antivirals in 100% of patients: Arbidol, Lopinavir/Ritonavir, Interferon-Alpha-2b, Oseltamivir, Ribavirin, Peramivir; Antibacterial/Antifungal in 37% of patients: Imipenem, Vancomycin, Levofloxacin; Antimalarial: HCQ in 1 study.	Mechanical ventilation in 51.9% of patients, ECMO in 25.9% of patients, Nasal cannula in 11.1% of patients, HFNC in 11.1% of patients.	Effects of the medications and interventions were not reported.	
Lu *et al.*[45]	To summarize the evidence on the effectiveness and safety of glucocorticoid therapy for patients with COVID-19.	Corticosteroids in 5 studies: Methylprednisolone in 4 studies.	NR.	In patients receiving versus not receiving glucocorticoid therapy: RR = 2.0 risk of death; −3.23 duration of fever; −1.0 lung inflammation absorption time; 2.43 Length of stay.	10
Shi *et al.*[46]	To assess the effectiveness and safety of antivirals for COVID-19 in children.	Antivirals: Lopinavir/Ritonavir, Arbidol, Interferon, Ribavirin, Oseltamivir, Combination of Ribavirin/Interferon, Favipiravir.	Oxygen therapy: 69% of patients receiving Arbidol *versus* 86% of patients not receiving Arbidol; Non-invasive mechanical ventilation: 22.5% of patients receiving Favipiravir *versus* 18.1% of patients receiving Arbidol.	For adults with COVID-19: Lopinavir/Ritonavir *versus* no antivirals: RR = 0.77 mortality; RR = 0.98 negative PCR result; RR = 1.02 radiographic abnormalities remission; Arbidol *versus* no antivirals: RR = 1.27 negative PCR result; RR = 1.23 radiographic abnormalities remission; RR = 1.02 incidence of clinical symptoms improvement; RR = 0.8 incidence of receiving oxygen therapy; Favipiravir *versus* Arbidol: RR = 1.18 rate of clinical recovery of day 7; RR = 1.03 respiratory failure. No direct evidence for children with COVID-19 was found and the effectiveness and safety of Antivirals for children with COVID-19 is uncertain.	9
		Antimalarial: HCQ.		HCQ *versus* none: RR = 0.93 negative PCR result; RR = 1.47 radiographic abnormalities remission.	
Wang *et al.*[47]	To evaluate the efficacy and safety of antibiotic agents in children with COVID-19.	Antibiotic in 19.4–100% of patients: Meropenem in 4 studies, Linezolid in 2 studies, Quinolones in 2 study, Cefoperazone in 3 studies, Sulbactam in 2 studies, Carbapenems in 2 studies, Tigecycline in 1 study, Moxifloxacin in 14 studies, Levofloxacin in 4 studies, Ceftriaxone in 1 study, Azithromycin in 5 studies, Imipenem in 2 studies, Doxycycline in 1 study, Cefepime in 1 study, Cepalosporins in 3 study, Piperacillin sulbactam in 1 study, Cefdinir in 1 study.	NR.	There was no evidence to support the use of antibiotic agents for children with COVID-19 in the absence of bacterial coinfection.	8

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Alzghari and Acuña[48]	To evaluate outcomes associated with tocilizumab treatment in patients with COVID-19.	IL-6 blockade: Tocilizumab (80–600 mg) in 6 studies.	NR.	Preliminary investigations are showing benefits with Tocilizumab for COVID-19; It is a potential supportive treatment for COVID-19. Patients remained clinically stable; 7.5% death.	3
		Corticosteroids: Methylprednisolone in 2 studies; Antivirals: Lopinavir in 1 study.		Effects of the medications and interventions were not reported.	
Zhong *et al.*[49]	To evaluate the efficacy and safety of current therapies for SARS, MERS, and COVID-19.	Antivirals: 4 Lopinavir/Ritonavir (400 mg/100 mg, 12/h, 5–21 days) in 4 studies, Arbidol (200 mg, 8/h, 5–21 days) in 3 studies, Interferon-α spray in 1 study, Interferon- α2b spray in 1 study.	NR.	On COVID-19, SARS & MERS: Lopinavir/Ritonavir: RR = 0.77 mortality, RR = 0.97 virological clearance, RR = 1.52 clinical improvement, RR = 0.46 ARDS; Arbidol: RR = 1.07 virological clearance; Arbidol & Lopinavir/Ritonavir: RR = 2.34 radiological improvement.	8
		Antimalarial: HCQ (400–800 mg, daily, 5–21 days) in 3 studies; HCQ (600 mg, daily, 10 days) ± Azithromycin (day 1: 500 mg; day 2–5: 250 mg daily) in 1 study.		HCQ: RR = 1.14 virological clearance, RR = 1.47 radiological improvement.	
Pascarella *et al.*[50]	To summarize the currently available data on the clinical features and treatment options for COVID-19.	Antivirals: Remdesivir, Lopinavir/Ritonavir.		The efficacy of specific Antivirals to treat COVID-19 has been shown in vitro & animal models; Lopinavir/Ritonavir: Reducing the viral load, no clinical benefit.	2
		Antimalarials: CQ (500 mg, 12/h)/HCQ (200 mg, 12/h).		CQ/HCQ: Efficacy in COVID-19 patients; may act synergistically with macrolides (e.g. azithromycin) for enhanced antiviral effect' Tracheal intubation should not be delayed in patients with a low oxygenation index, worsening of respiratory distress symptoms or multi-organ failure; ECMO could be a viable treatment option for patients with severe ARDS and not responding to treatment protocols.	
			Oxygen therapy, ECMO, Intubation.	Effect of other medications and interventions were not reported.	

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Veronese *et al.*[51]	To investigate the effectiveness of glucocorticoid therapy in patients with COVID-19.	Glucocorticoids in 31.2% of patients: Methylprednisolone in 2 studies.	NR.	Methylprednisolone did not show significant benefits; With a greater risk of ICU admission: 72.2% *versus* 35.3%; HR = 0.35 risk of death in subjects having ARDS for COVID-19; Longer duration of viral RNA detection: 15 *versus* 8.0 days.	4
Sarma *et al.*[52]	To evaluate the safety and efficacy of HCQ in the treatment of COVID-19 patients.	Intervention group: Antimalarials: 2 HCQ (400–600 mg, daily, 1–5 days) in 2 studies; HCQ (200–600 mg, 8/h, 10 days)/Azithromycin (First day 500 mg, 250 mg day 2–5) in 5 studies; Control group: Standard care in 3 studies.	NR.	HCQ: Less number of radiological progressions of lung disease (OR = 0.31), no difference in virological cure (OR = 2.37), death or clinical worsening of disease (OR = 1.37), and safety (OR = 2.19); 5 studies reported either the safety or efficacy of HCQ + Azithromycin.	10
Ford *et al.*[53]	To summarize the clinical outcomes of using antiretroviral drugs for the prevention and treatment of coronaviruses.	Intervention groups: Antivirals: 14 Lopinavir (200–400 mg, 12/h, 1–21 days)/Ritonavir (100–500 mg, 12/h, 1–21 days) in 14 studies, Arbidol in 1 study, Peramivir in 1 study, Oseltamivir in 1 study, Ganciclovir in 1 study, Interferon alfa-2b in 4 studies.		3.7% death in Lopinavir/Ritonavir group; It is uncertain whether in Lopinavir/Ritonavir and other antiretrovirals improve clinical outcomes or prevent infection among patients at high risk of acquiring COVID-19.	4
		Antibiotics in 3 studies; Immunoglobulins: Gama-globulin in 1 study; Corticosteroids in 3 studies: Methylprednisolone in 1 study; Traditional Chinese medicine in 2 studies; Control group: Supportive care alone in 1 study; Antivirals: Arbidol in 2 studies, Favipiravir in 1 study, No antivirals in 2 studies.	Oxygen supplementation in 4 studies.	Effects of the medications and interventions were not reported.	
Fu *et al.*[7]	To provide a comprehensive characterization of COVID-19 to better inform control and treatment efforts.	Antivirals in 90% of patients; Antibiotics in 71.5% of patients; Corticosteroids in 30.1% of patients; Immunoglobulin in 28.1% of patients; 17 studies used guidelines on COVID-19 Treatment and Prevention issued by the National Health Commission.	Oxygen therapy in 54.8% of patients, IMV in 22.2% of patients, Mechanical ventilation in 13.8% of patients, NIV in 8.5% of patients, CRRT in 3.3% of patients, ECMO in 1.6% of patients.	Death in 3.6% of patients; severe COVID-19 in 25.6% of patients; ARDS in 15.7% of patients, shock in 4.3% of patients; renal insufficiency in 2.7% of patients, cardiac failure in 6.5% of patients.	10

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Yang *et al.*[54]	To evaluate the influence of corticosteroids on patients with coronavirus infection.	Corticosteroids in 39.7% of patients (32 patients in ICU, 39 patients Non-ICU).		Patients with severe conditions were more likely to require corticosteroids therapy (RR = 2.36).	10
		Antivirals in 2 studies; Antibiotics in 2 studies.	ECMO in 1 study, CRRT in 1 study.	Effects of other medications and interventions were not reported.	
Gbinigie and Frie[55]	To establish the current evidence for the effectiveness of CQ and HCQ in treating COVID-19.	Antimalarial: HCQ (400 mg/day for 5 days and 600 mg/day for 6 days) (with or without Azithromycin) in 2 studies; CQ (dosage not reported) in 1 study.	NR	CQ *versus* control group: Inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course; Dosage 600 mg/daily: A higher frequency of negative viral load on day-6; Dosage 400 mg/daily: No difference between HCQ and standard treatment group on day-7. Some in vitro data supporting the ability of CQ and HCQ to inhibit SARS-CoV-2 activity.	3
Yousefifard *et al.*[56]	To identify potential treatment options for COVID-19.	Antivirals in 65.9% of patients: Lopinavir/Ritonavir in 9 studies, Oseltamivir in 7 studies, Arbidol in 5 studies, Gancivlovire in 1 study, 1 Ribavirin in 1 study.		Clinical improvement and mortality rate are similar in Lopinavir–Ritonavir treated and standard care groups; Administration of oseltamivir did not decrease ICU admission and need for ventilator or death; Antivirals have no effects on the mortality rate, outcome or the duration of hospital stay.	5
		All of the studies used Antibiotics, Immunoglobulins, Interferon, Corticosteroids (Methylprednisolone), Antiparasitics and Antifungals in addition to Antivirals.	Invasive or Non-invasive ventilation & ECMO in 1 study.	Effects of the medications and interventions were not reported.	
Tobaiqy *et al.*[57]	To report any evidence of therapeutics used for the management of COVID-19 patients in clinical practice.	Corticosteroids in 25 studies: Corticosteroid in 21 studies, Methylprednisolone in 3 studies, Dexamethasone in 1 study.		Corticosteroids should not be used routinely in patients with COVID-19 for treatment of viral pneumonia, ARDS or septic shock.	5
		Antivirals: Lopinavir in 3 studies, 18 Lopinavir/Ritonavir in 18 studies, Oseltamivir in 16 studies, Interferon alfa in 10 studies, Arbidol in 8 studies, Ganciclovir in 4 studies.		Absence of conclusive scientific evidence about Antivirals; No benefit of Lopinavir/Ritonavir treatment compared with standard care was observed.	
		Antimalarial: HCQ (200 mg, 8/h, 10 days) + Azithromycin in 1 study.		More virologically clearance in patients treated with HCQ (57.1%) than control group (12.5%).	

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
			Convalescent plasma therapy in 1 study and 6 patients.	Inadequate information about the efficacy of convalescent plasma.	
		Antibiotics: Moxifloxacin in 4 studies, Tigecycline in 1 study; Traditional Chinese medicine in 2 studies; Antifungals in 8 studies; Immunoglobulin in 7 studies.		Effects of other medications and interventions were not reported.	
Insiat Islam[58]	To review the published literature on the effectiveness of suggested and applied treatment to control COVID-19.	Clinical Studies: Glucocorticoids + IL-6 blockade + JAK inhibitors in 1 study; Antimalarials: CQ/HCQ in 1 study, Azithromycin plus HCQ in 1 study; Antivirals: Favipiravir ($n=35$) *versus* Lopinavir or Ritonavir ($n=45$), + Interferon alfa in all in 1 study; Lopinavir/Ritonavir in 3 studies; Arbidol in 1 study; Remdesivir in 1 study; Traditional Chinese Medicine in 3 studies: Qingfei paidu decoction in 1 study; Shufeng Jiedu in 1 study.	NR.	Clinical Studies: Glucocorticoids + IL-6 antagonist + JAK inhibitors + CQ/HCQ: Improved clinical outcome; Azithromycin plus HCQ: An improved efficacy to eradicate the virus; Favipiravir *versus* Lopinavir/Ritonavir: Shorter COVID-19 clearance and improved chest imaging; Lopinavir/Ritonavir: Reduced COVID-19 load, improved clinical symptoms; Lopinavir/Ritonavir + Arbidol + Shufeng Jiedu: Effective treatment; Remdesivir: Patient recovered; Traditional Chinese Medicine: Improved clinical symptoms and recovery.	2
		In vitro/Laboratory studies: 1 Lianhuaqingwen (Laboratory test using African green monkey kidney epithelial (VeroE6) cells and the human hepatocellular carcinoma (Huh-7) cells) in 1 study; Antimalarial: HCQ and CQ in 3 studies, Mefloquine in 1 study; JAK2 Inhibitor: Fedratinib in 1 study, Fedratinib in 1 study; JAK inhibitor: Baricitinib in 1 study; JAK 1 and 2 Inhibitor: Ruxolitinib in 1 study; Anti-inflammatory: Cepharanthine in 1 study; Anti-parasitic: Selamectin in 1 study; CRISPR/Cas13d strategy in 1 study; Antivirals: Remdesivir in 2 studies, Ribavirin in 1 study, Penciclovir + Nitazoxanide + Nafamostat + Favipiravir in 1 study.		*In vitro*/Laboratory test: All examined treatments, although potentiality effective against COVID-19, need either appropriate drug development or clinical trial to be suitable for clinical use.	
Guida[18]	To assess the effectiveness and safety of HCQ and CQ on the treatment of COVID-19.	Intervention group: Antimalarial & Antibiotic: HCQ (600 mg/daily), with or without Azithromycin in 20 patients; Control group: Standard care in 16 patients.	NR.	Viral load clearance in day 6: Intervention group: 70% Control group: 12.5%.	5

(Continued)

Table 2. (Continued)

Author	Objective(s)	Pharmaceutical treatments	Non-pharmaceutical treatments	Main findings	Quality assessment (AMSTAR-2)
Pacheco and Riera[9]	To identify, systematically assess and summarize the evidence on the efficacy and safety of the use of HCQ and CQ for COVID-19.	Antimalarial and Antibiotic: HCQ (400 mg, daily, 5 days) and (600 mg, daily, 6 days) with or without Azithromycin in 2 studies.	NR.	Dosage 600 mg/daily: A higher frequency of negative viral load on day-6; Dosage 400 mg/daily: No difference between HCQ and standard treatment group on day-7; There is very low evidence of certainty and its routine use for this situation should not be recommended until the results of ongoing studies could provide a proper assessment of their effects.	7
Borges do Nascimento *et al.*[19]	To review clinical, laboratory, epidemiological, and chest imaging data related to SARS-CoV-2.	43.4% Antivirals: 66.8% Oseltamivir, 6.6% Arbidol, 9.3% Ganciclovir, 1.3% Ritonavir, 1% Interferon-alpha; 44.6% Antibiotics: Most did not mention exact compound administered antibiotics, Different antibiotics in single patients (Vancomycin, Azithromycin, Meropenem, Cefaclor, Cefepime, Tazobactam), 8.7% Linezolid, 0.4% Moxifloxacin; 9.8% Corticosteroids; 12.4% Immunoglobulin; 2.5% Antifungal therapy; Fluid therapy; Vitamin K1.	38.9% Nasal cannula oxygen therapy, 7.1% NIV, 28.7% Mechanical ventilation, 0.9% ECMO, CRRT, Blood transfusions.	0.3% all-cause mortality, 8.3% ICU admission; It was not possible to perform subgroup analysis to check the effectiveness of antivirals, antibiotics and other medications on the prognosis. Studies were descriptive in nature and lacked suitable control groups for comparison of clinical efficacy.	9
Singh *et al.*[59]	To review the efficacy of CQ and HCQ in the treatment of patients with COVID-19.	Antimalarials in 2 studies: CQ in 1 study (dosage not reported); Intervention group: HCQ (600 mg/daily), with or without Azithromycin in 20 patients; Control groups: Standard care in 16 patients.	NR.	CQ: Inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course; HCQ with or without Azithromycin: Viral load clearance in day 6: 70% Intervention group, 12.5% Control group; Two small human studies have shown significant improvement in some parameters in patients with COVID-19.	2

Studies are listed in the chronological order of their publication dates.

ACE, Angiotensin-Converting Enzyme; ARDS, Acute Respiratory Distress Syndrome; CPAP, Continuous Positive Airway Pressure; CQ, Chloroquine; CRRT, Continuous Renal Replacement Therapy; ECMO, Extracorporeal Membrane Oxygenation; HCQ, Hydroxychloroquine; HFNC, High Flow Nasal Cannula; HR, Hazard Ratio; ICU, Intensive Care Unit; IL, Interleukin; JAK2, Janus Kinase2; IMV, Invasive Mechanical Ventilation; IVIG, Intravenous Immunoglobulin; MD; Mean Difference, MERS-CoV, Middle East Respiratory Syndrome Coronavirus; NIV, Non-Invasive Ventilation; NR, Not Reported; OR, Odds Ratio; PCR, Polymerase Chain Reaction; RCT, Randomiized Controlledd Trials;g RD, Risk Difference; RNA, Ribonucleic Acid; RR, Risk Ratio; RT-PCR, Real-time Reverse Transcription Polymerase Chain Reaction; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; WMD, Weighted Mean Difference.

blood cell count, ARDS, hospitalization, fever reduction, cardiac failure) that made comparisons across the studies and drawing conclusions challenging.

Antiviral agents. Most reviews reported antivirals as a common treatment for patients. The most commonly used antiviral treatment modalities included HIV protease inhibitor (e.g. lopinavir[20,23,25,28,30–34,39,42,44,46,48,53,56,58,60] and ritonavir),[19,20,23,25,28,30,31,33,39,42,44,46,49,50,53,56,58,60] Influenza treatments (e.g. arbidol hydrochloride,[20,23,28,30,31,33,34,44,46,49,53,56,58,60] and favipiravir),[20,23,46,53,58] neuraminidase inhibitors (e.g. oseltamivir),[19,23,31,33,44,46,53,56,60] nucleoside analogues (e.g. ribavirin),[23,28,31,33,34,44,46,56,58] nucleotide analogues (e.g. remdesivir[27,31,35,37,39,50,58] and ganciclovir),[19,23,33,53,60] and biological response modifier-cytokines (e.g. interferon alfa).[28,31,32,34,43,44,46,49,53,56,58,60] Study findings on the effectiveness of antiviral drugs in the treatment of COVID-19 were equivocal and varied greatly across different reviews. For example, the systematic review of case reports by Insiat Islam[58] showed that antiviral agents such as lopinavir/ritonavir and arbidol reduced SARS-CoV-2 viral load, and improved clinical symptoms. That study also reported that patients receiving favipiravir had a shorter SARS-CoV-2 clearance and improved chest imaging as compared with the lopinavir/ritonavir group.[58] However, in another review by Ford *et al.*, lopinavir/ritonavir use was associated with a non-statistically significant shorter time to clinical improvement and lower mortality compared to the control group.[53] Moreover, Liu *et al.*,[20] Xu *et al.*,[39] and Chowdhury *et al.*[42] reported no meaningful benefit for lopinavir/ritonavir. In addition, Shi *et al.* reported the safety and effectiveness of antiviral agents for children with COVID-19 as unclear.[46] Overall, four reviews did not specify what antiviral agents were used in the treatment of COVID-19 patients[7,43,48,54] and several studies did not report specific findings for antiviral agents used among the patients.

Antibiotic agents. Antibiotics to treat patients with COVID-19 were reported in 13 reviews.[7,19,23,25,28,31–33,43,47,54,56,60] Macrolides (e.g. azithromycin),[9,10,18,19,22,23,25,33,36,42,47,49,52,55,58,59] fluoroquinolone (e.g. moxifloxacin,[19,23,28,31,33,41,47,60] levofloxacin),[31,44,47] glycopeptides (e.g. tigecycline,[47,57] vancomycin),[19,31,44] cephalosporins (e.g. cefoperazone,[47] cefoselis,[31] cefdinir,[47] and cefepime),[19,31,47] beta-lactams (e.g. imipenem sulbactam,[47] meropenem,[19,31,47] piperacillin tazobactam),[31] and oxazolidinones (e.g. linezolid)[47] were the main classes of antibiotics used to treat COVID-19. Antibiotics were mainly used for addressing bacterial co-infections along with antivirals or antimalarial agents; however, their effectiveness was not directly investigated. Wang *et al.*, who specifically evaluated the efficacy and safety of antibiotic agents in children with COVID-19, concluded that there was no direct evidence to support their efficacy.[47] Six reviews did not specify the antibiotic agents used in the treatment of infected patients.[7,32,43,53,54,56]

Chloroquine and hydroxychloroquine. A total of 23 systematic reviews evaluated the efficacy of chloroquine and hydroxychloroquine on treating COVID-19 patients,[9,10,18,20,22,25,26,28,30,32,36,39,40,42,44,46,49,50,52,55,57–59] most of which concluded that these drugs were inefficient and unhelpful for COVID-19 patients. However, some in vitro data supported the ability of chloroquine and hydroxychloroquine in inhibiting the activity of SARS-CoV-2 and reported them as beneficial in both prophylactic and therapeutic interventions.[10,58] Moreover, several systematic reviews[9,18,20,22,25,26,36,42,49,52] that reported in favor of using this class of drugs, cited an open-label non-randomized controlled trial by Gautret *et al.*,[61] and concluded that hydroxychloroquine treatment (600 mg/daily) was associated with SARS-CoV-2 viral load reduction/disappearance, and its effects were reinforced by azithromycin. Other studies also reported that using a 400 mg/daily dosage led to no clinical difference between hydroxychloroquine and the standard treatment group on day 7.[9,10,20,22,42,52] Conversely, very few studies reported some clinically meaningful outcomes associated with the use of these drugs (e.g. a smaller number of cases showing radiological progression of lung disease,[25,49,52] faster fever recovery and cough relief,[26] and virological clearance).[57]

Corticosteroids and glucocorticoids. Corticosteroids including methylprednisolone and dexamethasone were another common drug category used to treat COVID-19, mainly in addition to other classes of drugs such as antivirals and antibiotics.[7,19,23,24,30–33,38–40,43,45,48,51,53,54,56–58] The evidence, however, was inconsistent about administering corticosteroids for COVID-19 patients. For example, Tobaiqy *et al.*[57] and Zhang *et al.*[33] recommended against using corticosteroids among COVID-19 patients due to increased risks of mortality. Lu *et al.* also reported higher rates of

death (Relative risk [RR] = 2.0) among COVID-19 patients who were receiving corticosteroids in comparison with those who did not.[45] Conversely, Yang *et al.*[54] and Alijotas-Reig *et al.*[40] showed that patients with severe conditions were more likely to benefit from corticosteroid therapy. In addition, Ye *et al.*[24] reported that corticosteroids were only beneficial in reducing mortality (Hazard ratio [HR] = 0.41) among COVID-19 patients who also had ARDS. Some studies also reported no clinically meaningful benefits or harms for using corticosteroids among COVID-19 patients.[38,39,51]

Other pharmacological treatments. Ten reviews reported that immunoglobulin was used to treat some of the COVID-19 patients.[7,19,23,31,32,40,43,53,56,57] These medications were used as co-interventions in COVID-19 treatment and their specific efficacy was not evaluated. Valk *et al.*[32] reported that the use of immunoglobulin was associated with improvement in clinical symptoms and a reduction in hospitalization period among COVID-19 patients. Moreover, Alijotas-Reig *et al.*[40] recommended a high intensity anti-inflammatory and immunomodulatory therapy for severe patients as a potential therapeutic option. In six studies, Interleukin-6 (IL-6) agents such as tocilizumab and sarilumab were used as supportive treatments for COVID-19.[25,30,39,40,48,58] Some studies showed that tocilizumab could improve clinical status in severe to critically ill patients.[39,40,48,58] The C-reactive protein level was significantly lower after the initiation of tocilizumab in patients.[30] In addition, five studies[19,41,44,56,57] reported the usage of antifungal agents in the treatment of patients in some studies, mainly as an add-on therapy. Traditional Chinese medicine[34,53,57,58] and herbal medicine[23,28,31] were some of the other treatment co-interventions examined for COVID-19, yet their effectiveness was not fully assessed and few details were provided for these interventions.

Non-pharmacological interventions. Oxygen therapy and invasive or non-invasive mechanical ventilation were the two main supportive non-pharmacological interventions used in COVID-19 treatment approaches.[7,19,25,29,31,32,43,44,46,50,53,54,56] As these interventions were mainly used as an add-on treatment in COVID-19 patients with severe or in critical conditions, reviews did not specifically assess or discuss their efficacy. As ARDS was one of the frequently reported complications among COVID-19 patients, the principles of treatment for these patients were focused on improving oxygenation and supporting the function of multiple organs.[33] However, included reviews did not specify the effectiveness of oxygen therapy and ventilation in COVID-19 patients. Moreover, two studies reported on the use of mesenchymal stromal cells but provided few details about its efficacy,[21,39] five reported on the use of convalescent plasma,[32,39,40,44,57] and three reported on the use of continuous renal replacement therapies (CRRT);[7,19,54] none of which reported on the specific efficacy of these interventions.

Adverse drug events

A total of 13 systematic reviews reported adverse drug events (ADEs) for hydroxychloroquine/chloroquine phosphate.[10,20,22,25,35,39,40,46,50,52,53,57,59] Two systematic reviews and meta-analyses showed that there was no statistically significant difference in the incidence of ADEs between hydroxychloroquine therapy and the control group (Odds ratio [OR] = 2.19, 95% confidence interval [CI] 0.59–8.18,[52] and RR = 1.65, 95% CI 0.50–5.50).[46] Studies found hydroxychloroquine to be safe with mild adverse reactions such as diarrhea, nausea, vomiting, rash, headache, lethargy, blurred vision, and transient abnormal liver functions.[22,25,34,39,50,52,55,59] Moreover, hydroxychloroquine was not found to increase the occurrence of abnormal liver function test results, increased serum creatinine level, rash, headache, or anemia in comparison with the control group.[25] Some studies reported QT prolongation associated with hydroxychloroquine treatment.[22,25,52,59] Hernandez *et al.* reported that more patients receiving hydroxychloroquine plus azithromycin had a QTc interval of 500 ms or greater [mean difference = 1.8%, 95% CI –14.9–18.5%]. Moreover, more patients had a QTc interval increase of ⩾ 60 ms compared to baseline (mean difference = 5.1%, 95% CI –7.6% to 17.8%) *versus* hydroxychloroquine alone.[25] Other electrocardiogram changes were first-degree atrioventricular block[22,59] and left bundle-branch block.[59] One patient died in the hydroxychloroquine arm on day three despite a negative RT-PCR.[52,59] Severe ADEs were not reported in patients treated with chloroquine,[10,59] but those receiving a higher dose of chloroquine therapy experienced a slight increase in anemia and a large increase in serum creatinine level compared with those receiving a lower dose.[25] Moreover, 23% (22 of 95) of patients receiving chloroquine had a QTc interval greater than 500 ms.[25]

ADEs were also reported in 60% of patients taking remdesivir,[27,39] and the most common ADEs were rash, diarrhoea, hypotension, nausea, abnormal liver function, and renal impairment. Serious ADEs (e.g. acute kidney injury, septic shock, multi-organ failure, and acute respiratory failure) were noted in 18–23% of patients and 8–12% of patients discontinued remdesivir because of mild or serious ADEs.[27,35,39] The review of Shi *et al.* reported no statistically significant difference in the incidence of ADEs (RR = 1.24, 95% CI 0.67–2.28) and serious ADEs (RR = 0.62, 95% CI 0.38–1.01) among patients receiving lopinavir/ritonavir and others groups.[46] The most common reported ADEs were gastrointestinal reactions, abnormal liver function, anemia, insomnia, bradycardia, or hypoxemia.[20,39,46,50,53] Moreover, 13% of patients were unable to complete the full course of treatment due to anorexia, nausea, abdominal discomfort, or diarrhoea.[39] In the study by Tobaiqy *et al.*, the patients who took up lopinavir/ritonavir also complained about psychiatric symptoms, gastrointestinal ADEs, skin eruptions, and hypokalemia. Abnormal liver function, raised serum uric acid, psychiatric symptom reactions, and gastrointestinal ADEs were also detected in the patients receiving favipiravir and arbidol.[57] Moreover, favipiravir caused diarrhoea, and two systematic reviews reported no ADEs for arbidol.[20,39] Furthermore, no obvious ADEs were reported in children receiving antiviral therapies.[46]

The combined therapy of herbal medicine with western medicine had minor ADEs including, nausea and vomiting, diarrhoea, liver damage, and reduced blood cell count. There was no statistically significant difference between the combination of herbal medicine and western medicine *versus* western medicine alone (risk difference = 0.06, 95% CI –0.04 to 0.15).[28,34] Valk *et al.* reported moderate fever after the transfusion of convalescent plasma[32] and no other adverse reactions were reported.[32,44] Moreover, ADEs were not reported for intravenous immunoglobulin (IVIG).[43] Mild adverse reactions were reported in patients treated with mesenchymal stromal cells (e.g. grade I allergic reaction, generalized skin rash, diarrhoea, transient desaturation, dyspnea, and hypotension).[21] Finally, hyperglycemia, hypernatremia, hypokalemia, coinfections (bacterial or fungal), multiple organ dysfunction syndrome, and ARDS were the most common ADEs associated with corticosteroid use and required routine monitoring.[24,45,57]

Discussion

This overview of reviews summarized the systematic reviews describing therapeutic interventions for COVID-19 patients. While the antiviral and antibiotic agents, corticosteroids, and antimalarial agents were the most common drug classes used to treat COVID-19, the systematic reviews showed no strong evidence to support their efficacy. Oxygen therapy and ventilatory support were also the most common supportive care in patients with respiratory distress and low oxygen saturation levels. The outcomes reported in the included review studies were either incomplete or unclear, and most did not report on ADEs of different treatment options which made interpretations and comparisons about the efficacy and safety of treatments challenging.

Given the lack of an effective antiviral treatment for COVID-19, drugs previously developed to treat other viral infections are being tested. The most widely used antiviral agents are lopinavir, ritonavir, oseltamivir, arbidol, remdesivir, and cytokines. The timing, duration, and dose of antiviral agents varied greatly across the studies, and most patients were provided with other interventions that may have contributed to outcomes such as recovery and death. Overall, although there are early findings about the potential promise in the safety and efficacy of combined interferon beta-1b, lopinavir–ritonavir, and ribavirin, the evidence supporting their efficacy and safety has been rather inconsistent and uncertain.[20,39,42,46,49,53,62] The evidence on remdesivir has also been mixed and requires further higher quality data for better assessment of its efficacy and safety. While remdesivir use was not associated with statistically significant clinical benefits and only led to a numerical reduction in time to clinical improvement among 237 patients enrolled in a randomized, double-blind, multicentre clinical trial in China,[63] there is some evidence that supports a modest improvement in clinical outcomes among COVID-19 patients who have received remdesivir.[27,35,37] Nonetheless, as outlined in several systematic reviews in our study, the certainty of the evidence for the efficacy and safety of antiviral agents in COVID-19 treatment remains low. On the other hand, a high proportion of patients with COVID-19 were treated with antibiotics, despite the lack of aetiological evidence. This is concerning as an emerging body of evidence suggests that secondary bacterial or fungal infections such as *Acinetobacter baumannii*, *Klebsiella pneumonia*, and *Aspergillus*

flavus may occur in COVID-19 patients.[47,64] For example, a brief report describing the characteristics of 3200 COVID-19-related deaths from Italy reported superinfection in 8.5% of patients.[65]

Despite the initial excitement about the potential significant effectiveness of chloroquine and hydroxychloroquine for treating COVID-19,[52,61,66] the findings of our overview are in line with more recent high-quality studies[67–69] such as the Randomized Evaluation of COVid-19 thERapY (RECOVERY) trial[70] that suggest little to no benefits in using these drugs for COVID-19 treatment. Moreover, in a large multinational study of over 96,000 patients with confirmed COVID-19 in 671 hospitals around the world, hydroxychloroquine or chloroquine, used alone or with a macrolide, were indeed harmful to in-hospital outcomes for COVID-19.[69,71] Findings from another well-designed recent randomized controlled trial also indicated that in comparison with standard of care, hydroxychloroquine was not associated with higher rates of negative conversion and led to a higher probability of experiencing ADEs among its recipients.[67] Overall, the harms of using this group of drugs seem to overweigh their benefits for COVID-19 patients and the US Food and Drug Administration's decision to caution against the use of these drugs seems well supported by the existing evidence.[72,73]

Corticosteroids were also assessed as largely unhelpful in most reviews. Patients with severe conditions were more likely to require corticosteroids and they were associated with increased mortality in patients with coronavirus pneumonia.[54] Moreover, recent studies have recommended against using corticosteroids for the routine treatment of COVID-19 patients due to increased risks of steroid-induced osteonecrosis of the femoral head (ONFH).[74,75] Corticosteroids may still be a viable option for patients in critical conditions or septic shock, and prescribing them with bisphosphonates and vitamin E might help address some of the complications such as mortality and mechanical ventilation.[76–78] Immunoglobulin, gamma globulin, traditional Chinese and herbal medicine were other treatment options for treating COVID-19; however, they were relatively uncommon at the time of writing this review and data about their efficacy are limited.[79]

Previous studies have shown that an increased level of cytokines, IL-6 in severe patients in particular, may be attributed to cytokine release syndrome.[80,81] As IL-6 plays an important role in the cytokine storm,[80,81] it may serve as a possible treatment approach in severe patients. Based on six systematic reviews that assessed tocilizumab, this IL-6 blockade agent could be beneficial in the treatment of severely ill COVID-19 patients. These findings are in line with recent cohort studies that have suggested that the IL-6 blockade does not impair the specific antibody response against SARS-CoV-2 and may help reduce the risk of death among severely ill COVID-19 patients;[82,83] nonetheless, they warrant further investigation in sufficiently controlled trials.

This overview identified oxygen therapy and ventilation as the two main non-pharmacological interventions used for COVID-19 patients. As the disease progresses, greater amounts of oxygen are needed. In patients with COVID-19, the decision to use high-flow oxygen *via* a nasal cannula or the initiation of non-invasive ventilation is controversial and there are no data describing whether these modalities were successful at avoiding intubation.[84] A systematic review on severe and critically severe COVID-19 patients suggested that the principles of treatment for these patients should be lung-protective and focus on improving oxygenation.[85] CRRT and convalescent plasma therapy were other therapeutics assessed by some reviews but their effects on COVID-19 patients were not fully evaluated. The result of a retrospective cohort study showed the patients in the CRRT group had better survival rates than those in the non-CRRT group.[86] Furthermore, case series showed that convalescent plasma therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases.[8,87,88] However, the optimal dose, time point, and the clinical benefits of this intervention need further investigations in larger and well-controlled trials.

Most systematic reviews scored poorly on the AMSTAR-2 tool; 29 were assessed as critically low, nine as low quality, and seven as moderate quality. Most of the included studies in the reviews were observational, which was indeed inevitable as the findings of large clinical trials are not fully available. We also noted that the findings of the studies were not likely to be biased due to overlap. Nonetheless, these limitations have significant implications for policy and clinical decision-making. It is important to ensure that the

urgency for summarizing information on the effective treatment options for COVID-19 is not used as a justification for low-quality evidence syntheses. Indeed, promptness and comprehensiveness must be balanced to ensure decision-makers and clinicians are not provided with misleading information. Moreover, reporting outcomes about the safety of treatment options for COVID-19 is of utmost importance and should not be overlooked.

We acknowledge four main limitations of our overview of reviews. First, the actual effects of different treatments is still unclear, and our understanding continues to improve; however, our findings are important and informative for the decisions that need to be made based on the existing evidence. Second, evaluating the efficacy of therapeutic interventions was not a primary objective in most of the included systematic reviews; therefore, sufficient information and details were not provided in some studies. Third, the heterogeneity of the studied population, unclear definition of treatment and outcome variables as well as comparison groups of reviews limited our statistical analysis and we could not conduct a meta-analysis or network meta-analysis. We are hoping to update our live overview as more high-quality data and statistically comparable outcomes become available. Finally, the methodological quality of reviews was very concerning and the evidence on treatments was mostly from a few countries, China in particular. It is important to revisit what we know as treatment data from other countries are released. Despite these limitations, this overview followed a rigorous methodological approach and contributes to the literature by providing a comprehensive summary of all available evidence about COVID-19 treatment options as well as assessing the confidence in the findings of the existing systematic reviews.

Conclusion

The number of reviews on pharmacological and non-pharmacological therapies for COVID-19 is rapidly increasing. However, many reviews still show significant methodological flaws limiting definite conclusions about the efficacy and safety of therapeutic interventions. In particular, very little is known about the cost-effectiveness of existing treatments, particularly in low and middle-income countries. More high-quality, evidence-based clinical trials with proper design and adequate sample size would help reach more reliable results about the use of specific therapeutic interventions in the treatment of COVID-19 in the short and long term. Overall, this review demonstrates that although some therapeutic interventions (e.g. corticosteroids, remdesivir) may be helpful to certain subgroups of COVID-19 patients, the available data are insufficient to strongly recommend any particular treatment to be used at a population level.

Author contribution(s)

Malahat Khalili: Conceptualization; Supervision; Validation; Data and narrative synthesis; Investigation; Methodology; Writing-original draft.

Maryam Chegeni: Data curation; Data and narrative synthesis; Investigation; Methodology; Writing-original draft.

Sara Javadi: Data curation; Data and narrative synthesis; Investigation; Methodology; Writing-review & editing.

Mehrdad Farokhnia: Conceptualization; Methodology; Project administration; Validation; Writing-review & editing.

Hamid Sharifi: Conceptualization; Project administration; Data and narrative synthesis; Methodology; Validation; Writing-review & editing.

Mohammad Karamouzian: Conceptualization; Data curation; Data and narrative synthesis; Investigation; Methodology; Project administration; Supervision, Validation; Visualization; Writing-review & editing.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Ethics

Given the secondary nature of this overview and no interaction with humans, ethics approval was not required.

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ORCID iD
Malahat Khalili https://orcid.org/0000-0001-6160-0913

Supplemental material

The reviews of this paper are available via the supplemental material section.

References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (2020, accessed May 19 2020).
2. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) – United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 343–346.
3. Khalili M, Karamouzian M, Nasiri N, *et al.* Epidemiological characteristics of COVID-19: a systematic review and meta-analysis. *Epidemiol Infect* 2020; 148: e130.
4. Johns Hopkins University. *COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)*. https://coronavirus.jhu.edu/map.html (2020; accessed 5 October 2020).
5. Lippi G, Sanchis-Gomar F and Henry BM. Coronavirus disease 2019 (COVID-19): the portrait of a perfect storm. *Ann Transl Med* 2020; 8: 497.
6. Bhimraj A, Morgan RL, Shumaker AH, *et al.* Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis*. Epub ahead of print 27 April 2020. DOI: 10.1093/cid/ciaa478
7. Fu L, Wang B, Yuan T, *et al.* Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect* 2020; 80: 656–665.
8. Shen C, Wang Z, Zhao F, *et al.* Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020; 323: 1582–1589.
9. Pacheco RL and Riera R. Hydroxychloroquine and chloroquine for COVID-19 infection. Rapid systematic review. *J Evid Based Healthc* 2020; 2: 74–92.
10. Gbinigie K and Frie K. Should chloroquine and hydroxychloroquine be used to treat COVID-19? A rapid review. *BJGP Open* 2020; 4: bjgpopen20X101069.
11. Statista. *Number of coronavirus (COVID-19) studies registered worldwide as of October 05, 2020, by region*. https://www.statista.com/statistics/1106306/coronavirus-clinical-trials-worldwide/ (2020; accessed 7 October 2020).
12. Higgins JP, Thomas J, Chandler J, *et al. Cochrane handbook for systematic reviews of interventions*. Hoboken, NJ: John Wiley & Sons, 2019.
13. Lunny C, Brennan SE, McDonald S, *et al.* Toward a comprehensive evidence map of overview of systematic review methods: paper 1 – purpose, eligibility, search and data extraction. *Syst Rev* 2017; 6: 231.
14. Lunny C, Brennan SE, McDonald S, *et al.* Toward a comprehensive evidence map of overview of systematic review methods: paper 2 – risk of bias assessment; synthesis, presentation and summary of the findings; and assessment of the certainty of the evidence. *Syst Rev* 2018; 7: 159.
15. McGowan J, Sampson M, Salzwedel DM, *et al.* PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016; 75: 40–46.
16. Shea BJ, Reeves BC, Wells G, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358: j4008.
17. Pieper D, Antoine S-L, Mathes T, *et al.* Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol* 2014; 67: 368–375.
18. Guida JP. Chloroquine, hydroxychloroquine and Covid-19: a systematic review of literature. *IAJMH* 2020; 3: 1–10.
19. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, *et al.* Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J Clin Med* 2020; 9: 941.
20. Liu W, Zhou P, Chen K, *et al.* Efficacy and safety of antiviral treatment for COVID-19 from evidence in studies of SARS-CoV-2 and other acute viral infections: a systematic review and meta-analysis. *CMAJ* 2020; 192: E734–E744.
21. Qu W, Wang Z, Hare JM, *et al.* Cell-based therapy to reduce mortality from COVID-19: systematic review and meta-analysis of human studies on acute respiratory distress syndrome. *Stem Cells Transl Med* 2020; 9: 1007–1022.
22. Das S, Bhowmick S, Tiwari S, *et al.* An updated systematic review of the therapeutic role of hydroxychloroquine in coronavirus disease-19 (COVID-19). *Clin Drug Invest* 2020; 40: 591–601.

23. Fajgenbaum DC, Khor JS, Gorzewski A, *et al.* Treatments administered to the first 9152 reported cases of COVID-19: a systematic review. *Infect Dis Ther* 2020; 9: 435–449.

24. Ye Z, Wang Y, Colunga-Lozano LE, *et al.* Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020; 192: E756–E767.

25. Hernandez AV, Roman YM, Pasupuleti V, *et al.* Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19: a living systematic review. *Ann Intern Med* 2020; 173: 287–296.

26. Rodrigo C, Fernando SD and Rajapakse S. Clinical evidence for repurposing chloroquine and hydroxychloroquine as antiviral agents: a systematic review. *Clin Microbiol Infect* 2020; 26: 979–987.

27. Jorgensen SC, Kebriaei R and Dresser LD. Remdesivir: review of pharmacology, pre-clinical data and emerging clinical experience for COVID-19. *Pharmacotherapy* 2020; 40: 659–671.

28. Ang L, Song E, Lee HW, *et al.* Herbal medicine for the treatment of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of randomized controlled trials. *J Clin Med* 2020; 9: 1583.

29. Schunemann HJ, Khabsa J, Solo K, *et al.* Ventilation techniques and risk for transmission of coronavirus disease, including COVID-19: a living systematic review of multiple streams of evidence. *Ann Intern Med* 2020; 173: 204–216.

30. Antwi-Amoabeng D, Kanji Z, Ford B, *et al.* Clinical outcomes in COVID-19 patients treated with tocilizumab: an individual patient data systematic review. *J Med Virol*. Epub ahead of print 21 May 2020. DOI: 10.1002/jmv.26038

31. Tahvildari A, Arbabi M, Farsi Y, *et al.* Clinical features, diagnosis, and treatment of COVID-19 in hospitalized patients: a systematic review of case reports and case series. *Front Med* 2020; 7: 231.

32. Valk SJ, Piechotta V, Chai KL, *et al.* Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database Syst Rev* 2020; 5: CD013600.

33. Zhang JJY, Lee KS, Ang LW, *et al.* Risk factors of severe disease and efficacy of treatment in patients infected with COVID-19: a systematic review, meta-analysis and meta-regression analysis. *Clin Infect Dis*. Epub ahead of print 14 May 2020. DOI: 10.1093/cid/ciaa576

34. Liu M, Gao Y, Yuan Y, *et al.* Efficacy and safety of integrated traditional Chinese and western medicine for corona virus disease 2019 (COVID-19): a systematic review and meta-analysis. *Pharmacol Res* 2020; 158: 104896.

35. Singh AK, Singh A, Singh R, *et al.* Remdesivir in COVID-19: a critical review of pharmacology, pre-clinical and clinical studies. *Diabetes Metab Syndr* 2020; 14: 641–648.

36. Singh AK, Singh A, Singh R, *et al.* Hydroxychloroquine in patients with COVID-19: a systematic review and meta-analysis. *Diabetes Metab Syndr* 2020; 14: 589–596.

37. Li Z, Wang X, Cao D, *et al.* Rapid review for the anti-coronavirus effect of remdesivir. *Drug Discov Ther* 2020; 14: 73–76.

38. Li H, Chen C, Hu F, *et al.* Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. *Leukemia* 2020; 34: 1503–1511.

39. Xu X, Ong YK and Wang DY. Role of adjunctive treatment strategies in COVID-19 and a review of international and national clinical guidelines. *Mil Med Res* 2020; 7: 22.

40. Alijotas-Reig J, Esteve-Valverde E, Belizna C, *et al.* Immunomodulatory therapy for the management of severe COVID-19. Beyond the anti-viral therapy: a comprehensive review. *Autoimmun Rev* 2020; 19: 102569.

41. Rawson TM, Moore LSP, Zhu N, *et al.* Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis*. Epub ahead of print 2 May 2020. DOI: 10.1093/cid/ciaa530

42. Chowdhury MDS, Rathod J and Gernsheimer J. A rapid systematic review of clinical trials utilizing chloroquine and hydroxychloroquine as a treatment for COVID-19. *Acad Emerg Med* 2020; 27: 493–504.

43. Zhang J, Yang Y, Yang N, *et al.* Effectiveness of intravenous immunoglobulin for children with severe COVID-19: a rapid review. *Ann Transl Med* 2020; 8: 625.

44. Rajendran K, Narayanasamy K, Rangarajan J, *et al.* Convalescent plasma transfusion for the treatment of COVID-19: systematic review. *J Med Virol* 2020; 92: 1475– 1483.

45. Lu S, Zhou Q, Huang L, *et al.* Effectiveness and safety of glucocorticoids to treat COVID-19: a rapid review and meta-analysis. *Ann Transl Med* 2020; 8: 627.
46. Shi Q, Zhou Q, Wang X, *et al.* Potential effectiveness and safety of antiviral agents in children with coronavirus disease 2019: a rapid review and meta-analysis. *Ann Transl Med* 2020; 8: 624.
47. Wang J, Tang Y, Ma Y, *et al.* Efficacy and safety of antibiotic agents in children with COVID-19: a rapid review. *Ann Transl Med* 2020; 8: 619.
48. Alzghari SK and Acuña VS. Supportive treatment with tocilizumab for COVID-19: a systematic review. *J Clin Virol* 2020; 127: 104380.
49. Zhong H, Wang Y, Zhang ZL, *et al.* Efficacy and safety of current therapeutic options for COVID-19 – lessons to be learnt from SARS and MERS epidemic: a systematic review and meta-analysis. *Pharmacol Res* 2020; 157: 104872.
50. Pascarella G, Strumia A, Piliego C, *et al.* COVID-19 diagnosis and management: a comprehensive review. *J Intern Med* 2020; 288: 192–206.
51. Veronese N, Demurtas J, Yang L, *et al.* Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. *Front Med (Lausanne)* 2020; 7: 170.
52. Sarma P, Kaur H, Kumar H, *et al.* Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: a systematic review and meta-analysis. *J Med Virol* 2020; 92: 776–785.
53. Ford N, Vitoria M, Rangaraj A, *et al.* Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment. *J Int AIDS Soc* 2020; 23: e25489.
54. Yang Z, Liu J, Zhou Y, *et al.* The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect* 2020; 81: e13–e20.
55. Gbinigie K and Frie K. Should azithromycin be used to treat COVID-19? A rapid review. *BJGP Open* 2020; 4: bjgpopen20X101094.
56. Yousefifard M, Zali A, Mohamed Ali K, *et al.* Antiviral therapy in management of COVID-19: a systematic review on current evidence. *Arch Acad Emerg Med* 2020; 8: e45.
57. Tobaiqy M, Qashqary M, Al-Dahery S, *et al.* Therapeutic management of patients with COVID-19: a systematic review. *Infect Prev Pract* 2020; 2: 100061.
58. Md Insiat Islam R. Current drugs with potential for treatment of COVID-19: a literature review. *J Pharm Pharm Sci* 2020; 23: 58–64.
59. Singh AK, Singh A, Shaikh A, *et al.* Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: a systematic search and a narrative review with a special reference to India and other developing countries. *Diabetes Metab Syndr* 2020; 14: 241–246.
60. Tobaiqy M, Qashqary M, Al-Dahery S, *et al.* Therapeutic management of COVID-19 patients: a systematic review. *medRxiv 2020.100061*. DOI: 10.1016/j.infpip.2020.100061
61. Gautret P, Lagier J-C, Parola P, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; 56: 105949.
62. Hung IF-N, Lung K-C, Tso EY-K, *et al.* Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020; 395: 1695–1704.
63. Wang Y, Zhang D, Du G, *et al.* Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; 395: 1569–1578.
64. Zhou M, Zhang X and Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. *Front Med* 2020; 14: 126–135.
65. Group C-S. *Characteristics of COVID-19 patients dying in Italy: report based on available data on March 20th, 2020*. Rome, Italy: Instituto Superiore Di Sanita, 2020.
66. Gao J, Tian Z and Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020; 14: 72–73.
67. Tang W, Cao Z, Han M, *et al.* Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020; 369: m1849.
68. Mahévas M, Tran V-T, Roumier M, *et al.* Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* 2020; 369: m1844.
69. Mehra MR, Desai SS, Ruschitzka F, *et al.* Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19:

a multinational registry analysis. *Lancet* 2020; 395: P1820.

70. Horby P and Landau R. *No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19*. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19 (2020; accessed 7 October 2020).
71. Funck-Brentano C and Salem J-E. Chloroquine or hydroxychloroquine for COVID-19: why might they be hazardous? *Lancet* 2020; S0140-6736: 31174–31170.
72. Food and Drug Administration. *FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems*. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or (2020; accessed 7 October 2020).
73. Rana DR and Dulal S. Therapeutic application of chloroquine and hydroxychloroquine in clinical trials for COVID-19: a systematic review. *medRxiv 2020.03.22.20040964*. DOI: 10.1101/2020.03.22.20040964
74. Guo KJ, Zhao FC, Guo Y, *et al.* The influence of age, gender and treatment with steroids on the incidence of osteonecrosis of the femoral head during the management of severe acute respiratory syndrome: a retrospective study. *Bone Joint J* 2014; 96: 259–262.
75. Tang C, Wang Y, Lv H, *et al.* Caution against corticosteroid-based COVID-19 treatment. *Lancet* 2020; 395: 1759–1760.
76. Liu L-H, Zhang Q-Y, Sun W, *et al.* Corticosteroid-induced osteonecrosis of the femoral head: detection, diagnosis, and treatment in earlier stages. *Chin Med J* 2017; 130: 2601.
77. Jia YB, Jiang DM, Ren YZ, *et al.* Inhibitory effects of vitamin E on osteocyte apoptosis and DNA oxidative damage in bone marrow hemopoietic cells at early stage of steroid-induced femoral head necrosis. *Mol Med Rep* 2017; 15: 1585–1592.
78. Lai K-A, Shen W-J, Yang C-Y, *et al.* The use of alendronate to prevent early collapse of the femoral head in patients with nontraumatic osteonecrosis: a randomized clinical study. *JBJS* 2005; 87: 2155–2159.
79. Song Y, Zhang M, Yin L, *et al.* COVID-19 treatment: close to a cure? – A rapid review of pharmacotherapies for the novel coronavirus. *Int J Antimicrob Agents* 2020; 56: 106080.
80. Ye Q, Wang B and Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect* 2020; 80: 607–613.
81. Tang Y, Liu J, Zhang D, *et al.* Cytokine storm in COVID-19: the current evidence and treatment strategies. *Front Immunol* 2020; 11: 1708.
82. Masiá M, Fernández-González M, Padilla S, *et al.* Impact of interleukin-6 blockade with tocilizumab on SARS-CoV-2 viral kinetics and antibody responses in patients with COVID-19: a prospective cohort study. *EBioMedicine* 2020; 60: 102999.
83. Guaraldi G, Meschiari M, Cozzi-Lepri A, *et al.* Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020; 2: e474–e484.
84. Anesi GL, Manaker S, Finlay G, *et al.* *Coronavirus disease 2019 (COVID-19): critical care issues*. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-critical-care-issues#H368577810 (2020; accessed 2 May 2020).
85. Zhang H-y, Gong Z, Jiao F, *et al.* Clinical features, treatments and outcomes of severe and critical severe patients infected with COVID-19: a system review and meta-analysis. *Research Square* 2020. Preprint. DOI: 10.21203/rs.3.rs-17307/v1
86. Yang Y, Shi J, Ge S, *et al.* Effect of continuous renal replacement therapy on all-cause mortality in COVID-19 patients undergoing invasive mechanical ventilation: a retrospective cohort study. *medRxiv 2020.03.16.20036780*. DOI: 10.1101/2020.03.16.20036780
87. Zeng QL, Yu ZJ, Gou JJ, *et al.* Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *J Infect Dis* 2020; 222: 38–43.
88. Duan K, Liu B, Li C, *et al.* Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci USA* 2020; 117: 9490–9496.