Overzichtstabel van klinische studies en prospectieve vergelijkende studies naar medicamenteuze behandelingen van COVID-19.
Deze tabel laat een overzicht zien van de gevonden klinische trials en vergelijkende studies naar medicamenteuze behandeling van COVID-19.
De studies staan gerangschikt op middel en datum van publicatie. De literatuur wordt dagelijks bekeken en zo nodig wordt de tabel aangevuld.

Medication/treatment	Published	1st author	Title	Journal	Status
Updated: May 14, 2020 (* indicates a new added article)					
1.1 Chloroquine/Hydrochloroquine					
Chloroquine	April 01, 2020	Huang	Treating COVID-19 with chloroquine	Journal of Molecular Cell Biology	Uncorrected manuscript
	April 24, 2020	Borba	Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial	JAMA Network Open	Peer-reviewed (published)
Hydrochloroquine	April 10, 2020	Chen	Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial	medRxiv	Preprint and has not been certified by peer review
Hydroxychloroquine Azithromycin	March 20, 2020	Gautret	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial	International Journal of Antimicrobial Agents	Peer-reviewed (in press)
	May 01, 2020	Bessière	Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit	JAMA Cardiology	Peer-reviewed (published)
	May 01, 2020	Mercuro	Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19)	JAMA Cardiology	Peer-reviewed (published)

	May 11, 2020	Rosenberg	Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State	JAMA	Peer-reviewed (published)
Chloroquine, Hydroxychloroquine Azithromycin	April 29, 2020	Saleh	The Effect of Chloroquine, Hydroxychloroquine and Azithromycin on the Corrected QT Interval in Patients with SARS-CoV-2 Infection	Circulation: Arrhythmia and Electrophysiology	Ahead of print (not clearly stated whether this paper has been certified by peer review)
1.2. Remdesivir					
Remdesivir	April 29, 2020	Wang	Remdesivir in adults with severe COVID-19: a randomised,double-blind, placebo-controlled, multicentre trial	Peer-reviewed (published)	Peer-reviewed (published)
1.3. Azitromycine					
1.4. Lopinavir/Ritonavir					
Lopinavir/Ritonavir	March 18, 2020	Cao	A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19	The New England Journal of Medicine	Peer-reviewed (published)
Lopinavir/Ritonavir Arbidol	March 23, 2020	Li	An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI) Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial	medRxiv	Preprint and has not been certified by peer review *this preprint is available under two different titles
Combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin	May 08, 2020	Hung	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	The Lancet	Peer-reviewed (published)
2.1 Ribavirine					

2.2 Favipiravir					
Favipiravir **Lopinavir/Ritonavir**	March 18, 2020	Cai	Experimental Treatment with Favipiravir for COVID-19: An Open-LabelControl Study	Engineering	Preprint and has been certified by peer -review
Favipiravir **Arbidol**	April 08, 2020	Chen	Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial	medRxiv	Preprint and has not been certified by peer review
Favipiravir **Baloxavir marboxil** **Lopinavir/Ritonavir**	May 05, 2020	Lou	Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: an Exploratory Randomized, Controlled Trial	medRxiv	Preprint and has not been certified by peer review
2.3 Convalescent plasma					
3.1 Meplazumab					
Meplazumab	March 24, 2020	Bian	Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial	medRxiv	Preprint and has not been certified by peer review
3.2 Tocilizumab					
Tocilizumab	May 01, 2020	Sciascia	Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19	Clinical and Experimental Rheumatology	Published (not clearly stated whether this paper has been certified by peer review)
	May 09, 2020	Colaneri	Tocilizumab for Treatment of Severe COVID-19 Patients: Preliminary Results from SMAtteo COvid19 REgistry (SMACORE))	Microorganisms	Peer-reviewed (published)
3.3 Baricitinib					
Baricitinib	April 23, 2020	Cantini	Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact	The Journal of Infection	Published (not clearly stated whether this paper has been certified by peer review)
4.1 Corticosteroid					
	March 12, 2020	Wang	Early, low-dose and short-term application of corticosteroid treatment in patients with severe	medRxiv	Preprint and has not been certified by peer review

			COVID-19 pneumonia: single-center experience from Wuhan, China.		
	April 11, 2020	Fang	Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19	The Journal of Infection	Published (not clearly stated whether this paper has been certified by peer review)
Methylprednisolone	April 28, 2020	Wang	A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia	Signal Transduction and Targeted Therapy	Peer-reviewed (published)

Studieresultaten Medicamenteuze behandeling COVID-19

Deze tabel vat de resultaten van studies naar medicamenteuze behandeling bij COVID-19 samen. De studies staan gerangschikt op middel en datum van publicatie. De literatuur wordt dagelijks bekeken en zo nodig wordt de tabel aangevuld. De kwaliteit van deze studies is beoordeeld, zie tabel 'Studiekwaliteit Medicamenteuze behandeling COVID-19'.

Chloroquine							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Huang, et al. 2020	Type of study: Randomized clinical trial Setting: Confirmed COVID-19 patients were randomized in a clinical trial from 27 Jan 2020 to 15 Feb 2020 Country: China Source of funding: Not described	Inclusion criteria: • age ≥18 years old • diagnosed with COVID 19 according to WHO interim guidance (28 January 2020) Exclusion criteria: • pregnant females • Documented allergic history to Chloroquine • Documented history of haematological system diseases • Documented history of chronic liver and kidney diseases • Documented history of cardiac arrhythmia or chronic heart diseases • Documented history of retina or hearing dysfunction • Documented history of mental illnesses • Use of digitalis due to the previous disease. N total at baseline: N = 22 Intervention: 10 Control: 12 Important characteristics: Age, mean (IQR):	**Chloroquine** 500mg orally twice-daily for 10 days	**Lopinavir/Ritonavir** 400/100mg orally twice-daily for 10 days.		Negative for SARS CoV-2 RT-PCR, n/N (%) Day 7 I: 7/10 (70%) C: 7/12 (58%) RR 1.20 (95%CI 0.60-2.40) Day 10 I: 9/10 (90%) C: 9/12 (75%) RR 1.20 (95%CI 0.84-2.00) Day 14 I: 10/10 (100%) C: 11/12 (92%) RR 1.09 (95%CI 1-1.33) Hospital discharge - day 14 *Hospital discharge defined by temperature returned to normal for more than 3 days; the respiratory symptoms improved significantly; the pulmonary imaging showed that the inflammation was obviously absorbed; and the detection of respiratory pathogenic nucleic acid was negative twice in a row (the sampling time is at least 1 day apart).* I: 10/10 (100%) C: 6/12 (50%) RR 2 (1.33-4.00) Clinical recovery – day 10 *defined by: no fever, axilla temperature ≤36.6 C or oral temperature ≤37.2 C or rectal/ tympanic temperature ≤37.8 C; respiratory rate ≤24/minute on room air; oxygen saturation > on room air; mild or absent cough)* I: 8/10 (80%) C: 7/12 (58%)	Remarks: • Randomization method unclear • Small sample sizes • 'Days from onset to treatment' longer in control group Authors conclusion: In sum, our preliminary results suggest that Chloroquine could be an effective and inexpensive option among many proposed therapies, e.g. Lopinavir/Ritonavir.

		I: 41.5y (33.8-50.0) C: 53.0 (41.8-63.5) P=0.09 Sex, n/N (%) male: I: 7/10 (70%) *(inconsistent numbers)* C: 6 /12(50%) P=0.41 Cases severe n/N (%): I: 3/10 (30%) C: 6/12 (50%) [Further, comorbidities, laboratory parameters and symptoms at admission are reported in the supplement] Groups mainly comparable at baseline, except for 'days from onset to treatment', which is longer in the control group I: 2.50 (2.00-3.75) C: 6.50 (4.75-8.50) P<.001)				RR 1.37 (95%CI 0.80-2.80) <u>CT scan improvement</u> *defined by exudation or consolidation of the lesion absorbed; the lesion area was gradually narrowed; and t here might be residual linear fibrosis* Day 10 I: 2/10 (20%) C: 1/12 (8%) RR 2.4 (95%CI 0.14-12.32) Day 14 I: 10/10 (100%) C: 9/12 (75%) RR 1.33 (95%CI 1.00-2.00) <u>Frequency of adverse events</u> <u>Intervention, control n/N(%)</u> Total No. of Adverse Events I: 9 (90%) (9 adverse events in 5 patients) C: 10 (83%) P=0.99 Gastrointestinal: Vomiting I: 5/10 (50%), C: 1/12 (8.33%) P=0.06 Abdominal pain I: 1/10 (10%), C: 2/12 (16.67%) P=0.99 Nausea I: 4/10 (40%), C: 5/12 (42%) P=0.99 Diarrhea I: 5/10 (50%), C: 8/12 (67%) P=0.67 Neurological Dizziness I: 0/10 (0%), C: 2/12 (17%) P=0.48 Headache I: 0/10 (0%), C: 1/12 (8%) P=0.99 Psychosis I: 0/10 (0%), C: 1/12 (8%) P=0.99 Rash or itchy	

						I: 1/10 (10%), C: 0/12 (0%) P=0.45 Respiratory Cough I: 4/10 (40%), C: 6/12 (50%) P=0.69 Shortness of breath I: 1/10 (10%), C4/12 (33%) P=0.32	
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Borba et al., 2020	Type of study: Randomized, double-blinded, phase IIb clinical trial Setting: Hospitalized COVID-19 patients were randomized in the clinical trial between March 23 and April 5 2020 at Hospital e Pronto-Socorro Delphina Rinaldi Abdel Aziz Country: Manaus, Western Brazilian Amazon Source of funding: This study was funded by the Government of the Amazonas State, Farmanguinhos (Fiocruz), SUFRAMA, CAPES, FAPEAM, and	Inclusion criteria: • age > 18 years • respiratory rate >24 rpm and/or heart rate higher than 125 bmp (in the absence of fever) • and/or peripheral oxygen saturation <90% in ambient air • and/or shock (defined as mean arterial pressure <65 mmHg, with the need for vasopressors medicine or oliguria or a lower level of consciousness Exclusion criteria: • age < 18 years N total at baseline: N = 81 Intervention (I): 41 (high dosage CQ arm) Control (C): 40 (low dosage treatment) Important characteristics: Intervention group Mean age: 54.7 ± 13.7 Male gender: 31/41(75.6%) Control group Mean age: 47.4 ± 13.3	High dosage CQ (600mg CQ (4x150mg tablets, twice daily for 10 days, total dose 12g) CQ 150mg tablets (Farmanguinhos, Fiocruz, Brazil).	Low dosage CQ (450mg CQ (3x150mg tablets + 1 placebo) twice daily on day 0, 3x150mg tablets +1 placebo tablet followed by 4 placebo tablets from D1 to D4, and then 4 placebo tablets twice daily from D5-D9, total dose 2.7g) Placebo tablets (Farmanguinhos, Fiocruz, Brazil).	Length of follow-up: 13 days Loss-to-follow-up: Not reported	Safety outcomes: No differences in hematological or renal toxicity was seen between the groups. Death at D13 High dosage:16/41 (39%) Low dosage: 6/40 (15%)	Comments: Preliminary results, follow-up until day 28 is ongoing with a larger sample size Most patients were confirmed COVID-19 by RT-PCR posteriori (62/81, 76.5%). The non-confirmed patients presented compatible clinical and epidemiological COVID-19 presentation and were analysed together Author's conclusion: Preliminary findings suggest that the higher CQ dosage (10-day regimen) should not be recommended for COVID-19 treatment because of its potential safety hazards.

	federal funds granted by a coalition of Brazilian senators.	Male gender: 10/40 (75%) <u>Groups comparable at baseline?</u> High dosage group is slightly older. History of heart disease was more frequent among patients receiving the higher CQ dosage (p=0.05					
Hydroxychloroquine							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Chen et al., 2020	<u>Type of study:</u> Randomized clinical trial <u>Setting:</u> Confirmed COVID-19 patients were randomized in a parallel-group trial from February 4 to February 28 <u>Country:</u> China, Wuhan <u>Source of funding:</u> This work was supported by the Epidemiological Study of COVID-19 Pneumonia to Science and Technology Department of Hubei Province (2020FCA005)	<u>Inclusion criteria</u>: • age > 18 years • positive diagnosis COVID-19 by detection of SARS-CoV-2 by RT-PCR • diagnosis of pneumonia on chest CT • mild respiratory illness, defined by SaO2/SPO2 ratio > 93% or PaO2/FIO2 ratio > 300 mmHg in hospital room conditions <u>Exclusion criteria</u>: • severe or critical respiratory illness; or participation in trial does not meet patient's maximum benefit or safe follow up criteria • retinopathy and other retinal diseases • conduction block and other arrhythmias • severe liver disease • pregnant or breastfeeding • severe renal failure • potential transfer to another hospital within 72h of enrolment	Hydroxychloroquine + standard treatment: Oral hydroxychloroquine sulfate tablets, 400 mg/d (200 mg/bid) between days 1 and 5	Standard treatment: oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids	<u>Length of follow-up</u>: At least six days of follow-up at the time of the present analysis <u>Loss-to-follow-up</u>: N/a	<u>Pulmonary recovery[1]</u> Intervention Exacerbated: 2 (6.5%) Unchanged: 4 (12.9%) Moderately improved: 6 (19.4%) Significantly improved: 19 (61.3%) Control Exacerbated: 9 (29.0%) Unchanged: 5 (16.1%) Moderately improved: 12 (38.7%) Significantly improved: 5 (16.1%) P <0.05 <u>Changes in time to clinical recovery (TTCR)[2]</u> Not clearly described [1]Pulmonary recovery is defined as: exacerbated, unchanged, moderately improved when less than 50% of pneumonia were absorbed, and significantly improved when more than 50% of pneumonia were absorbed [2]TTCR is defined as the return of body temperature and cough relief, maintained for more than 72 h	

		• received any trial treatment for COVID-19 within 30 days before the current study <u>N total at baseline</u>: N = 62 Intervention (I): 31 (hydroxychloroquine, HCQ + standard treatment) Control (C): 31 (standard treatment) <u>Important characteristics</u>: Intervention group Mean age: 44.1 ± 16.1 Male gender: 14 (45.2%) Control group Mean age: 45.2 ± 14.7 Male gender: 15 (48.3%) Groups comparable at baseline.					
Hydroxychloroquine Azithromycin							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Gautret et al., 2020	<u>Type of study:</u> Open-label non-randomized clinical trial <u>Setting:</u> French confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th	<u>Inclusion criteria</u>: • age > 12 years • PCR documented SARS-CoV-2 carriage in nasopharyngeal sample at admission whatever their clinical status <u>Exclusion criteria</u>: • known allergy to hydroxychloroquine or chloroquine or had another known contraindication to	Intervention (I) Hydroxychloroquine 600mg (1dd) (n=20) Intervention (II) Depending on their clinical presentation, azithromycin was added to the treatment 500mg on day1 followed by 250mg per day, the next four days to prevent bacterial	Patients who refused the treatment or had an exclusion criteria, served as controls in Marseille centre. Patients in other centers did not receive hydroxychloroquine and served as controls	<u>Length of follow-up</u>: At least six days of follow-up at the time of the present analysis <u>Loss-to-follow-up</u>: 6 hydroxychloroquine-treated patients were lost in follow-up during the trial	<u>Virological clearance at day-6 post-inclusion</u> Intervention (I&II): 14/20 (70%) Control: 2/16 (12.5%) P <0.001 <u>Virological clearance at day-6 post-inclusion</u> Intervention (I): 8/14 (57.1%) Intervention (II): 6/6 (100%) Control: 2/16 (12.5%) P<0.001	The described intervention (II) was not planned and documented before the start of the study These preliminary results suggest a synergistic effect of the combination of hydroxychloroquine and azithromycin Clinical follow-up and occurrence of side-effects will be described in a

	<u>Country:</u> France <u>Source of funding:</u> This work was supported by the French Government Méditerranée Infection 10-IAHU-03)	treatment with the study drug, including retinopathy, G6PD deficiency and QT prolongation breastfeeding and pregnant patients were excluded • based on their declaration and pregnancy test results when required. <u>N total at baseline</u>: N = 36 • Intervention (I): 20 (hydroxychloroquine) • Intervention (II): 6 (hydroxychloroquine + azithromycin) • Control: 16 <u>Important characteristics</u>: Intervention group Mean age: 51.2 ± 18.7 Male gender: 9 (45%) Control group Mean age: 37.3 ± 24.0 Male gender: 6 (37.5%) Groups comparable at baseline? Hydroxychloroquine-treated patients were older than control patients (51.2 years vs. 37.3 years) (p=0.06)	super-infection under daily electrocardiogram control (n=6)		because of early cessation of treatment <u>Reasons:</u> • 3 patients were transferred to intensive care unit, including one transferred on day2 post-inclusion who was PCR-positive on day1, one transferred on day3 post-inclusion who was PCR-positive on days1-2 and one transferred on day4 post-inclusion who was PCR positive on day1 and day3; • 1 patient died on day3 post inclusion and was PCR-negative on day2; • 1 patient decided to leave the hospital on day3 post-inclusion and was PCR-negative on days1-2. • 1 patient stopped the treatment on day3 post-		further paper at the end of the trial

					inclusion because of nausea and was PCR-positive on days1-2-3.		
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Bessière et al., 2020	Type of study: Retrospective study Setting: between March 15 and March 29, 2020 Intensive Care Unit (ICU) Hospices Civils de Lyon Country: France Source of funding: funding is not reported Conflicts of interest: the authors declare no conflict of interests	Inclusion criteria: -critically ill patients with COVID-19 -COVID-19 confirmed by positive reverse transcription–polymerase chain reaction results on respiratory samples admitted to the ICU who receivedhydroxychloroquine with or without azithromycin Exclusion criteria: contraindication, including corrected QT (QTc) intervals greater than 460 milliseconds (Bazett formula). N total at baseline: N=40 Intervention: 22 Control: 18 Important characteristics Age, median, 68 years	Monotherapy: hydroxychloroquine alone Treatment regimen: • hydroxychloroquine 200mg, twice a day, for 10 days	Combination therapy: hydroxychloroquine + azithromycin Treatment regimen: • hydroxychloroquine 200mg, twice a day, for 10 days • azithromycin (250mg, daily, for 5 days)	Follow-up period: not reported	Prolonged QTc (defined as an increase in QTc intervals of more than 60 milliseconds (ΔQTc >60 milliseconds) compared with baseline or as aQTc of 500 milliseconds or greater): observed in 14 patients (36%) (10 with ΔQTc >60 milliseconds and 7 with QTc ≥500 milliseconds) after a duration of antiviral treatment of 2 to 5 days. No ventricular arrhythmia, including torsades de pointes, was recorded. Increase in QTc of 500 milliseconds or greater, n(%): I: 1 of 22 (5%) C: 6 of 18 (33%) P=.03 Ceasing of antiviral treatment before completion (n, %): 7 patients (17.5%) following ECG abnormalities and in 10 (25%) for acute renal failure.	Remarks: -retrospective study -n=20 (50%) received other treatments favouring prolonged QT in ICU in addition to hydroxychloroquine alone or hydroxychloroquine + azithromycin. Authors conclusion: This study raises safety concerns about the use of hydroxychloroquine with or without azithromycin for patients with COVID-19, particularly when both drugs are administered together. The finding that QTc intervals increased in more than 90% of patients raises concerns about the widespread use of hydroxychloroquine,

		[IQR, 58-74 years] Sex, N (%) male: 32 [80%]) <u>QTc before start of antivirals, median (IQR), ms</u> -QTc ≥500 ms or ΔQTc >60 ms (n = 14): 416 (383-440) -QTc <500 ms and ΔQTc ≤60 ms (n = 26): 415 (401-425) P=.88 It is unclear whether groups were comparable at baseline.					with or without azithromycin, to treat COVID-19 in settings where patients cannot be adequately monitored. In our cohort, close monitoring of patients (including continuous QTc interval monitoring, daily ECGs, and laboratory tests), which led to an interruption of these drugs for 17 patients (42.5%), may have averted further complications, including drug-induced torsades de pointes.
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Mercuro et al. 2020	<u>Type of study:</u> Retrospective, observational study <u>Setting:</u> Single-center (Beth Israel Deaconess Medical Center in Boston, Massachusetts) study evaluating hospitalized patients who received at least 1 day of hydroxychloroquine while inpatients and were admitted between March	<u>Inclusion criteria</u>: • Adult hospitalized patients • received at least 1 day of hydroxychloroquine while inpatients • at least 1 positive COVID-19 nasopharyngeal polymerase chain reaction test result <u>Exclusion criteria</u>: Not described <u>N total at baseline</u>: N = 90 I: 53 C: 37 <u>Important characteristics</u>: - Age, mean (SD): 60.1 year (16.7) - Sex, n/N (%) male: 46/90 (51%)	Hydroxychloroquine + azithromycin <u>Treatment regimen:</u> The standard regimen was 400mg of hydroxychloroquine twice on day 1, then 400 mg daily on days 2 through 5. Regimen for azithromycin not described.	Hydroxychloroquine monotherapy <u>Treatment regimen:</u> The standard regimen was 400mg of hydroxychloroquine twice on day 1, then 400 mg daily on days 2 through 5.	<u>Follow-up period:</u> Not specified, but median follow-up was 9 days among those who remained hospitalized	<u>maximum QTc during treatment</u> median (IQR) I: 458 (449-492) ms C: 479.5 (443.5-501.5) ms <u>change in QTc from baseline to maximum QTc</u> median (IQR) I: 23 (10-40) ms C: 5.5 (−14 to 31) ms <u>change in QTc >60 ms</u> Total group: 10/90 (11%) I: 7/53 (13%) C: 3/37 (8%) <u>peak QTc >500 ms</u> Total group: 18/90 (20%) I: 11/53 (21%) C: 7/37 (19%) <u>QT prolongation resulting in TdP:</u> I: 1/53 (2%)	<u>Remarks:</u> - baseline QTc scores were higher in group with hydroxychloroquine monotherapy - 19 patients (21%) had no follow-up electrocardiograms - follow-up period not reported <u>Authors conclusion:</u> In a cohort study of 90 hospitalized patients with coronavirus disease 2019, use of hydroxychloroquine with or without azithromycin for treatment of COVID-19 was associated with frequent QTc prolongation, and those taking

	1st and April 7th 2020. Country: USA Source of funding: Not reported Conflicts of interest: None	- Body mass index, mean (SD): 31.5 (6.6) - Hypertension, n/N (%) yes: 48/90 (53%) - Diabetes mellitus, n/N (%) yes: 26/90 (29%) - Time from symptom onset, median (IQR): 8 (5-12) days *Groups comparable at baseline?* Baseline QTc was higher in hydroxychloroquine (C) group (p<0.001) C-reactive protein and Lactate dehydrogenase were higher in Hydroxychloroquine + azithromycin (I) group				C: 0/37 (0%) QT prolongation resulting in prematurely terminating treatment: total group: 10/90 (11%)	hydroxychloroquine and azithromycin had greater QT prolongation than those taking hydroxychloroquine alone. One patient developed torsades de pointes. Clinicians should carefully weigh risks and benefits if considering hydroxychloroquine and azithromycin, with close monitoring of QTc and concomitant medication usage.
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Rosenberg et al.,	Type of study: Retrospective, multicentre cohort study Setting: 25 high COVID-19 volume hospitals in the New York City (NYC) metropolitan region between March 15 and 28, 2020 Country: New York, US Source of funding: Dufort, Tesoriero	Inclusion criteria: Laboratory confirmed COVID-19 Exclusion criteria: - <24h length of stay - not admitted between 3/15-3/28 - no COVID-19 laboratory confirmation - incomplete chart - chloroquine treatment N total at baseline: N = 1438 Intervention 1: 735 Intervention 2: 271 Intervention 3: 211 Control: 221 Important characteristics: Age, median I1: 61.4 I2: 65.5	I1: Hydroxychloroquine + azithromycin I2: Hydroxychloroquine alone I3: Azithromycin alone *Hydroxychloroquine* Dosage: 200, 400 or 600 mg Frequency: once or twice a day [See Supplementary file} *Azithromycin* Dosage: 200, 250, 400 or 500 mg Methods: oral or IV Frequency: only once, once or twice a day	Neither hydroxychloroquine or azithromycin. Some of them received few other medications, such as aspirin and lisinopril	The date of final follow-up was April 24,2020.	**In-hospital death, n (%) *** I1: 189 (25.7) I2: 54 (19.9) I3: 21 (10.0) C: 28 (12.7) HR (95%CI) I1 vs C: 1.35 (0.76-2.40) HR (95%CI) I2 vs C: 1.08 (0.63-1.85) HR (95%CI) I3 vs C: 0.56 (0.26-1.21) HR (95%CI) I2 vs I3: 1.92 (0.99-3.74)	Remarks: From a sample of 7914 patients with COVID-19 a total of 2362 records were randomly selected, and 1438 were abstracted and included in the analyses. Some of the confidence intervals are wide, which might reflect limited power for some analyses. Authors conclusion: Among patients hospitalized in metropolitan New York with COVID-19, treatment with hydroxychloroquine, azithromycin,or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality.

		I3: 62.5 C: 64.0 Sex, n/N (%) male: I1: 456 (62.0) I2: 158 (58.3) I3: 134 (63.5) C: 110 (49.8) Groups comparable at baseline? Groups were not fully comparable, due to differences in race/ethnicity, age, pre-existing conditions and several clinical severity features within 24h of admission.	Number of prescriptions varied between 1-3 times.				However, the interpretation of these findings maybe limited by the observational design.
Chloroquine, Hydroxychloroquine and Azithromycin							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Saleh, et al. 2020	Type of study: prospective, observational study Setting: March 1st and March 23rd, 2020; in-depth analysis of patients of 3 of 14 hospitals in the Northwell Health system. Country: USA Source of funding: None Conflicts of interest: None	Inclusion criteria: • hospitalized patients • >18 years of age with • PCR confirmed COVID-19 • treated with chloroquine/ hydroxychloroquine ± azithromycin Exclusion criteria: • Patients chronically on hydroxychloroquine for autoimmune diseases such as lupus • those with a documented hypersensitivity to any of the agents • patients that refused the therapies N total at baseline: N = 201 Intervention: 82 Control: 119 Important characteristics:	Monotherapy: either chloroquine or hydroxychloroquine Treatment regimens • Chloroquine: 500mg by mouth 2/day for one day, 500 mg by mouth 1/day for four days Hydroxychloroquine: 400mg by mouth 2/d for one day, 200mg by mouth 2/d for four days	Combination therapy: either chloroquine or hydroxychloroquine + azithromycin Treatment regimens • Chloroquine: 500mg by mouth 2/day for one day, 500 mg by mouth 1/day for four days • Hydroxychloroquine: 400mg by mouth 2/d for one day, 200mg by mouth 2/d for four days • Azithromycin 500 mg by mouth or intravenous daily for five days The decision to treat with chloroquine/hydroxychloroquine ± azithromycin was based on the clinical decision of the admitting physician and pre-described	Follow-up period: Not specified, but minimum 24 days based on reported duration of stay in hospital	maximum QTc during treatment mean ± SD I: 453.3 ± 37.0 ms C:470.4 ± 45.0 ms p = 0.004 change in QTc from baseline to maximum QTc, mean ± SD I: 32.8 ± 28.6 ms C: 41.6 ± 42.7 ms p = 0.19 peak QTc >500 ms I: 7/ (8.6%) C: 11/ (9.2%) P=1.00 QT prolongation resulting in TdP: I: 0/82 (0%) C: 0/119 (0%) QT prolongation resulting in prematurely terminating treatment: total: 7/201 (3.5%) I: 2/82 (2.4%)	Remarks: -this is an analysis on a subsample of a prospective cohort -comparability of intervention groups at baseline is unclear Authors conclusion: The main findings of this study were: (1) the use of chloroquine/hydroxychloroquine and azithromycin led to a significantly greater increase in the corrected QT interval when compared to monotherapy with either chloroquine or hydroxychloroquine, (2) prolongation of the QTc only led to premature discontinuation of these medications in 3.5% of patients and (3) there were no instances of the primary

		Age, mean (SD): 58.5 year (9.1) Sex, n/N (%) male: 115/201 (57%) <u>Baseline QTc intervals:</u> I: 438.9 ± 25.0 ms C: 439.9 ± 24.7 ms p = 0.79 It is unclear whether groups were comparable at baseline.		healthcare system guidelines.		C: 5/119 (4.2%) <u>Arrhythmogenic death:</u> I: 0/82 (0%) C: 0/119 (0%)	endpoint of TdP in the entire cohort**.** Further investigation of this combination therapy is needed, especially given the lack of randomized controlled trials showing efficacy.
Remdesivir							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Wang Yerning et al. 2020	<u>Type of study:</u> Randomised, double-blind, placebo-controlled, multicentre trial <u>Setting:</u> 10 hospitals in Wuhan, Hubei, between Feb 6 and March 12, 2020 <u>Country:</u> China <u>Source of funding:</u> Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing	<u>Inclusion criteria</u>: • Men and non-pregnant women with COVID-19 • Aged at least 18 years • RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less • within 12 days of symptom onset Eligible patients of child-bearing age (men and women) agreed to take effective contraceptive measures (including hormonal contraception, barrier methods, or abstinence) during the study period and for at least 7 days after the last study drug administration	Remdesivir *Treatment regimens* Intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) for a total of 10 days (both provided by Gilead Sciences, Foster City, CA, USA).	Placebo *Treatment regimens* The same volume of placebo infusions for a total of 10 days (provided by Gilead Sciences, Foster City, CA, USA)	<u>Follow-up period:</u> 28 days	**Primary clinical endpoint** <u>Clinical improvement</u> *Defined as a 2-point reduction in patients' admission status on a 6-point ordinal scale, or live discharge from the hospital, whichever came first.* n/N (%) *Day 7:* I: 4/158 (3%) C: 2/78 (3%) *Day 14:* I: 42/158 (11%) C: 18/78 (23%) *Day 28:* I: 103/158 (65%) C: 45/78 (58%) <u>Time to clinical improvement</u> Median (IQR) days I: 21 (13–28) C: 23 (15–28) HR 1.23 (95% CI: 0.87 to 1.75) Subgroup analysis ≤10 days from symptom onset: I: 18 (12–28)	<u>Remarks:</u> - number of patients needed according to power calculation was not reached, because no patients were enrolled after March 12, because of the control of the outbreak in Wuhan. Based on the termination criteria specified in the protocol, the data safety and monitoring board recommended that the study be terminated. - At this stage, the interim analysis was abandoned. When all the other assumptions stayed the same, with the actual enrolment of 236 participants, the statistical power was reduced from 80% to 58%. <u>Authors conclusion:</u> Our trial found that intravenous remdesivir did not significantly improve the

	Science and Technology Project Conflicts of interest: One author has served as non-compensated consultant to Gilead Sciences on its respiratory antiviral program, outside the submitted work. All other authors declare no competing interests.	Exclusion criteria: • pregnancy or breast feeding; • hepatic cirrhosis; • alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal; • known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m²) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis; • possibility of transfer to a non-study hospital within 72 h; • enrolment into an investigational treatment study for COVID-19 in the 30 days before screening N total at baseline: N = 237 Intervention: 158 Control: 79 Important characteristics: Age, median (IQR) I: 66 (57–73) C: 64 (53–70) Sex, n/N (%) male: I: 89/158 (56%) C: 51/78 (65%) Time from symptom onset to starting study treatment, n/N (%) of ≤10 days I: 71/155 (46%) C: 47/78 (60%) *Groups comparable at baseline?*				C: 23 (15–28) HR 1.52 (95% CI: 0.95 to 2.43) **Secondary outcomes** Proportion of patients in each category of the 6-point scale *Day 7* OR: 0.69 (0.41–1.17) *Day 14* OR: 1.25 (0.76–2.04) *Day 28* OR 1.15 (0.67–1.96) All-cause mortality at day 28, n/N (%) I: 22/158 (14%) C: 10/78 (13%) Difference: 1.1% (95% CI: -8.1 to 10.3) Duration of invasive mechanical ventilation, median (IQR) days I: 7·0 (4·0 to 16·0) C: 15·5 (6·0 to 21·0) Difference: –4·0 (–14·0 to 2·0) Duration of oxygen support, median (IQR) days I: 19·0 (11·0 to 30·0) C: 21·0 (14·0 to 30·5) Difference: –2·0 (–6·0 to 1·0) Duration of hospital admission, median (IQR) days I: 25·0 (16·0 to 38·0) C: 24·0 (18·0 to 36·0) Difference: 0·0 (–4·0 to 4·0) **Virological measures** Proportions of patients with viral RNA detected and viral RNA load *Measured by quantitative RT-PCR* Viral load decreased over time similarly in both groups. When adjusted for baseline sputum viral load at enrolment, the remdesivir group	time to clinical improvement, mortality, or time to clearance of virus in patients with serious COVID-19 compared with placebo. We found that this dose regimen of intravenous remdesivir was adequately tolerated but did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19. However, we could not exclude clinically meaningful differences and saw numerical reductions in some clinical parameters. In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies. Note: 6-point ordinal scale: 6 = death; 5 = hospital admission for extracorporeal membrane oxygenation or mechanical ventilation; 4 = hospital admission for non-invasive ventilation or high-flow oxygen therapy; 3 = hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation);

		More patients with hypertension, diabetes, or coronary artery disease in the remdesivir group than the placebo group. More patients in the control group than in the remdesivir group had been symptomatic for 10 days or less at the time of starting remdesivir or placebo treatment, and a higher proportion of remdesivir recipients had a respiratory rate of more than 24 breaths per min. No other major differences in symptoms, signs, laboratory results, disease severity, or treatments were observed between groups at baseline.				showed no significant difference at day 5 from placebo, but a slightly more rapid decline in load (p=0.0672). The cumulative rate of undetectable viral RNA of nasopharyngeal and oropharyngeal swabs by day 28 was 153 (78%) of 196 patients, and the negative proportion was similar among patients receiving remdesivir and those receiving placebo. **Safety outcomes** <u>Treatment-emergent adverse events</u> I: 102/155 (66%) C: 50/78 (64%) <u>Serious adverse events,</u> I: 28/155 (18%) C: 20/78 (26%) <u>Premature discontinuations of study drug</u> I: 18/155 (12%) C: 4/78 (5%)	2 = hospital admission but not requiring oxygen therapy; 1 = discharged or having reached discharge criteria (defined as clinical recovery—ie, normalisation of pyrexia, respiratory rate <24 breaths per minute, saturation of peripheral oxygen >94% on room air, and relief of cough, all maintained for at least 72 h)
Lopinavir–Ritonavir							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Cao et al., 2020	<u>Type of study:</u> Open-label individually randomized controlled trial, from Jan 18, 2020, to Feb 3, 2020 <u>Setting:</u> Jin Yin-Tan Hospital, Wuhan, Hubei Province <u>Country:</u>	<u>Inclusion criteria:</u> • Male / non-pregnant female • Age ≥18y • Diagnostic specimen positive for SARS-CoV-2 on RT-PCR • pneumonia confirmed by chest imaging • oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen	14 days Lopinavir–ritonavir (400 mg and 100 mg, orally) twice a day plus standard care (*for details, see description control group*)	14 days Standard care alone *Standard care:* *As necessary, supplemental oxygen, non-invasive and invasive ventilation, anti-biotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO).*	7, 14 and 28 days Results based on intention-to-treat analysis. 3 patients in the intervention group died between randomization and start of the intervention. Relevant findings from the modified intention-to-treat	Results are provided as median [IQR] unless stated otherwise **Clinical improvement** <u>Time to clinical improvement</u> (days); defined as 2-point improvement on 7-category scale, or discharge from hospital; see most right column for 7 categories): I: 16 [13-17] C: 16 [15-18] *hazard ratio: 1.31 [95% CI 0.95 to 1.85]; P = 0.09), no difference*	<u>Authors conclusion:</u> • Lopinavir–ritonavir treatment added to standard supportive care was not associated with clinical improvement or mortality. • The modified analysis showed modest favour of the treatment group. • The mortality rate (22.1%) indicates that the study population consists of severely ill patients.

	China <u>Source of funding:</u> Major Projects of National Science and Technology on New Drug Creation and Development (2020ZX09201001)+ (2020ZX09201012); the Chinese Academy of Medical Sciences (CAMS) Emergency Project of Covid-19 (2020HY320001); and a National Science Grant for Distinguished Young Scholars (81425001/H0104).	(Fio2) (Pao2:Fio2) at or below 300 mg Hg. <u>Exclusion criteria:</u> • physician decision that involvement in the trial was not in the patient's best interest • presence of any condition that would not allow the protocol to be followed safely • known allergy or hypersen-sitivity to lopinavir–ritonavir • known severe liver disease (e.g., cirrhosis, with an alanine aminotransferase level >5× the upper limit of the normal range or an aspartate amino-transferase level >5× the upper limit of the normal range) • use of medications that are contra-indicated with lopinavir–ritonavir and that could not be replaced or stopped during the trial period (details in appendix at NEJM.org); • pregnancy or breast-feeding, or known HIV infection (concerns about development of resistance to lopinavir–ritonavir if used without combining with other antiretrovirals) • Patients who were unable to swallow received lopinavir–ritonavir through a nasogastric tube. <u>N total at baseline</u>: N = 199 Intervention: 99 Control: 100			analysis excluding these 3 patients (intervention, N=96), is placed in the most right column.	<u>Clinical improvement</u>, n (%) defined as 2-point improvement on 7-point scale Day 7 I: 6/99 (6%) C: 2/100 (2%) *no difference* Day 14 I: 45/99 (46%) C: 30/100 (30%) *difference, 15.5 percentage points; 95% CI, 2.2 to 28.8 = in favour of INT group* Day 28 I: 78/99 (79%) C: 70/100 (70%) *no difference* <u>Clinical deterioration</u> Defined as 1-point increase in 7-point scale HR 1.01 (0.76, 1.34) n*o difference between groups* **Mortality** <u>Mortality at 28-days</u>, n/N (%) I: 19/99 (19%) C: 25/100 (25%) *difference, −5.8 percentage points; 95% CI, −17.3 to 5.7 = in favour of INT group* Earlier (≤12d after onset symptoms): I: 8/99 (19%) C: 13/100 (27%) Later (≥12d after onset symptoms): I: 11/99 (19%) C: 12/100 (23%) <u>Time from randomization to death</u> (days) I: 9 [6-13] C: 12 [6-15] *no difference* **Adverse events** n/N (%) Any adverse events, any grade I: 46/95 (48%)	<u>Modified intention-to-treat analysis:</u> excluding 3 patients in intervention group, with early death after randomization but before start intervention <u>Time to clinical improvement in days</u> (median [IQR]); I: 15 [13-17] C: 16 [15-18] *hazard ratio, 1.39; 95% CI, 1.00 to 1.91 = in favour of intervention group* <u>Sub-group analysis: randomization ≤12 days vs. 12 days after onset illness</u> Time to clinical improvement in both groups not associated with lopinavir–ritonavir treatment, *see manuscript for details* <u>Seven-category ordinal scale:</u> 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6, hospitalized, requiring ECMO, invasive mechanical ventilation, or both;

		Important characteristics: Intervention group: Age (median [IQR]): 58 [50-68] Male: 61 (62%) Control group: Age (median [IQR]): 58 [48-68] Male: 59 (59%) *At baseline*: There were no important between-group differences in demographics, baseline laboratory test results, distribution of ordinal scale scores, or NEWS2 scores at enrolment. *During trial*: systemic glucocorticoids were administered in 33.0% of patients in the intervention group and in 35.7% of patients in the control group.				C: 49/99 (50%) *No difference* Any adverse event, grade 3 / 4 I: 20/95 (21%) C: 11/99 (11%) *More often in intervention* Serious adverse events, grade 3-4 I: 17/95 (18%) C: 31/99 (31%) *More often in controls* **Other** ICU length of stay (days) I: 6 [2-11] C: 11 [7-17] *difference, −5 days; 95% CI,* *−9 to 0 = in favour of INT group* Survivors I: 9 [5-44] C: 11 [9-14] Non-survivors I: 6 [2-11] C: 12 [7-17] Duration invasive mechanical ventilation (days) I: 4 [3-7] C: 5 [3-9] *no difference* Oxygen support (days) I: 12 [9-16] C: 13 [6-16] *no difference* Hospital stay (days) I: 14 [12-17] C: 16 [13-18] *no difference* Time from randomization to discharge (days) I: 12 [10-16] C: 14 [11-16]	7, death.

						difference, 1 day; 95% CI, 0 to 3 = in favour of INT group Mechanical ventilation for respiratory failure during study period, n/N (%) *Non-invasive* I: 10/99 (10%) C: 19/100 (19%) *Invasive* I: 14/99 (14%) C: 18/100 (18%) *More in control group* **Viral loads/clearance:** Viral RNA loads over time *No difference between groups; see manuscript for details* Percentage of patients with detectable viral RNA for SARS-CoV-2 *No difference between groups on any sampling day; see manuscript for details*	
Lopinavir–Ritonavir Arbidol							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Li et al., 2020	Type of study: Randomized controlled study Setting: In Guangzhou Eighth People Hospital, 44 Patients with Mild/Moderate COVID-19 were assigned to 3 groups Country:	Inclusion criteria: 1) age between 18 and 80 years old 2) SARS-CoV-2 infection confirmed by real-time PCR (RT-PCR) from pharyngeal swab 3) mild clinical status, defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever,	- 21 patients received LPV/r (lopinavir/ritonavir) - 16 patients received arbidol monotherapy	- 7 patients received no antiviral medication as control	Length of follow-up: 21 day period Loss-to-follow-up: N/a	**Time to positive-to-negative conversion of SARS-CoV-2 nucleic acid in pharyngeal swab, in days (mean/SD, 95%CI)** LPV/r: 8.70(6.00),(5.89,11.51) Arbidol: 7.63(5.32),(4.79,10.46) Control: 7.00(5.94),(1.50,12.50) **Conversion rate from moderate to severe/critical clinical status (%)** LPV/r: 8/21 (38.1%) Arbidol: 2/16(12.5%) Control: 1/7(14.3%) **At 7 days after initiating treatment**:	Authors conclusion: - "LPV/r or arbidol monotherapy seems little benefit for improving the clinical outcome of mild/moderate COVID-19" - "LPV/r might lead to more adverse events. Due to the limitation of small sample size, further verification is needed in the future" Own noted limitations: - "The sample size is too small to reach the adequate

	China, Guangzhou <u>Source of funding:</u>	respiratory symptoms and pneumonia on imaging [5] 4) the following lab findings: creatinine ≤110μmol/L, creatinine clearance rate (eGFR) ≥60 ml/min/1.73m2, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN, and total bilirubin (TBIL) ≤2 × ULN 5) willing to participate the study and sign the informed consent. <u>Exclusion criteria</u>: 1) known or suspected to be allergic to LPV/r or arbidol; 2) having severe nausea, vomiting, diarrhea or other complaints affecting oral intake or absorption in the digestive tract; 3) taking other drugs that may interact with LPV/r or arbidol; 4) having serious underlying diseases, including but not limited to heart, lung, or kidney disease, liver malfunction, or mental diseases affecting treatment compliance; 5) complicating with pancreatitis or hemophilia prior to the trial; 6) Pregnant or lactating women; 7) having the suspected or confirmed history of alcohol or substance use disorder 8) having participated in other drug trials in the past month 9) deemed otherwise unsuitable for the study by the researchers.				**Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%)** LPV/r: 9/21(42.9%) Arbidol: 10/16(62.5%) Control: 5/7(71.4%) **Antipyresis rate (%)** LPV/r: 8/11(72.7%) Arbidol: 5/9(55.6%) Control: 2/2(100%) **Rate of cough alleviation (%)** LPV/r: 9/19 (47.4%) Arbidol: 4/9(44.4%) Control: 2/6(33.3%) **Rate of improvement on chest CT (%)** LPV/r: 10/19(52.6%) Arbidol: 7/15(46.7%) Control: 6/6 (100%) **At 14 days after initiating treatment:** **Rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid by pharyngeal swab (%)** LPV/r: 16/21(76.2%) Arbidol: 14/16(87.5%) Control: 5/7(71.4%) **Antipyresis rate (%)** LPV/r: 10/11 (90.9%) Arbidol: 9/9 (100%) Control: 2/2 (100%) **Rate of cough alleviation (%)** LPV/r: 17/19 (89.5%) Arbidol: 9/9 (100%) Control: 5/6 (83.3%) **Rate of improvement on chest CT (%)** LPV/r: 16/19(84.2%) Arbidol: 10/15(66.7% Control: 6/6 (100%)	power (1-Beta error > 0.8) in many parameters." - "the study did not enroll severely or critically ill patients, or patients with many comorbidities who are at increased risk of poor outcome and was conducted in only one center." - "the study was not completely blinded, so it is possible to influence the outcome."

		N total at baseline: N = 44 LPV/r: 21 Arbidol: 16 Control: 7 Important characteristics: LPV/r: Male gender (n, %): 11(52.4%) Age, in years (mean, SD, range): 52.2(15.2;27-79) Arbidol: Male gender (n, %): 7(43.7%) Age, in years (mean, SD, range): 49.4(14.6;30-73) Control: Male gender (n, %): 4(57.1%) Age, in years (mean, SD, range): 40.9(12.7;28-62)					
Combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin							

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Hung, et al. 2020	Type of study: multicentre, prospective, open-label, randomised, phase 2 trial Setting: Feb 10 and March 20, 2020; in 6 major hospitals Country: Hong Kong Source of funding: The Shaw-Foundation, Richard and Carol Yu, May Tam Mak Mei Yin, and Sanming Proj ect of Medicine	Inclusion criteria: ● patients admitted to ● hospital age ≥18 years ● virologically confir med ● COVID-19 Exclusion criteria: Not descrbied, but patients excluded due to: 2nd and 3rd degree cardiac arrhythmia, severe depression, and pregnancy N total at baseline: 127 Intervention: 86 Control: 41 Important characteristics: Age, median (IQR): I: 51.0y [31.0-61.3] C: 52.0y [33.5-62.5] Sex, n/N (%) male: I: 45/86 (52%) C: 23/41 (44%) Time from onset to start treatment, days: I: 5 (4-7) C: 4 (3-8) Groups comparable at baseline.	Combination treatment: Recruited and treated <7 days from symptom onset: ● 14 days of oral lopinavir–ritonavir (400 mg/100 mg) every 12 h ● ribavirin 400 mg every 12 h ● subcutane ous injection interferon beta-1b 1 mL (8 million international units [IU]) on alternate days depending on day of drug commencement from symptom onset: day 1–2: 3 doses of interferon beta-1b day 3–4,: 2 doses day 5–6,: 1 dose. Recruited and treated 7-14 days from symptom onset: interferon beta-1b injection was omitted	Lopinavir–ritonavir 14 days of oral lopinavir–ritonavir (400 mg/100 mg) every 12 h	Follow up period: 30 days after discharge Lost to follow-up: No losses	**Virological endpoints:** Time to negative RT-PCR result in nasopharyngeal swab, median [IQR]: I: 7 days [5–11]) C: 12 days [8–15] HR 4·37 [95% CI 1·86–10·24] Time to negative RT-PCR result in all swabs: I: 8 days [6-12] C: 13 days [8-15] **Disease severity, median [IQR]** NEWS2 of 0 maintained for 24h I: 4 days [3–8] C: 8 days [7–9] HR 3.92 [95% CI 1.66–9.23] SOFA of 0: I: 3 days [1-8] C: 8 days [6.5-9] Length of hospital stay: I: 9 days [7–13] C: 14.5 days [9.3–16] HR 2.72 [1.2–6.13] 30-day mortality, n/N (%): I: 0/84 (0%) C: 0/41 (0%) **Safety** Serious adverse events I: 0/84 (0%) C: 1/41 (2%) Duration of nausea: I: median 2 days [IQR 1-2] C: median 2 days [IQR 1-2] Duration of diarrhoea I: median 3 days [IQR 3-3] C: median 3 days [IQR 3-3]	Remarks: This was an open label trial, without placebo group. Authors conclusion: Triple antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin were safe and superior to lopinavir–ritonavir alone in shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19.
Favipiravir Lopinavir/Ritonavir							

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison (C)	Follow-up	Outcome measures and effect size	Comments
Cai, 2020	Type of study: Controlled open label Setting: National Clinical Research Center for Infectious Diseases (The Third People's Hospital of Shenzhen) Country: Shenzhen, China Source of funding: National Science and Technology Major Project (2017ZX10204401, 2018ZX10711001, 2017ZX10103011, 2018ZX09711003, and 2020YFC0841700), Sanming Project of Medicine in Shenzhen (SZSM201412003 and SZSM201512005), Shenzhen Science and Technology Research and Development Project (20200207300000 1), China Postdoctoral Science Foundation	Inclusion criteria: Age 16–75 years Nasopharyngeal swabs samples tested positive for the novel coronavirus RNA Duration from disease onset to enrolment < 7days Willing to take contraception during the study and within 7 days after treatment No difficulty swallowing pills Exclusion criteria: Severe clinical condition (meeting one of the following criteria: a resting respiratory rate greater than 30 per minute, oxygen saturation below 93%, oxygenation index (OI) < 300 mmHg (1 mmHg = 133.3 Pa), respiratory failure, shock, and/or combined failure of other organs that required ICU monitoring and treatment) Chronic liver and kidney disease and reaching end stage Previous history of allergic reactions to FPV or LPV/RTV Pregnant or lactating women Women of a childbearing age with a positive pregnancy test, breastfeeding, miscarriage, or within 2 weeks after delivery Participation in another clinical trial against SARSCoV-2 treatment currently or in the past 28 days N total at baseline: N = 80	**Favipiravir (FPV):** FPV (Zhejiang Hisun Pharmaceutical Co., Ltd., 200 mg per tablet) given orally, 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14. Treatment continued until viral clearance was confirmed or until 14 days had passed. In addition, all participants received IFN-a1b 60 mg (Beijing Tri-Prime Gene Pharmaceutical Co., 30 μg per ampule) twice daily by aerosol inhalation. Standard care included oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, and antiemetic drugs.	**Lopinavir (LPV) / Ritonavir (RTV):** LPV/RTV (AbbVie Inc., 200 mg/50 mg per tablet), given orally. The dose was LPV 400 mg/RTV 100 mg twice daily. Treatment continued until viral clearance was confirmed or until 14 days had passed. In addition, all participants received IFN-a1b 60 mg (Beijing Tri-Prime Gene Pharmaceutical Co., 30 μg per ampule) twice daily by aerosol inhalation. Standard care included oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, and antiemetic drugs.	Length of follow-up: 14 days Loss-to-follow-up: N/a	Median time of viral clearance (days) I: 4 (IQR: 2.5–9) C: 11 (IQR: 8–13) P<.001 Chest CT changes 14 days after start of treatment, n/N (%) *Improved* I: 32/35 (91%) C: 28/45 (62%) *Worsened* I: 1/35 (3%) C: 9/45 (20%) *Constant* I: 2/35 (6%) C: 8/45 (18%)P=.004 Adverse events, n/N (%) *Any adverse event* I: 4/35 (11%) C: 25/45 (56%) P<.001 *Diarrhea* I: 2/35 (6%) C: 5/45 (11%) P=.46 *Vomiting* I: 0/35 (0%) C: 5/45 (11%) P=.06 *Nausea* I: 0/35 (0%) C: 6/45 (13%) P=.03 *Rash* I: 0/35 (0%) C: 4/45 (9%) P=.13 *Liver or kidney injury* I: 1/35 (3%) C: 3/45 (7%) P=.63 *Other* I: 1/35 (3%)	Remark: 56 patients with laboratory-confirmed COVID-19 were screened, 35 were eligible and included in the intervention group. 91 laboratory-confirmed COVID-19 patients who had started treatment with LPV/RTV were screened, 45 were eligible and included in the control group. Authors conclusion: Patients treated with FPV appeared to have faster viral clearance and better chest imaging changes than patients treated with LPV/RTV.

	(2019M660836), Guangdong Special Fund for Science and Technology Innovation Strategy in 2020, and the Science and Technology Emergency Project for the prevention and control of the novel coronavirus by the Department of Science and Technology of Guangdong Province (2020B111105001).	Intervention: 35 Control: 45 <u>Important characteristics</u>: Intervention group (FPV) Median age (IQR) 43 (35.5-59) Male gender: 14/35 (40.0%) Control group Median age (IQR) 49 (36-61) Male gender: 21 (46.7%) Groups comparable at baseline. <u>Also described:</u> • Onset symptoms • Laboratory findings				C: 2/45 (4%) P=1.00	

Favipiravir/ Arbidol							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Chen et al., 2020	Type of study: Prospective, multicenter, open-label, randomized superiority trial in Setting: 3 sites: Hospital of Wuhan University, Wuhan Leishenshan Hospital and The Third People's Hospital of Hubei Province. Country: China Source of funding: This work was supported by the National Key Research and Development Program of China (2020YFC0844400).	Inclusion criteria: • Age ≥18 years • Voluntarily signed informed consent • Initial symptoms were within 12 days • Diagnosed as COVID-19 pneumonia. Exclusion criteria: • Allergic to favipiravir or arbidol • ALT/AST increased to over 6 times of normal upper range, or with Child-Pugh • Severe/critical patients whose expected survival time <48 hours • Female in pregnancy • HIV infection • Considered unsuitable by researchers N total at baseline: N = 240 Intervention: 120 (analysed, n=116) Control: 120 Important characteristics: Age <65y n (%): I: 87 (75%) C: 79 (66%) Sex, n/N (%) male: I: 59/116 (51%) C: 51/120 (43%) Groups comparable at baseline. Also described:	**Favipiravir:** routine treatment + favipiravir tablets (1600mg each time on the first day, twice a day; 600mg each time from the second day to the end of the experiment, twice a day). The course of treatment in both groups was 7-10 days. If necessary, the treatment time could be extended to 10 days according to the judgment of researchers.	**Arbidol:** routine treatment + arbidol (200mg each time, 3 times a day, from the first day to the end of the trial). The course of treatment in both groups was 7-10 days. If necessary, the treatment time could be extended to 10 days according to the judgment of researchers.	Length of follow-up: 7 days (primary outcome) 14 days (further follow-up) Loss-to-follow-up: No loss to follow up Intention-to-treat analysis: Intervention: N=120 allocated N=4 withdrew consent N=116 completed treatment N=116 analyzed Control group: N=120 allocated N=112 completed treatment N=120 analyzed	Clinical recovery rate at day 7, n/N (%): *Total patients - recovered:* I: 71/116 (61%) C: 62/120 (52%) P=0.14 *Moderate patients:* I: 70/98 (71%) C: 62/111 (56%) P=0.02 *Severe or critical patients:* I: 1/18 (6%) C: 0/9 (0%) P=0.47 *Patients with hypertension and/or diabetes*: I: 23/42 (55%) C: 18/35 (52%) P=0.77 Presence of fever I: 71/116 (61.2%) C: 74/120(61.7%) *No difference* Presence of cough I: 78/116 (67.2%) C: 73/120 (60.8%) *No difference* Duration of fever & cough relief latency *Latency to fever reduction and cough relief in the favipiravir group was significantly shorter than that in the arbidol group (P<0.0001).* Incidence auxiliary oxygen therapy, n/N (%) I: 21/116 (18%) C: 27/120 (23%) P=0.40 *Patients with hypertension and/or diabetes:* I: 9/42 (21%) C: 10/35 (29%) P=0.47	Remark: Inclusion criteria: initial symptoms were within 12 days before inclusion. No information about duration of symptoms onset and potential difference between groups. Authors conclusion: Among patients with confirmed COVID-19, favipiravir, compared to arbidol, did not significantly improve the clinically recovery rate by 7 days. Favipiravir significantly improved time-to-relief for fever and cough. Antiviral-associated adverse effects associated with favipiravir are mild and manageable.

		• % moderate/severe/critical cases • Comorbidities • Symptoms • Laboratory findings				<u>All-cause mortality, n/N (%)</u> I: 0/116 (0%) C: 0/120 (0%) <u>Dyspnea after taking medicine, n/N (%):</u> I: 4/116 (3%) C: 14/120 (12%) P=0.02 <u>Respiratory failure, n/N (%)</u> I: 1/116 (1%) C: 4/120 (3%) P=0.37 <u>Antiviral-associated adverse effects, n/N (%):</u> *Abnormal LFT* I: 10/116 (9%) C: 12/120 (10%) P=0.72 *Raised serum uric acid* I: 16/116 (14%) C: 3/120 (3%) P=0.002 *Psychiatric symptom reactions* I: 5/116 (4%) C: 1/120 (1%) P=0.11 *Digestive tract reactions* I: 16/116 (14%) C: 14/120 (12%) P=0.62	

Favipiravir, Baloxavir Marboxil, Lopinavir/Ritonavir							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Lou et al., 2020	Type of study: Exploratory randomized controlled trial (!:1:1:) Setting: Hospitalized COVID-19 patients were randomized in the clinical trial and was initiated on February 3, 2020 in the First Affiliated Hospital, Zhejiang University School of Medicine. Country: Zhejiang, China Source of funding: Not reported.	Inclusion criteria: • Adults 18 – 85 years • Confirmed COVID-19 (by real time RT-PCR) • No difficulty in swallowing oral drugs • Exclusion criteria: • Known allergies • Critical illness : respiratory failure and mechanical ventilation; shock; other organ failure requiring ICU monitoring and treatment; • Renal insufficiency • Abnormal ALT or AST levels N total at baseline: N = 29 Baloxavir: n=10 Favipiravir: n=9 Control: n=10 Important characteristics: • Baloxavir group Mean age: 53.5 ± 12.5 Male gender: 7/10 (70%) • Favipiravir group Mean age: 58.0 ± 8.1 Male gender: 7/9 (77%) • Control group Mean age: 46.6 ± 14.1 Male gender: 7/10 (70%) Groups comparable at baseline? Control group is slightly younger.	Baloxavir marboxil: • 80 mg once a Day 1 and Day 1 4; for patients who are still positive in virological test, they can be given again on Day 7, no more than three additional doses + antiviral treatment Favipiravirl: • The first dose was 1600 mg or 2200mg orally, followed by 600 mg each time, three 5 times a day, and the duration of administration was not more than 14 days + antiviral treatment	Control: • The existing antiviral treatment included lopinavir/ritonavir (400mg/100mg, bid, po.) or 8 darunavir/cobicistat (800mg/150mg, qd, po.) and arbidol (200mg, tid, po.) • All of them were used in combination with interferon-α inhalation (100,000 iu, tid or qid)	Length of follow-up: 14 days after the initiation of the trial Loss-to-follow-up: Not reported One patient in the baloxavir marboxil group, and two patients in the favipiravir group were transferred to ICU within seven days after trial initiation.	Negative test results by day 14: No differences in hematological or renal toxicity was seen between the groups. • Total group: 24/29 (82.8%) • Baloxavir: 7/10 (70%) • Favipiravir: 7/9 (77%) • Control: 10/10 (100%) Viral load was monitored every day for each patient Authors stated: *the results indicate that the addition of either baloxavir or favipiravir did not appear to improve the medium T1/2 time for patients to achieve undetectable viral RNA compared to the control group.* Drug concentrations: To determine whether the apparent lack of benefits by the addition of either baloxavir or favipiravir is related to their pharmacological exposure in the COVID-19 patients, drug concentrations were measured in the patients Adverse events: Most frequent adverse events occurring in the study population were similar among all groups.	Comments: • The number of patients were rather limited. • The treatment scheme and medication time before the initiation of the trial was different among the patients, which makes their progression of the disease at the beginning of the trial quite different. Author's conclusion: This exploratory trial does not prove that baloxavir marboxil was effective in COVID-19 Patients. Because the free drug concentration of baloxavir marboxil is far below than its EC_{50} values (more than 100 times). Under the current dosage, the insufficient exposure of favipiravir also resulted in no additional antiviral benefit by adding favipiravir to the existing standard treatment.

Meplazumab							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Bian, 2020	Type of study: Open-label controlled add-on clinical trial (not randomized) Setting: Hospital of Fourth Military Medical University Country: Xi'an, China Source of funding: National Science and Technology Major Project	Inclusion criteria: • Men and women 18-78 year • Patients with common, severe or critical COVID-19 pneumonia (laboratory and clinical diagnosed) • Subjects must understand the study and be willing to participate Exclusion criteria: • Allergic reactions or a history of allergy to any of the ingredients • Patients not suitable to participate by judgment of the investigator. N total at baseline: N = 28 Intervention (I): 17 (meplazumab) Control (C): 11 (hospitalized patients who met inclusion criteria and with no exclusion criteria signs) Important characteristics: Intervention group Median age (IQR) 51 (49-67) Male gender: 11 (64.7%) Control group Median age (IQR) 64 (43-67) Male gender: 5 (45.5%) Groups comparable at baseline.	10 mg meplazumab administered on day 1, day 2 and day 5 by intravenous infusion within 60-90 minutes. * + standard care (for details see description control group) *11 patients received 3 doses, 6 patients received 2 doses.	Recommended therapy according to the Diagnosis and Treatment for 2019 Novel Coronavirus Diseases, including antiviral treatment, glucocorticoid treatment and antibiotic treatment.	Length of follow-up: There were 18 study visits from baseline to day 28. Loss-to-follow-up: N/a	**Overall improvement rate (%)** *Categorized according to the diagnosis and treatment 2019 Novel Coronavirus Diseases* *Day 7* I: 3/17 (17.6) C: 0/11 (0) *Day 14* I: 8/17 (47.1) C: 3/11 (27.3) *Day 21* I: 14/17 (82.4) C: 6/11 (54.4) *Day 28* I: 16/17 (94.1) C: 9/11 (81.8) **Improvement on chest radiographic analysis** *% of patients that improved >50% compared with baseline* *(also data on 25%, 25-50% available)* *Day 7* I: 5.9% C: 0% *Day 14* I: 47.1% C:0% *Day 21* I: 70.6% C: 27.3% *Day 28* I: 82.4% C: 54.5% **Clearance of the virus (%)** *Evaluated by negative-conversion rate* *Day 7* I: 13/17 (76.5) C: 3/11 (27.3) *Day 14* I: 16/17 (94.1)	Remarks: -this was **not** a randomized controlled trial Authors conclusions: The adding of meplazumab 20–30 mg in patients with COVID-19 who have received recommended treatment, increased the virological clearance rate, promoted the recovery of chest radiographic and lymphocytopenic, decreased the inflammation index (CRP), accelerating the improvement of disease without serious adverse event.

						C: 6/11 (54.4) *Evaluated by time to negative (median days)* I: 3 C: 13 HR (95%CI): 0.37 (0.155-0.833) P-value: 0.014 **Lymphocyte count <0.8 (%)** *Baseline* I: 64.7% C: 72.7% *Day 7* I: 29.4% C:54.5% *Day 14* I: 17.6% C: 36.4% *Day 21* I: 5.9% C: 27.3% *Day 28* I: 17.6% C: 27.3% **ALT and/or AST ≥ 2 ULN (%)** I: 2/17 (11.8) C: 2/11 (18.2) No deaths were reported.	

Tocilizumab							
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment**		**Follow-up**	**Outcome measures and effect size**	**Comments**
Sciascia et al. 2020	Type of study: pilot prospective open, single-arm Setting: multicentre study, 4 hospitals of ASL Città di Torino; Country: Italy Source of funding, conflicts of interest: Funding not reported; no competing interests reported	Hospitalised critically ill adult patients • PCR-confirmed COVID-19 infection • Pulmonary involvement, assessed either by oxygen saturation <93% if breathing ambient air, or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) <300 mm Hg • markedly deranged pro-inflammatory and pro-thrombotic profile (at least 3 of the following): C-reactive protein (CRP) > x 10 normal values; ferritin >1000 ng/ml; D-dimer x 10 normal values; LDH x 2 the upper limits Exclusion criteria: Not specified N total at baseline: N = 63 Important characteristics: Age, mean (SD): 62.6±12.5 Sex, n/N (%) male: 56/63 (89%)	Tocilizumab (TCZ) • Either intravenous (8 mg/kg; n=34) or Subcutaneous (324 mg; n=29). • A second administration within 24 h was given in 52/63 patients. • The route of administration was not pre-determined but disposed according to the drug availability		Follow-up duration: At least 14 days after admission	Mortality at 14 days: Total: 7/63 (11%) Intravenous: 4/31 (12.9%) Subcutaneous: 3/29 (10.3%) *diff: -2.6; OR 1.16 (95% CI: 0.24-5.65), p=0.86* Time from admission to death (n=7): mean 5±1.5 days Severe-to-moderate adverse events: None reported Laboratory parameters: *Improvement*: ferritin, C-reactive protein, D-dimer and lymphocytes count *No improvement*: LDH IL-6 levels: increase, most evident after 14 days Respiratory parameters: *Pa02/Fi02* (mean±SD): improved, albeit heterogeneous at follow-up: admission: 152±53; day 7: 283.73±115.9, day 14: 302.2±126, p<0.05) *Mechanical ventilation:* Admission: 5 patients (of which 1 died on day 6); Day 14: 2 patients Death: D-dimer levels at baseline	Remarks: -This was a prospective, single arm study (not controlled, not randomized). -Route of administration was heterogeneous and based on availability -Background therapies, including antiviral agents, were not protocolled Authors conclusion: **I**n hospitalised adult patients with severe COVID-19, TCZ might be considered a safe option. An improvement in respiratory and laboratory parameters was also observed. Future controlled trials in patients with severe illness are urgently needed to confirm or exclude the possibility of a treatment benefit with IL-6 target therapy.

						(HR 5.01; 95%CI 1.04–29.17) predictor of death. IL-6 levels at baseline, NO predictor of death. Survival: *use of TCZ within 6 days from admission associated with increased likelihood of survival* (HR 2.2 95% CI 1.3–6.7, p<0.05	
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Colaneri, et al. 2020	Type of study: Retrospective matched study Setting: Single centre Country: Italy Source of funding: This research received no external funding	Inclusion criteria: patients with confirmed diagnosis of COVID-19 disease referred to the IRCCS Policlinico San Matteo Hospital of Pavia, Italy from February 2020 Exclusion criteria: Patients with >65% missing data N total at baseline: N = 42 Intervention: 21 Control: 21 Important characteristics: Age, median (IQR): I: 62.33 (18.68) C: 63.74 (16.32) Sex, n/N (%) male: I: 19 (90.5) C: unknown Hospitalization, days, median (IQR): I: 2.00 (6) C: 14.00 (4) Groups comparable at baseline.	SOC + Tocilizumab: (The first administration was 8 mg/kg (up to a maximum 800 mg per dose) of Tocilizumab intravenously, repeated after 12 h if no side effects were reported after the first dose)	Standard of Care (SOC): Treatment with a combination of hydroxychloroquine (200 mg bid), azithromycin (500 mg once), prophylactic dose of low weight heparin, and methylprednisolone (a tapered dose of 1 mg/kg up to a maximum of 80 mg) for 10 days	Follow-up period: 7 days	**ICU admission**, OR (95% confidence interval) 0.11 (0.00 and 3.38) p = 0.22 **7-day mortality**, OR (95% confidence interval) 0.78 (0.06 and 9.34) p = 0.84 **Laboratory data,** median (IQR): LDH, 100 U/L day 7: I: 430 (169) C: 397 (237) Lymphocytes, 10^9/mL day 7: I: 0.96 (0.62) C: 0.90 (0.80) Neutrophils, 10^9/mL day 7: I: 5.73 (6.37) C: 7.44 (6.70) ALT, U/L day 7: I: 72.00 (33.00) C: 40.00 (44.50) CRP, mg/L day 7: I: 0.63 (0.45) C: 6.07 (16.42) PLT, 109/mL day 7: I: 296 (174.00) C: 313 (128.50)	Remarks: This is a retrospective analysis. Subjects were matched, based on propensity score. Variables inserted in the final propensity score matching model were sex, age, LDH, and neutrophils. Authors conclusion: TCZ administration did not reduce ICU admission or mortality rate in a cohort of 21 patients. Additional data are needed to understand the effect(s) of TCZ in treating patients diagnosed with COVID-19

Baricitinib							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Cantini et al., 2020	Type of study: Open-label, non-randomized pilot trial Setting: March 16 to 30, 2020 Country: Italy Source of funding: Partly supported by the Italian Ministry of Health "Ricerca Corrente " Linea 1	Hospitalized patients with moderate COVID-19 pneumonia, older than 18 years Inclusion criteria: ● SARS-Co-V2 positive nasal/oral swabs ● presence of at least 3 of the following symptoms: fever, cough, myalgia, fatigue ● evidence of radiological pneumonia Exclusion criteria: ● history of thrombophlebitis ● latent tuberculosis infection ● pregnancy/lactation N total at baseline: N = 24 Intervention: 12 Control: 12 Important characteristics: Age, median (IQR): 63.5y (57.5 to 72.2) Sex, n/N (%) male: 10/12 (83%) Groups comparable at baseline.	standard of care therapy (lopinavir/ritonavir tablets 250 mg/bid and hydroxychloroquine 400 mg/day/orally for 2 weeks) + baricitinib tablets 4 mg/day Antibiotics were scheduled only in the case of suspected bacterial infection.	standard of care therapy (lopinavir/ritonavir tablets 250 mg/bid and hydroxychloroquine 400 mg/day/orally for 2 weeks) Antibiotics were scheduled only in the case of suspected bacterial infection.	Follow-up period: Current study follow-up of 2 weeks. Additional follow-up of 6 weeks to monitor longer term effects mentioned, but not reported	Adverse events (AE): No serious AEs reported Therapy withdrawn: I: 1/12 (8.3%; after 10 days) C: not reported Bacterial/opportunistic infections, trombo-flebitis, hematologic toxicity I: 0/12 C: 0/12 ICU transfer: I: 0/12 (0%) C: 4/12 (33%) Discharged at 2 weeks: I: 7/12 (58%) C: 1/12 (8%) Fever, SpO2, PaO2/FiO2, CRP, and MEWS, baseline compared to 2-weeks: Statistically greater improvement in intervention group compared with controls (p: 0.000; 0.000; 0.017; 0.023; 0.016, respectively). Other clinical, laboratory and respiratory parameters, baseline compared to 2-weeks: no statistical difference between interv ention and control group.	Remarks: This study was a open-label, non-randomized pilot trial. Because of study limitations and low statistical power, the results should be interpreted with caution. The therapy withdrawn (n=1; due to consistent transaminases elevation (AST: 267 U/L; ALT: 298 U/L)) was probably due to the antiviral therapy rather than to the baricitinib treatment, which is mainly renal-metabolized. Authors conclusion: These preliminary results on 12 patients with moderate COVID19 pneumonia confirmed the safety of baricitinib therapy in a clinical context different from rheumatoid arthritis.

Corticosteroid							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Fang et al., 2020	Type of study: Retrospective, observational study Setting and country: Branch of Anhui Provincial Hospital Funding and conflicts of interest: Funding not reported; authors declared no conflicts of interest	Inclusion criteria: • confirmed COVID-19 infection • admitted to the hospital Exclusion criteria: not reported N total at baseline: 78 Patients were divided into 'general group' and 'severe group' Important characteristics: ***General group (N=55):*** Age (mean ± SD): I: (N=9): 40.2 ± 12.6 C:(N=46): 39.9 ±15.5 Male/N (%): I: (N=9): 5 (55.6) C:(N=46): 22 (47.8) ARDS n/N (%): I: 0/9 C: 0/46 Groups comparable at baseline. ***Severe group (N=23):*** Age (mean ± SD): I: (N=16): 60.6 ±13.6 C: (N=7): 54.3 ±15.4 Male/N (%): I: (N=16): 12 (75) C: (N=7): 5 (71.4) ARDS n/N (%): I: 8/16 (50%)	***General group:*** Treatment + Corticosteroid: oral prednisolone (median hydrocortisone-equivalent dose, 237.5 mg/day (IQR, 206.3-300.0 mg/day) for a median duration of 7 days (IQR, 5.5-8.0 days) ***Severe group:*** Treatment + Corticosteroid: intravenous prednisolone (median hydrocortisone-equivalent dose, 250.0 mg/day (IQR, 250.0-250.0 mg/day) for a median duration of 4.5 days (IQR, 3.5-5.8 days).	Treatment without corticosteroid therapy	Length of follow-up: Unclear Loss-to-follow-up: n.a.: retrospective cohort study	Virus clearance *defined as time to SARS-CoV-2 RNA clearance (days), mean ± SD:* **General group (N=55):** I: (N=9): 17.6 ± 4.9 C:(N=46): 18.7 ±7.7 P=0.667 **Severe group (N=23):** I: (N=16): 18.8 ±5.3 C:(N=7): 18.3 ±4.2 P=0.84	Remarks: -this is a retrospective, observational study -due to differences in baseline characteristics (more severe patients were treated with corticosteroids, leading to differences between groups regarding e.g. age, comorbidities and laboratory findings), patients were divided into a general and a severe group with separate data analysis. Authors conclusion: *[after summarizing another retrospective study]* In conclusion, low-dose corticosteroid therapy may not delay viral clearance in patients with COVID-19; however, this still needs to be confirmed by well-designed and large-scale RCTs with a longer follow-up duration.

		C: 1/7 (14%) P=0.176 Groups comparable at baseline.					
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Wang et al., 2020	Type of study: Retrospective cohort study Setting: The Third People's Hospital of Hubei Province Country: China Source of funding: No funding. Conflicts of interest: The authors have declared that no competing interest exists.	Inclusion criteria: people aged >18 years old with laboratory (PT-PCR) confirmed COVID-19 infection, admitted to the hospital between January 18th, and February 28th, 2020. Exclusion criteria: patients transferred to other hospitals or with no abnormal radiological findings. N total at baseline: 115 (73 corticosteroid group, 42 non-corticosteroid group) Important characteristics: Age (range): Corticosteroid: 61(42-68) Non-corticosteroid: 51(34-65) Male/N (%): Corticosteroid: 37/73 (50.7%) Non-corticosteroid: 21(50%) Comorbidities No. (%): Corticosteroid: 34(46.6%) Non-corticosteroid: 11(26.2%) *"The corticosteroid group had more comorbidities, lower lymphocyte count and higher LDH. A multivariate analysis was performed to adjust for the confounding effect of disease severity."*	**Corticosteroid:** 73 cases received corticosteroid of various dosages. Of these, 31 were non-critical cases and 42 were critical.	**Non-corticosteroid:** 42 cases did not receive corticosteroids. It is not described how many were critical/non-critical.	Length of follow-up: Follow-up time was counted until the occurrence of either mortality or intensive care unit submission. Loss-to-follow-up: Not applicable (retrospective study)	Adverse outcome (mortality or intensive care submission): Corticosteroid: 24/73 (32.9%) Non-corticosteroid: 5/42 (11.9%) Authors: "Patients who were treated with corticosteroid were found to have a 2.155-fold increased risk of either ICU admission or mortality, although not statistically significant."	Remarks: The results can be biased by incomparable baseline cohorts, or unknown confounders. Author's conclusion: "No evidence suggests that adult patients with COVID-19 will benefit from corticosteroids in this study. Considering the severe complications triggered by glucocorticosteroid such as psychosis, viraemia, diabetes and avascular necrosis, the patients might be more likely to be harmed with such treatment. More studies are need to evaluate the clinical curative effect, as well as the appropriate dosages and duration of corticosteroid treatment in COVID-19."

Methylprednisolone							
Study reference	**Study characteristics**	**Patient characteristics**	**Intervention (I)**	**Comparison / control (C)**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Wang Ying et al, 2020	Type of study: Retrospective cohort study Setting: At the isolation ward of Union Hospital of Huazhong University of Science and Technology from January 20 to February 25, 2020. Country: Wuhan, China Source of funding: None Conflicts of interest: None	Inclusion criteria: Severe cases with COVID-19 pneumonia. The clinical classification is based on the coronavirus pneumonia diagnosis and treatment plan (trial version 5) developed by the National Health Committee of the People's Republic of China. Severe case was defined when any of the following criteria was met: (1) respiratory distress, respiratory rate per min ≥ 30; (2) in the resting state, means oxygen saturation ≤ 93%; (3) arterial blood oxygen partial pressure/oxygen concentration ≤ 300 mmHg Exclusion criteria: Not reported N total at baseline: N = 46 Intervention: 26 Control: 20 Important characteristics: Age (median years (IQR))) I: 54 (48-63) C: 53 (48-63) Gender: (M, %) I: 38	Low-dose methylprednisolone treatment with the dosage of 1–2 mg/kg/day for 5–7 days via intravenous injection. The specific dosage and duration of methylprednisolone for the patients were determined according to the clinical manifestations, leukocyte count, lymphocyte count, inflammatory index, and lesion range. Oxygen therapy, antiviral therapy (a-interferon, Kaletra [lopinavir/ritonavir]), immunoenhancement therapy (thymosin), prevention of bacterial infection, relieving cough eliminating phlegm, and nutritional support were commonly used for all of the 46 patients.	No methylprednisolone treatment Oxygen therapy, antiviral therapy (a-interferon, Kaletra [lopinavir/ritonavir]), immunoenhancement therapy (thymosin), prevention of bacterial infection, relieving cough eliminating phlegm, and nutritional support were commonly used for all of the 46 patients.	Follow-up period: Not reported, but minimum of 14 days (Third CT scan was performed at day 14).	Mortality (%) I: 2 (7.7) C: 1 (5) P-value = 0.714 Length of ICU hospitalization (IQR) I: 8 (6-9) C: 15 (9-19) P-value: <0.001 Length of hospitalization (IQR) I: 14 (11-16) C: 22 (18-26) P-value: <0.001 Mechanical ventilation (%) I: 3 (11.5) C: 7 (35) P-value: 0.05 SpO_2 Patients in the intervention group had faster SpO_2 improvement. Chest CT In terms of chest CT scan on day 7 and 14, the absorption degree of the focus was significantly better in the patients with methylprednisolone treatment. Inflammatory markers Patients in the intervention group had a faster decrease in C-reactive protein and interleukin-6, compared to control. No significant differences were observed in other inflammatory markers.	Remarks: Benefiting from condition monitoring and refined management, no serious methylprednisolone treatment-induced complications were observed in the present cohort. Authors conclusion: In conclusion, early, low-dose and short-term application of methylprednisolone was associated with better clinical outcomes in severe patients with COVID-19 pneumonia, and should be considered before the occurrence of ARDS. Nevertheless, future randomized controlled trials are desperately in need to confirm these findings and further study the mid- and long-term outcomes after discharge.

		C: 50 <u>Respiratory frequency, per min (IQR)</u> I: 28(21 -36) C: 24(20-30) Respiratory frequency at admission differed significantly between the treatment groups. No other differences exist at admission.					

Overzichtstabel van casestudies, niet gerandomiseerde studies en retrospectieve studies naar medicamenteuze behandelingen van COVID-19.
Deze tabel laat een overzicht zien van de gevonden casestudies, niet-gerandomiseerde en retrospectieve studies naar medicamenteuze behandelingen weer van COVID-19.De studies staan gerangschikt op middel en datum van publicatie. De literatuur wordt dagelijks bekeken en zo nodig wordt de tabel aangevuld.

Medication/treatment	Published	1st author	Title	Journal	Status
Updated: May 14, 2020 (* indicates a new added article)					
1.1 Chloroquine/Hydrochloroquine					
Hydrochloroquine	May 07, 2020	Geleris	Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19	The New England Journal of Medicine	Peer-reviewed (published
Hydrochloroquine Azithromycin	March 30, 2020	Molina	No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection	Médecine et maladies infectieuses	Published
Hydrochloroquine Azithromycin	April 11, 2020	Gautret	Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study	Travel Medicine and Infectious Disease	Peer-reviewed (published)
	April 24, 2020	Chorin	The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin	Nature Medicine	Published and has not been certified by peer review
	May 05, 2020	Million	Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France	Travel Medicine and Infectious Disease	Peer-reviewed (published)
	May 11, 2020	Davido	Hydroxychloroquine plus azithromycin: a potential interest in reducing in-hospital morbidity due to COVID-19 pneumonia (HI-ZY-COVID)?	medRxiv	Preprint and has not been certified by peer review

Chloroquine	April 29,2020	Van den Broek	Chloroquine-induced QTc Prolongation in COVID-19 Patients	Netherlands Heart Journal	Peer-reviewed (published)
Chloroquine and Clarithromycin	April 24, 2020	Millán-Oñate	Successful recovery of COVID-19 pneumonia in a patient from Colombia after receiving chloroquine and clarithromycin	Annals of Clinical Microbiology and Antimicrobials	Peer-reviewed (published)
Chloroquine and tocilizumab	***May 04, 2020**	**Xu**	**Combined treatment of tocilizumab and chloroquine on severe COVID-19: a case report**	**QJM: An International Journal of Medicine**	**Published review status unknown**
1.2. Remdesivir					
Remdesivir	April, 2013	Hillaker	Delayed Initiation of Remdesivir in a COVID-19 Positive Patient	Journal of the American College of Clinical Pharmacy	Peer-reviewed (published)
	April 10, 2020	Grein	Compassionate Use of Remdesivir for Patients with Severe Covid-19	The New England Journal of Medicine	Peer-reviewed (published)
1.3. Azitromycine					
1.4. Lopinavir/Ritonavir					
Lopinavir/Ritonavir Arbidol	March 11, 2020	Deng	Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study	Journal of Infection	Peer-reviewed (published)
	April, 2020	Zhu	Arbidol Monotherapy is Superior to Lopinavir/ritonavir in Treating COVID-19	Journal of Infection	Peer-reviewed (published)
Lopinavir/Ritonavir	March, 2020	Ye	Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019	European Review for Medical and Pharmacological Science	Peer-reviewed (published)
Lopinavir/Ritonavir	March 19, 2020	Nicastri	Coronavirus disease (COVID-19) in a paucisymptomatic patient: epidemiological and clinical challenge in	Eurosurveillance	Peer-reviewed (published)

			settings with limited community transmission, Italy, February 2020		
Lopinavir/Ritonavir	March 31, 2020	Cheng	Lopinavir/ritonavir did not shorten the duration of SARS CoV-2 shedding in patients with mild pneumonia in Taiwan	Journal of Microbiology, Immunology and Infection	Peer-reviewed (published)
1.5 Multiple antiviral drug treatments					
Chloroquine **Arbidol** **Lopinavir/Ritonavir**	April 24, 2020	Huang	Chloroquine, arbidol (umifenovir) or lopinavir/ritonavir as the antiviral monotherapy for COVID-19 patients: a retrospective cohort study	Research Square	Preprint and has not been certified by peer review
Lopinavir/Ritonavir **Ribavirin** **Interferon alfa-1b**	April 30, 3030	Zhang	The novel coronavirus (COVID-19) pneumonia with negative detection of viral ribonucleic acid from nasopharyngeal swabs: a case report	BMC Infectious Diseases	Peer-reviewed (published)
2.1 Ribavirine					
2.2 Favipiravir					
2.3 Convalescent plasma					
Convalescent plasma	March 23, 2020	Duan	The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study	medRxiv	Preprint and has not been certified by peer review
	April 06, 2020	Duan	Effectiveness of convalescent plasma therapy in severe COVID-19 patients	PNAS	Peer-reviewed (published)
	March 27, 2020	Shen	Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma	JAMA	Preliminary communication
	March 31, 2020	Zhang	Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection	Chest	Peer-reviewed (published)
	April 2, 2020	Ahn	Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea	J Korean Med Sci.	Peer-reviewed (published)

	April 11, 2020	Pei	Convalescent Plasma to Treat COVID-19: Chinese Strategy and Experiences	medRxiv	Preprint and has not been certified by peer review
	April 15, 2020	Ye	Treatment with convalescent plasma for COVID-19 patients in Wuhan, China	Journal of Medical Virology	Peer-reviewed (published)
3.1 Meplazumab					
3.2 Siltuximab					
Siltuximab	April 3, 2020	Gritti	Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support	medRxiv	Preprint and has not been certified by peer review
3.3 Tocilziumab					
Tociliziumab	March 27, 2020	Michot	Tocilizumab, an anti-IL6 receptor antibody, to treat Covid-19-related respiratory failure: a case report	Annals of Oncology	Peer-reviewed (published)
	March 28, 2020	Ferray	A Case of Novel Coronavirus Disease 19 in a Chronic Hemodialysis Patient Presenting with Gastroenteritis and Developing Severe Pulmonary Disease	American Journal of Nephrology	Published
	March, 2020	Xu	Effective Treatment of Severe COVID-19 Patients with Tocilizumab	chinaRxiv	Preprint and has not been certified by peer review
	March 31, 2020	Cellina	Favorable Changes of CT Findings in a Patient With COVID-19 Pneumonia After Treatment With Tocilizumab	Diagnostic and interventional imaging	Published
	April 02, 2020	Mihai	COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD	Annals of the Rheumatic Diseases	Peer-reviewed (published)
	April 06, 2020	Luo	Tocilizumab treatment in COVID-19: A single center experience	Journal of Medical Virology	Published

	April 13, 2020	De Luna	Rapid and Severe Covid-19 Pneumonia With Severe Acute Chest Syndrome in a Sickle Cell Patient Successfully Treated With Tocilizumab	American Journal of Hematology	Preprint (peer-reviewed)
	April 16, 2020	Di Giambenedetto	Off-label Use of Tocilizumab in Patients with SARS-CoV-2 Infection	Journal of Medical Virology	Peer-reviewed (published)
	April 21, 2020	Morisson	Letter to the Editor: Acute hypertriglyceridemia in patients with COVID-19 receiving tocilizumab	Journal of Medical Virology	Peer-reviewed (published)
	April 25, 2020	Radbel	Use of Tocilizumab for COVID-19-Induced Cytokine Release Syndrome A Cautionary Case Report	Chest	Peer-reviewed (published)
	May 05, 2020	***Alattar**	**Tocilizumab for the treatment of severe coronavirus disease 2019**	**Journal of Medical Virology**	**Peer-reviewed (published)**
	May 12, 2020	***Sánchez-Montalvá**	**Early outcomes of tocilizumab in adults hospitalized with severe COVID-19 An initial report from the Vall d'Hebron COVID-19 prospective cohort study.**	**medRxiv**	**Preprint and has not been certified by peer review**
4 Immunomodulerende middelen					
	March 21, 2020	Cao	High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019	Open Forum Infectious Disease	Published
	April 12, 2020)	Zhong	Clinical characteristics and immunosuppressants management of coronavirus disease 2019 in solid organ transplant recipients	American Journal of Transplantation	Preprint (peer-reviewed)
	April 16, 2020	Iwabuchi	Therapeutic potential of ciclesonide inahalation for COVID-19 pneumonia: Report of three cases	Journal of Infection and Chemotherapy	Published (not clearly stated whether this paper has been certified by peer review)
Eculizimab	April 27, 2020	Diurno	Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience	European Review for Medical and Pharmacological Science	Peer-reviewed (published)
5 Multiple treatments					

Multiple treatments	April 03, 2020	Liu	Successful Treatment of Severe COVID-19 Pneumonia in a Liver Transplant Recipient	American Journal of Transplantation	Peer-reviewed (published)
	April 09, 2020	Novi	COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role?	Multiple Sclerosis and Related Disorders	Peer-reviewed (published)
	April 16, 2020	Liu	Clinical features and multidisciplinary treatment outcome of COVID-19 pneumonia: A report of three cases	Journal of the Formosan Medical Association	Peer-reviewed (published)
	April 17, 2020	Xiong	Family cluster of three recovered cases of pneumonia due to severe acute respiratory syndrome coronavirus 2 infection	BMJ Case Reports	Peer-reviewed (published)

Studieresultaten medicamenteuze behandeling COVID-19: Beschrijvende studies

Deze tabel geeft beschrijvende studies naar medicamenteuze behandeling bij COVID-19 samenvattend weer.

De studies staan gerangschikt op middel en datum van publicatie. De literatuur wordt dagelijks bekeken en zo nodig wordt de tabel aangevuld.

NB: Deze studies zijn niet gerandomiseerd, zijn vaak retrospectief uitgevoerd en betreffen vaak kleine groepen. De medicamenteuze behandelingen zijn vaak algemeen beschreven.

Hydrochloroquine						
Study reference	**Study characteristics**	**Patient characteristics**	**Treatment**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Geleris et al., 2020	Type of study: Retrospective observational study Setting: Study was conducted at the acute care hospital in northern Manhattan from March 7 to April 8, 2020. Country: United States of America Source of funding: Supported in part by grants and by the the National Institutes of Health.	Inclusion criteria: • Positive test result for the virus SARS-CoV-2 • Hospitalization from March 7 to April 8, 2020 Exclusion criteria: Patients who were intubated, who died, or who were transferred to another facility within 24 hours after presentation to the emergency department N total at baseline: Hydroxychloroquine N= 811 No Hydroxychloroquine N= 565 Important characteristics: Age, no. (%): Hydroxychloroquine: <40 yr:80 (9.9) 40-59 yr: 217 (26.8) 60-79 yr: 367 (45.3) ≥80 yr: 147 (18.1) No Hydroxychloroquine: <40 yr: 105 (18.6) 40-59 yr: 142 (25.1) 60-79 yr: 220 (38.9) ≥80 yr: 98 (17.3)	Treatment: 811 (58.9%) patients received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of 5 days)	Length of follow-up: Median follow-up of 22.5 days Loss-to-follow-up: 6 patients who received hydroxychloroquine due to clinical worsening or loss to follow-up.	Clinical outcome: The primary end point was the time from study baseline to intubation or death. For patients who died after intubation, the timing of the primary end point was defined as the time of intubation. Laboratory tests , median (IQR): *Hydroxychloroquine* D-Dimer, µg/mL: 1.25 (0.76–2.28) Ferritin, nh/mL: 785 (420–1377) Lacatate dehydrogenase, U/L: 414 (322–546) C-reactive protein, mg/L: 125 (75–199) Procalcitonin, ng/mL: 0.21 (0.11–0.53) Neutrophil count per mm^3: 5.06 (3.64–7.26). Lymphocyte count per mm^3: 0.94 (0.65–1.28) *No hydroxychloroquine* D-Dimer, µg/mL: 1.1 (0.59–2.35) Ferritin, nh/mL: 481 (213–989) Lacatate dehydrogenase, U/L: 333 (246–448) C-reactive protein, mg/L: 76 (20–150) Procalcitonin, ng/mL: 0.14 (0.09–0.39) Neutrophil count per mm^3: 4.53 (2.72–6.81). Lymphocyte count per mm^3: 1.02 (0.64–1.47) Intubation or death Hydroxuchloroquine, no. of events/no. of patients at risk (%) 262/811 (32.3)	Remarks: • Given the observational design and the relatively wide confidence interval, the study should not be taken to rule out either benefit or harm of hydroxychloroquine treatment. • Randomized, controlled trials of hydroxychloroquine in patients with Covid-19 are needed Authors conclusion: In this observational study involving patients with Covid-19 who had been admitted to the hospital, hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death.

Hydrochloroquine Azithromycin						
Study reference	**Study characteristics**	**Patient characteristics**	**Treatment**	**Follow-up**	**Outcome measures and effect size**	**Comments**
Molina et al., 2020	Type of study: Observational study Setting: French confirmed COVID-19 patients Country: France Source of funding: Not reported	N total at baseline: N = 11 Important characteristics: Mean age: 58.7 (20-77) Male gender: 7 (63.7%) Comorbidities: 8 had significant comorbidities associated with poor outcomes (obesity: 2; solid cancer: 3; hematological cancer: 2; HIV-infection: 1).	200 mg of oral hydroxychloroquine sulfate (3dd, 10 days) combined with azithromycin (500 mg on D1 followed by 250 mg per day for the next four days).		-At the time of treatment initiation, 10/11 had fever and received nasal oxygen therapy. -Within 5 days, one patient died, two were transferred to the ICU. In one patient, hydroxychloroquine and azithromycin were discontinued after 4 days because of a prolongation of the QT interval from 405 ms before treatment to 460 and 470 ms under the combination. - Mean through blood concentration of hydroxychloroquine was 678 ng/mL (range: 381–891) at days 3–7 after treatment initiation. -Repeated nasopharyngeal swabs in 10 patients (not done in the patient who died) using a qualitative PCR assay (nucleic acid extraction using Nuclisens Easy Mag®, Biomerieux and amplification with RealStar SARS CoV-2®, Altona), were still positive for SARS-CoV2 RNA in 8/10 patients (80%, 95% confidence interval: 49–94) at days 5 to 6 after treatment initiation.	Remarks: Letter to the editor Authors conclusion: These virologic results stand in contrast with those reported by Gautret et al. and cast doubts about the strong antiviral efficacy of this combination. Furthermore, in their report Gautret et al. also reported one death and three transfers to the ICU among the 26 patients who received hydroxychloroquine, also underlining the poor clinical outcome with this combination
Study reference	**Study characteristics**	**Patient characteristics**	**Treatment**	**Follow-up**	**Outcome measures and effect size**	**Comments**

Gautret et al., 2020	Type of study: Observational study Setting: French confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th Country: France Source of funding: This work was supported by the French Government Méditerranée Infection 10-IAHU-03)	Inclusion criteria: • Relatively mildly infected patients treated with hydroxychloroquine in combination with azithromycin over a period of at least three days • Patients with no contraindications for the offered treatment. Exclusion criteria: Not described N total at baseline: N = 80 Important characteristics: Median age: 52.5 [42-62] Male gender: 43 (53.8%)	200 mg of oral hydroxychloroquine sulfate (3dd, 10 days) combined with azithromycin (500 mg on D1 followed by 250 mg per day for the next four days). For patients with pneumonia and NEWS score≥5, a broad-spectrum antibiotic (ceftriaxone) was added to hydroxychloroquine and azithromycin. The treatment was either not started or discontinued when the QTc (Bazett's formula) was > 500 ms. Symptomatic treatments, including oxygen, were added when needed.	Length of follow-up: At least six days of follow-up at the time of the present analysis Lost to follow-up: • Three patients were transferred to the ICU, of whom two improved and returned to the infectious disease (ID) ward • One patient was still in the ICU at the time of writing • One patient died in the ID ward	Discharge: 65/80 (81.3%) were discharged with a low NEWS scores (61/65, 93.8%) Oxygen therapy: 12/80 (15%) required oxygen therapy Contagiousness as assessed by PCR: A marked decrease was observed after six days of treatment. The number of patients presumably contagious (with a PCR Ct value <34) steadily decreased overtime and reached zero on Day12. Length of stay in the ID ward: Mean time from initiation to discharge (n=65): 4.1 ± 2.2 days Mean length of stay (n=65): 4.6 ± 2.1 days	Criteria for discharge changed over the course of the study. It should be noted that the six patients under hydroxychloroquine and azithromycin combination were described in the previous paper, with a six-day follow-up (N=6). These patients were also included in the present study, with a longer follow-up.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Chorin et al., 2020	Type of study: Retrospective analysis Setting: New York University School of Medicine Country: USA Source of funding: Not reported	Patients with the respiratory syndrome COVID-19, admitted for lower airway disease (e.g. non-resolving cough, chest infiltrates on X-ray and persistent fever, with or without blood-oxygen desaturation) Inclusion/exclusion criteria: Not specified N: 84 Age in years, mean±SD: 63 ± 15, range 18 to 88 Sex, n/N (%) male: 74% QTc baseline (mean ± s.d.): 435 ± 24 ms	Treatment: hydroxychloroquine (HY) and azithromycin (AZ) HY: 400 mg 2/d on the first day, then 200 mg 2/d AZ: 500 mg per day	Length of follow-up: Average ECG follow-up after HY/AZ exposure was (mean±SD) 4.3 ± 1.7 days Lost to follow up: n.a.	Maximum QTc (mean ± s.d.): 463 ± 32 ms Day occurrence of maximum QTc (mean ± s.d.): day 3.6 ± 1.6 of therapy QTc severely prolonged (>500ms): 9/84 (11%) QTc increase in high-risk group (n=9) Baseline: 447 ± 30 ms Follow-up: 527 ± 17 ms Torsades de pointes events: 0/84 Status at end of follow-up: Death, multi-organ failure: 4/84 (5%) Admitted to hospital: 64/84 (76%) Discharged: 16/84 (19%)	Remarks: This is a retrospective analysis. Inclusion and exclusion criteria were not specified, and details about for example onset of symptoms and disease severity are not provided. Authors conclusion: In our work, we found that in patients with COVID-19 who were treated with HY/AZ, the QTc was significantly prolonged. This discrepancy suggests that QT prolongation may be influenced by patient attributes such as the presence of co-morbidities and the severity of the disease. [..] We therefore suggest that the QTc should be followed repeatedly in patients with COVID-19 who are treated with HY/AZ, particularly in those with co-morbidities and in those who are treated with other QT-prolonging medications.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Million et al., 2020	Type of study: Retrospective observational study Setting: Individuals with PCR-documented SARS-CoV-2 were included from March 3 to March 31. Country: France Source of funding: This work was funded by ANR-15-CE36-0004-01 and by ANR infection 10-IAHU-03, and was also supported by Région Provence-Alpes-Côte d'Azur. This work had received financial support from the Mediterranean Infection Foundation.	Inclusion criteria: • Patients with no contraindications for HCG (as described by Gautret et al., 2020) Exclusion criteria: • Patients described in the two previous studies by Gautret et al., 2020 were excluded (n=94) • Reasons for exclusion are specified (total n=350) N total at baseline: N = 1061 Important characteristics: Mean age: 43.6 ± 15.6 (range 14 – 95) Male gender 492 (46.4%)	Treatment: All patients were treated with HCQ (200 mg three times daily for ten days) + AZ (500 mg on day 1 followed by 250 mg daily for the next four days) for at least three days.	Length of follow-up: Patients who received at least three days of treatment and eight days of follow-up Loss-to-follow-up: N/a	Good clinical outcome and virological cure: 973/1061 (91.7%) Prolonged viral carriage: 47/1061 (4.4%) and was associated to a higher viral load at diagnosis (p< .001) but viral culture was negative at day 10 Poor clinical outcome: 46 /1061 (4.3%) and 8 died (0.75%) (74-95 years old)	Remarks: • It was a single observation study and a significant bias could possibly be existed. • Patients described in the two previous studies by Gautret et al., 2020 were excluded in this analsysis • Majority of patients had relatively mild disease at admission (95%). Authors conclusion: Administration of the HCQ+AZ combination before COVID-19 complications occur is safe and associated with very low fatality rate in patients. Author's Note: Since this analysis was completed, and as of the 29th of April, 2020, two more patients in the PClinO group died resulting in an overall 0.9% case fatality rate (CFR) for these 1061 patients.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Davido et al., 2020	Type of study: Monocentric retrospective study Setting: Monocentric retrospective study conducted from 2th March to 17th April 2020, in adults hospitalized in a tertiary hospital for COVID-19. Country: France Source of funding: Not reported	Inclusion criteria: • adults admitted in medicine for a COVID-19 infection confirmed by SARS-CoV-2 PCR and/or a compatible pulmonary CT-scan Exclusion criteria: • patients discharged from ICU to a medicine ward • opposition to collect data expressed by the patient. N total at baseline: HCQ+AZI ≥ 48h: 45 Other regimen: 87 - azithromycin alone (n=28) - lopinavir/ritonavir (n=14) - no targeted therapy (n=36) - HCQ+AZI <48 hours (n=9) Important characteristics: Mean age: HCQ+AZI ≥ 48h: 58 ± 17 Other regimen: 59 ± 16 Male sex – no (%) HCQ+AZI ≥ 48h: 31 (68.9) Other regimen: 55 (63.2)	Treatment: -All patients under oxygen received systematically a beta-lactam for at least 5 days, using preferentially ceftriaxone to treat a potential super-infection. -Patients were eligible to a targeted therapy against COVID-19 considering the following indications: i) patient presenting a clinical pneumonia confirmed by SARS CoV-2 PCR requiring oxygen therapy (independently of the CT scan findings); ii) high suspicion of COVID-19 pneumonia considering the clinical presentation and confirmed by a pulmonary CT-scan showing ground-glass opacity affecting ≥ 10% of the whole parenchyma. Patients had systematically an EKG to evaluate the corrected QT interval using the Framingham formula, and monitored 2 times per week during10 days. A loading dose at day 1 with 800 mg/day was administered followed by a maintenance dose of 400 mg/day up to 600 mg/day in case of obesity (body mass index (BMI) > 30) for a total 10 days. In addition, 500 mg of azithromycin was prescribed the first day, followed by 250 mg for 4 days.	Length of follow-up: The patients were followed-up until hospital discharge. Loss-to-follow-up: N/a	Observations: Patient characteristics: age, sex, diabetes, cardiovascular risk factor, smoking habits, obesity, chronic pulmonary disease, Charlson comorbidity score, Infection characteristics: delay between onset of symptoms and admission, presence of super-infection, C-reactive protein (CRP) and white blood cell count (WBC) at admission, percentage of lung injuries on CT-scan if applicable, positive PCR amplifying the betacoronavirus E gene and the SARS-CoV-2 RdRp gene on nasopharyngeal swab or sputum, Clinical outcome: intensive care unit (ICU) support: n=27 death: 10 (37%) Laboratory tests in patients with and without HCQ+AZI ≥ 48h: HCQ+AZI ≥ 48h: Median lymphocyte count (IQR) - /mm3: 920 (710-1160) Median C-reactive protein (CRP) (IQR) – mg/L: 90.5 (55-152) Others regimen: Median lymphocyte count (IQR) - /mm3: 1065 (745-1530) Median C-reactive protein (CRP) (IQR) – mg/L: 62 (14-106)	Remarks: • This article is a preprint and has not been certified by peer review. • The number of patients were rather limited. • It was a single observation study and a significant bias could possibly be existed. • To confirm the conclusions of the observation, a randomized controlled trial and a study on the mechanism of HCQ/azithromycin for the treatment of COVID-19. Authors conclusion: The present study suggests a potential interest of the combination therapy using HCQ/azithromycin for the treatment of COVID-19 in in-hospital patients.

Chloroquine						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Van den Broek et al., 2020	Type of study: Retrospective cohort study Setting: Hospital, St. Antonius Hospital, Utrecht/Nieuwegein Country: The Netherlands Source of funding: Not reported	Patients with suspected of having COVID-19 who are hospitalized. N total at baseline: 95 Important characteristics: Age, mean (range): 65 (18-91) Sex, n/N (%) male: 63/95 (66%) ICU, n/N (%) 21/95 (22%)	Treatment: The dosage regimen for chloroquine was a loading dose of 600mg followed by 300mg twice daily (starting 12 h after the loading dose), with a total treatment duration of 5 days. Chloroquine was not prescribed to patients with a baseline QTc interval duration of >500ms, in accordance with hospital policy. In patients with a QTc prolongation >500ms during chloroquine treatment, dose reduction was effectuated, or treatment was stopped.	Length of follow-up: The ECG recording during maintenance therapy (at least 12 h after the loading dose) was used to assess the QTc-prolonging potential.	*Computer interpreted* Mean QTc before chloroquine treatment (ms) (95% CI): 444 (373–515) Mean QTc after chloroquine treatment (ms) (95% CI): 479 (394–564) Mean difference (ms) (95% CI) 35 (28–43), P<0.01 *Manually interpreted* Mean QTc before chloroquine treatment (ms) (95% CI): 432 (360–505) Mean QTc after chloroquine treatment (ms) (95% CI): 466 (383–549) Mean difference (ms) (95% CI) 34 (25–43), P<0.01	Remarks: This is a retrospective analysis. Inclusion and exclusion criteria were not specified, and details about for example onset of symptoms and disease severity are not provided. Authors conclusion: Chloroquine treatment in patients with COVID-19 significantly prolonged the QTc interval by 34–35ms; 23% of patients had a QTc interval exceeding 500ms.These findings highlight the need for ECG monitoring when prescribing chloroquine to COVID-19 patients.

Chloroquine and Clarithromycin						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Millán-Onate et al., 2020	Type of study: Case-study Setting: Hospital San Jose de Buga, a mid-complexity private institution Country: Colombia Source of funding: • Funding: none • The authors declare that they have no competing interests	N=1 • 34-year-old male • Case from Buga, Valle del Cauca, Colombia, returned from Spain • rRT-PCR confirmed the SARS-CoV-2 infection. class II-obesity	Treatment: chloroquine and clarithromycin At the fourth day of hospital admission, it was decided to add chloroquine, phosphate, to the treatment (orally 300 mg, base, q12h) per 10 days plus continuing oseltamivir and antibiotics. Our patient received 5 days of chloroquine per 5 days at 600 mg per day (divided into two doses, 300 mg/day base). The first intended use of chloroquine in our patient was as monotherapy, but unintentionally for SARS-CoV-2, he also received 5 days of an erythromycin analogue, clarithromycin	Length of follow-up: 9 days	Observations: Laboratory findings, assessed pathogens, chest computed tomography At ninth day, the leukocyte counts became normal, with no other significant clinical findings, except for a mild elevation of the C-reactive protein. His clinical condition significantly improved. There is no fever nor cough. A control sample for rRT-PCR for SARS-CoV-2 took this day was negative. The patient is discharged this day. He will remain isolated at home for 14 days at a separated room.	Remarks: This is a case study Authors conclusion: We cannot be sure of the antiviral effect of chloroquine and clarithromycin, but both drugs were well tolerated, easy to administrate, and specifically, in our case, they were not associated with adverse effects. Although that just based in one case, we cannot recommend the use of these drugs, our patient improved significantly, and his clinical manifestations ceased, including becoming negative for the SARS-CoV-2 infection, as observed in the rRT-PCR test.

Chloroquine and Tocilizumab						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Xu et al., 2020	Type of study: Case report (n=1) Setting: Hospital Country: China Source of funding: This work was supported by the Suzhou Science and Technology development projects (SYSD2016168, SYSD2017114, GSWS2019061). Conflict of interest: The authors have no potential conflicts of interest to disclose	N total at baseline: N = 1 Important characteristics: ● 63-year-old man ● diagnosed with infection by SARS-CoV-2 real time polymerase chain reaction test screening (Feb 17, 2020) Admitted to the hospital on Feb 25, 2020	Treatment: Chloroquine: 500mg bid orally after admission and maintained for 7 days. Single dose of tocilizumab, 8 mg/kg intravenously on day 4.	Length of follow-up: 16 days Lost to follow up:] n.a.	Described variables: Day-to-day report of laboratory results and viral clearance is described.	Remarks: This was a case report (n=1) Authors conclusion: We report our observation of a patient with severe Covid-19, who was successfully treated with tocilizumab and CQ. The combination therapy appears to us a promising therapy protocol in patients with severe COVID-19, which should be studied urgently in future.

Remdesivir						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Hillaker et al, 2020	Type of study: Case-study Setting: Country: Italy Source of funding:	N=1 • 40y old male • Tested at testing center 3 days after onset of COVID-19 symptoms • Admitted to hospital 5 days after onset of COVID-19 symptoms	Treatment: A request for compassionate use remdesivir was submitted on the same hospital day as the positive COVID-19 PCR result. Supportive measures, in addition to a 5-day course of hydroxychloroquine, were maintained until remdesivir could be supplied on day 9 of hospitalization, 13 days after symptom onset. Pharmaceuticals described: Hydrochloroquine, azithromycin,	Length of follow-up: 16 days of illness (hospital days: 12)	Observations: Day-to-day description of test results, symptoms, and treatment.	Remarks: This is a case study Authors conclusion: Late initiation of remdesivir may be effective in treating SARS-CoV-2, unlike antivirals utilized for different disease states, such as oseltamivir, which are most effective when started as soon as possible following symptom onset. Urgent action is needed by regulatory agencies to work with drug manufacturers to expedite the study and approval of investigational agents targeting SARS-CoV-2 as well as to meet manufacturing demands.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**

Grein et al., 2020	Type of study: compassionate use cohort study Setting: hospitals spreaded over United States, Canada, Japan and Europe Country: United States (22 patients), Japan (9), Italy (12), Austria (1), France (4), Germany (2), Netherlands (1), Spain (1) and Canada (1). Source of funding: Funded by Gilead Sciences	Inclusion/exclusion criteria: 1. Confirmed SARS-COV-2 infection by reverse transcription polymerase chain reaction assay 2. Either oxygen saturation of ≤94% while breating ambient air or need for oxygen support. 3. Creatinine clearance ≥ 30ml/minute 4. Serum levels of alanine aminotransferase and aspartate aminotransferase ≤5x upper limit of normal range 5. Agreed to no use of other investigational agents for COVID-19 N total at baseline: 61 Important characteristics: Age, median (IQR): 64 (23-82) Sex, n/N (%) male: 40/53 (75%) Invasive ventilation, n/N (%): 34/53 (67%): Mechanical ventilation, n/N (%): 30/53 (57%) EMCO, n/N (%): 4/53 (8%)	Treatment: 10 day course: 200 mg intravenous remdesivir on day 1, followed by 100mg daily for 9 days. Supportive therapy was provided at the discretion of the clinicians. 34 received invasive ventilation and 19 received non invasive oxygen support	Length of follow-up: at least 28 days after the beginning of treatment with remdesivir or until discharge or death. Lost to follow up: 8 persons were excluded before follow up because of missing postbaseline information (7 patients) and an erroneous remdesivir start date (1 patient).	Clinical improvement: Overall: over a median follow up of 18 days, after receiving the first dose of remdesivir 36/53 (68%) showed an improvement in the category of oxygen support, whereas 8/53 showed worsening. Non-invasive group: all 12 patients without oxygen support improved, 5/7 (71%) of patients receiving noninvasive oxygen support (NIPPV or high flow supplemental oxygen). Invasive group: 17/30 (57%) of patient receiving mechanical ventilation improved, 3/4 patients (75%) using EMCO stopped receiving it, all were alive at follow up. Mortality: Overall: 7/53 (13%) died after completion of remdesivir treatment Safety: Overall: 32/53 (60%) reported side effects including increased hepatic enzymes, diarrhea, rash, renal impairment and hypotension. 12/53 (23%) had serious adverse events including multiple organ-dysfunction syndrome, septic shock, acute kidney injury, and hypotension. Most were reported in patients who were receiving invasive ventilation at baseline. 4/53 (8%) discontinued remdesivir treatment because of worsening of preexisting renal failure (1), multiple organ failure (1) and elevated aminotransferases (2).	Remarks: Findings need to be confirmed by a randomized, placebo-controlled trials. Authors conclusion: "This preliminary report describes the clinical outcomes in a small cohort of patients who were severely ill with Covid-19 and were treated with remdesivir. Although data from several ongoing randomized, controlled trials will soon provide more informative evidence regarding the safety and efficacy of remdesivir for Covid-19, the outcomes observed in this compassionate-use program are the best currently available data. Specifically, improvement in oxygen-support status was observed in 68% of patients, and overall mortality was 13% over a median follow-up of 18 days."

Lopinavir/Ritonavir						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Deng et al., 2020	Type of study: Single centre retrospective cohort study Setting: the Fifth Affiliated Hospital of Sun Yat-Sen University Country: China Source of funding, conflicts of interest: No external funding received; no conflicts of interest reported	Inclusion criteria: • laboratory-confirmed COVID-19 • age ≥18y • with pneumonia without invasive or non-invasive ventilation. No other exclusion criteria were applied at this stage. N total at baseline: N = 33 Characteristics: Combination group: N = 16 Age: 41y ± 14 Male: 7/16 (44%) Monotherapy group: N = 17 Age: 47y ± 17 Male: 10/17 (59%) Groups comparable at baseline.	Treatment: Treatments initiated after diagnosis. • Combination therapy: oral arbidol + lopinavir/ritonavir • Monotherapy group: oral lopinavir/ritonavir Administration period: The administration period is about 5–21 days Dosage Arbidol was given at a dose of 200 mg every 8 h and lopinavir (400 mg) /ritonavir (100 mg) orally every 12 h until coronavirus was detected negative by RT-PCR for three times.	Length of follow-up: 14 days Loss-to-follow-up: N/a	Primary endpoint negative conversion rate of SARS- CoV-2 from the date of COVID-19 diagnosis (day7, day14), and assessed whether the pneumonia was progressing or improving by chest CT (day7). Reported: • Comorbidities • Laboratory indices • % tested positive in stool • % needing support measures • adverse effects (no numbers) After 7 / 14 days: • % nasopharyngeal specimens negative for SARS-CoV-2 by RT-PCR • % chest CT improvement % tested positive in stool	Remarks: Descriptive study Authors conclusion: In typical patients without invasive ventilation, our study shows that oral arbidol and LPV/r in the combination group is associated with a significant elevated negative conversion rate of coronavirus' test in 7-day and 14-day, compared with LPV/r only in the monotherapy group. Furthermore, combination therapy is associated with a significantly improved the chest CT scans in 7-day. Fortunately, all the patients did not develop acute respiratory failure during the treatment period, but it was not clear whether it was an effect of antiviral drug.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Zhu et al., 2020	Type of study: Retrospective analysis of patients that receiver either treatment A or B Setting: Third People's Hospital of Changzhou and the Sec- ond People's Hospital of Wuhu. Country: China Source of funding: This work was supported by the Natural Science Foundation of Jiangsu Province [BK20180183] and the Science and Technology Project of Changzhou [CJ20179030].	Inclusion/exclusion criteria: • patients diagnosed with COVID-19, according to Chinese guideline for diagnosis and treatment of COVID-19 Not further specified N total at baseline: N = 50 Intervention: 34 Control: 16 Important characteristics: Age, median (IQR): I: 40.5 (34.8-52.3) C: 26.5 (23.3-52.5) P=0.16 Sex, n/N (%) male: I: 20/34 (59%) C: 6/16 (38%) P=0.23 Groups comparable at baseline. Also described: Laboratory and radiology findings.	A: Lopinavir/ritonavir (400mg/100mg, twice a day for a week) B: Arbidol (0.2g arbidol, three times a day) + conventional therapy, including oxygen inhalation (2L/min for half an hour, three times a day), atomized inhalation of recombinant human interferon-α2b injection (5 million units, twice a day)	Length of follow-up: Up to 14 days after admission Loss-to-follow-up: Not applicable Intention-to-treat analysis: Not applicable	**Efficacy** ORF1ab and N genes no difference in baseline Ct values between the two groups (P>0.05). Undetectable viral load day 7: A: 23.5% of patients B: 50% of patients Undetectable viral load day 14: A: 44.1% of patients B: 100% of patients Duration of positive RNA test: *Shorter for control (arbidol) group compared to intervention (lopinavir/ritonavir) (P<0.01).* **Safety** Slight elevation of ALT (54U/L) on admission: A: 0/34 B: 1/16 Leucopenia (whiteblood cell count < 4 ×10 9 /L) on admission: A: 1/34 B: 2/16 *White blood cell counts in the three patients became normal after giving one subcutaneous injection of granulocyte colony-stimulating factors (G-CSF, 150 μg for once* Elevated level (< 125 U/L) of ALT in first week of admission: A: 3/34 B: 3/16 ($\chi 2 = 0.047$, P = 0.99).	Remarks: • This study is not an RCT, but retrospective analysis Authors conclusion: On day 14 after the admission, no viral load was de- tected in the arbidol group, but the viral load was found in 44.1% of the patients treated with lopinavir/ritonavir. Furthermore, no apparent side effects were found in both groups. Our data indicate that arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19.

Ye, 2020	Type of study: Retrospective study Setting: A total of 47 patients with COVID-19 infection who were admitted to Rui'an People's Hospital from January 22 to 29, 2020 were recruited Country: China Source of funding: Zhejiang Natural Science Foundation: LY19H160015. Medical Science and Technology Project of Zhejiang Province: 2019324310. Ruian Science and Technology Bureau (MS2020023).	Inclusion criteria: Not specified Exclusion criteria: Not specified N total at baseline: N = 47 Intervention: 42 Control: 5 Important characteristics: Intervention group: Male: 21 (50%) Control group: Male: 1 (20%) Groups comparable at baseline? There is a substantial imbalance between intervention and control group.	The intervention group was treated with LPV/r (AbbVie Ltd, North Chicago, IL, USA) and adjuvant drugs. The per ml of LPV/r oral liquid contained 80 mg lopinavir and 20 mg ritonavir. Usage and dosage: 5 ml/time (400/100 mg) for adults, twice a day or 10 ml/time (800/200 mg) once a day with food. The schemes of adjuvant drugs were the same as the control group.	Control group was treated with pneumonia-associated adjuvant drugs only.	Length of follow up: 10 days since the patients had received treatment Loss-to-follow-up: N/a	Clinical improvement Body temperature: Patients in the intervention group returned to normal body temperature in a shorter time. Intervention group: 4.8±1.94 days vs. control group: 7.3±1.53 days, p=0.0364. Abnormal proportion of lymphocytes, Hb, granulocyte and CRP in the intervention group show a decrease. Number of days required for nCoV-RNA negative result: intervention group: 7.8±3.09 days vs. control group: 12.0±0.82 days, p=0.0219 Abnormal ALT and AST (%): First measurement after treatment ALT / ALS I: 9.5% / 19% C:25% / 25% Second measurement after treatment I: 11.1% / 16.7% C: N/a / N/a Third measurement after treatment I: 22.7% / 18.2% C: N/a / N/a

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Nicastri et al., 2020	Type of study: Case-study Setting: Country: Italy Source of funding:	N=1 • Male in late 20s • Italian citizen, evacuated from China and place in 14-day quarantine in military complex afterwards • Only case of the 56 asymptomatic citizens that screened positive on nasopharyngeal swab (RT-CPR for COVID-19) after quarantine phase	Treatment: off-label oral treatment with lopinavir/ ritonavir (400/100 mg every 12 h)	Length of follow-up: 13 days	Observations: Description of naso- and oropharyngeal swab results, stool sample results and clinical characteristics (body temperature, symptoms) and days of treatment.	Remarks: This is a case study Authors conclusion: This paucisymptomatic case with detailed clinical and virological results is likely to impact on the clinical management of COVID-19 in settings with limited community transmission. Further studies are needed to better understand the clinical spectrum of COVID-19 at hospital and community levels, the role of pauci-/ asymptomatic subjects in viral transmission and the clinical relevance of viral persistence in non-respiratory samples as potential sources of SARS-CoV-2 spread.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**

Cheng et al., 2020	Type of study: Case series Setting: - Country: Taiwan Source of funding: -	N=5 Age (years): range 46-56 Male gender (n): 2 All were confirmed cases of COVID-19 infection, using real-time RT-PCR.	Treatment: Lopinavir and ritonavir (LPV/r) (n=2). For 1 patient they reported a dosage of lopinavir (200 mg)/ritonavir (50mg) as two pills twice daily. The other patient received two pills twice daily (dosage not specified). Others were not prescribed LPV/r (n=3).	Length of follow-up: Until discharge, which ranges from day 24-32.	Observations: In all cases the mean Ct values of the initial sputum samples, collected on illness days 1-3, increased in samples collected on illness days 8-10. LPV/r was administered on illness days 5-8 (n=1) or day 2-14 (n=1). Ct values increased 0.9 points per day between those two time points, compared to an increase of 1.0 per day in cases which were not administered with LPV/r. One of the cases receiving LPV/r had episodes of vomiting and severe watery diarrhoea. LPV/r was discontinued at day 8.	Remarks: This was a case report. Authors conclusion: In conclusion, LPV/r may not be recommended for COVID-19 patients with mild pneumonia, and additional medications should be studied in scaled-up observation studies.

Multiple antiviral drug treatments						
Huang et al., 2020	Type of study: retrospective cohort study Setting: Huizhou Municipal Central Hospital between Jan 19 and Mar 16, 2020 Country: China Source of funding: The study was supported by the Project supported by the Chinese National Natural Science Foundation (81700096), the foundation of the First Affiliated Hospital of Guangzhou Medical University (ZH201802) and Guangzhou Medical University (2017[160]).	N=27 • laboratory-confirmed hospitalized COVID-19 patients, non-severe • chloroquine phosphate, n=10; arbidol, n=11; lopinavir/ritonavir, n=6 • *Age:* Chloroquine group: 51 years (IQR, 35-63), Arbidol group: 42 years (IQR, 37-57) and Lopinavir/ritonavir group: 47 years (IQR, 42-51), p=0.963 • *Gender:* Chloroquine group: 4 females (40%), Arbidol group: 7 females (63.6%) and Lopinavir/ritonavir group: 4 females (66.7%), p=0.496) • *Co-morbidities:* Chloroquine group: 3 hypertensive patients (30%) and 2 diabetic patients (20%). Arbidol group: 3 hypertensive patients (27.3%). Lopinavir/ritonavir group: 1 hypertensive patient (16.7%).	Three antiviral monotherapies: 1) chloroquine phosphate: 500 mg 12-hourly 2) arbidol (Umifenovir) 200 mg 8-hourly 3) lopinavir/ ritonavir) 400 mg/100 mg 12-hourly, not exceeding 10 days of use	Length of follow-up: 30 days	Primary outcome: viral shedding interval: determined by the RT-PCR of the respiratory specimen. As for the primary outcome, the median viral shedding interval in the lopinavir/ritonavir group was 13.0 days (95% CI: 12.2-23.8), while it was significantly shorter in the chloroquine group at only 5.0 days (95% CI: 0.4-9.6) (p=0.003). A reduced median interval was also observed in the arbidol group, at 8.0 days (95% CI: 4.9-11.1) (p=0.008). Secondary outcomes: the length of hospital stay, hospitalisation expenses, the percentage of patients who still tested positive for SARS-CoV-2 at day 10 and day 14 and the adverse events associated with each therapy. *The length of hospital stay* was shorter in the chloroquine (9.3 ± 1.8 days, p<0.001) and arbidol groups (11.7 ± 3.7 days, p<0.001), when compared with the lopinavir/ritonavir group (19.7 ± 4.4 days).	Remarks The included patients had been treated with different antiviral monotherapies (chloroquine phosphate, arbidol (Umifenovir) or lopinavir/ritonavir) and were identified from electronic medical records. Authors conclusions: Chloroquine and arbidol could not only shorten the viral shedding interval but also decreased the hospitalisation duration and hospitalisation expenses of non-severe, COVID-19 patients.

Zhang et al., 2020	Type of study: case-study Setting: hospital Country: China Source of funding: This work is supported by National Science and Technology Major Project (2017ZX10103011). LY is supported by the Chinese Ministry of Education Changjiang Scholar Program (Q2018288). The funders contributed to the clinical patient care and management, and data analysis. The authors declare that they have no competing interests.	N=1 • 46-year-old man • admitted to the University of Hong Kong-Shenzhen Hospital on 19 January. • was transferred on 23 January 2020 to another hospital with 11-days history of fever of 38 °C and coughing.	Treatment: The patient received combination of interferonalfa-1b and ribavirin, lopinavir and ritonavir for antiviral treatment at different stages. Other medication was also given to him in combination for anti-inflammation, intestinal microbial regulation, phlegm elimination, liver protection and pulmonary fibrosis prevention purposes. We provided oxygen supply to him using BIPAP ventilator and high-flow humidification oxygen therapy instrument to facilitate respiration.	Length of follow-up: 22 days	Observations: The detection of the patient's upper respiratory tract specimen was SARS-COV-2 negative repeatedly while that of BALF sample was positive for SARS-COV-2 virus. CT scanning of the lungs on 12 February confirmed the improvement and the patient was discharged on the following day.	Remarks: This is a case study Authors conclusion: Although it is largely supportive, our treatment scheme was proven to be effective in helping the patient combating the virus. Detection of SARS-COV-2 RNA in BALF samples is of great importance in confirming of the infection in the similar cases to the one described in this report. Our report highlights the importance to carry out bronchoscopy and detection of SARS-COV-2 RNA from BALF samples as complementary interventions in addition to monitoring epidemiological changes, clinical symptoms, and chest CT findings of the unconventional COVID-19 pneumonia cases like the one described in this report, which will be informative and clinically significant in guiding the prognosis of the disease.

Convalescent plasma						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Duan et al. 2020*	Type of study: pilot study (multi-center) Setting: three hospitals, from January 23, 2020, to February 19, 2020 Country: China Source of funding, conflict of interest: This study was funded by Key projects of the Ministry of Science and Technology China "Preparation of specific plasma and specific globulin from patients with a recovery period of COVID19 infection" (project number: 2020YFC0841800).This work was also supported by Shanghai Guangci Translational Medicine Development Foundation. No conflict of interests were reported in the article.	Inclusion criteria patients: Severe COVID-19 patients (by clinical classification) 1) Age ≥18 years; 2) Respiratory distress, RR ≥30 beats/min; 3) Oxygen saturation level less than 93% in resting state; 4) Partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤300 mmHg (1 mmHg=0.133 kPa) Exclusion criteria patients: 1) Previous allergic history to plasma or ingredients (Sodium Citrate); 2) Cases with serious general conditions, such as severe organ dysfunction, who were not suitable for CP transfusion N total at baseline: Patients N=10 Donors N=10 Characteristics patients: -Median age: 52.5 years (IQR 45.0-59.5 years) -Male gender: n=6 --Underlying chronic diseases: n=4	Convalescent plasma (CP) transfusion: One dose of 200 mL inactivated convalescent plasma (CP) with neutralization activity >1:640 was transfused into the patients within 4 hours following the WHO blood transfusion protocol. Inclusion criteria donors for CP transfusion: 1). Normality of body temperature for more than 3 days; 2). Resolution of respiratory tract symptoms; 3). Two consecutively negative results of sputum SARSCoV-2 of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay (one-day sampling interval).	Length of follow-up: 3 days for the improvement of clinical symptoms, laboratory and radiological parameters. Loss-to-follow-up: none	*Improvement of clinical symptoms* All symptoms in the 10 patients, especially fever, cough, shortness of breath and chest pain, disappeared or largely improved within 1-3 days upon CP transfusion. *Reduction of pulmonary lesions on chest CT examinations* All patients showed different degrees of absorption of pulmonary lesions after CP transfusion. *Increase of neutralizing antibody titers and disappearance of SARS-CoV-2 RNA* Neutralizing antibody titers were determined before and after CP transfusion in all patients except one. *Outcome of patients treated with CP as compared to a recent historic control group* Baseline characteristics of patients between CP treatment group and control group showed no significant differences, while clinical outcomes of these two groups were different: 3 cases Discharged while 7 cases in much improved status and ready for discharge in CP group, as compared to 3 deaths, 6 cases in stabilized status and one case in improvement in the control group ($p<0.001$). *Adverse effects of CP transfusions* Patient 2 showed an evanescent facial red spot. No serious adverse reactions or safety events were recorded after CP transfusion.	Remarks: *The two published papers by Duan et al. are about the same study population First study to explore the feasibility of CP therapy in COVID-19 Authors conclusion: This pilot study on CP therapy showed a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients. One dose of CP with high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. The optimal dose and treatment time point, as well as the definite clinical benefits of CP therapy, need to be further investigated in randomized clinical studies.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Shen et al, 2020	Type of study: case series Setting: infectious disease department, Shenzhen Third People's Hospital, from January 20, 2020, to March 25, 2020 Country: China Source of funding, conflict of interest: This work was supported by the National Science and Technology Major Project, Sanming Project of Medicine in Shenzhen, China Postdoctoral Science Foundation, Shenzhen Science and Technology Research and Development Project, National Natural Science Foundation of China, Shenzhen Science and Technology Research and Development Project, and The Key Technology R&D Program of Tianjin. No conflicts of interests were reported in the article.	Inclusion criteria patients: Critically ill patients with laboratory confirmed COVID-19, diagnosed using quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) (GeneoDX Co, Ltd) if they fulfilled the following criteria: (1) had severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; (2) PAO2/FIO2 of <300 (PAO2 measured in mmHg and FIO2 measured as fraction of inspired oxygen); and (3) were currently or had been supported with mechanical ventilation. Exclusion criteria patients: Not reported. N total at baseline: Patients N= 5 Donors N= 5 Characteristics patients: Age (range): 36-73 years Male gender: n=3 4/5 patients had no preexisting medical conditions.	Convalescent plasma (CP) transfusion: 400 mL of convalescent plasma was obtained from each donor by apheresis, and the plasma was immediately transfused to the recipients on the same day it was obtained. Plasma was administred between 10 and 22 days after hospital admission. Inclusion criteria donors for CP transfusion: The donors had recovered from SARSCoV-2 infection. And were tested negative for SARS-CoV-2 and other respiratory viruses and other viruses (e.g. HIV, Hepatitis) The donors had been well for at least 10 days, with a serum SARS-CoV-2–specific ELISA antibody titer higher than 1:1000 and a neutralizing antibody titer greater than 40.	Length of follow-up: Patients were followed until discharge, up to March 25, 2020. Most parameters are reported up to 12 days posttransfusion. Loss-to-follow-up: none	*PAO_2/FIO_2* The PAO_2/FIO_2 improved from baseline to 12 days after CP transfusion (range 172 to 276 vs. range 284-366) *Cycle threshold value* After CP transfusion Ct levels improved, within 1 day. Ct levels became negative within 1-12 days. *Sequential organ failure assessment (SOFA)* The SOFA scored decreased from baseline to 12 days after CP transfusion (range 2-10 points vs. range 1-4 points) *ARDS* ARDS was resolved in 4 patients at day 12 after CP transfusion. *Inflammatory markers* Values of the inflammatory biomarkers CRP, procalcitonin and IL-6 (1 patient not tested) decreased in all patients after CP transfusion. *Mechanical ventilation* 3/5 patients were weaned from mechanical ventilation within 2 weeks after CP transfusion. *Discharge* 3/5 patients were discharged from the hospital, with lengths of stay between 51-55 days. As of March 25, 2020 2/5 patients remained hospitalized, with lengths of stay of 37 days.	Remarks: In the current study, all patients received antiviral agents, including interferon and lopinavir/ritonavir, during and following convalescent plasma treatment. Authors conclusion: In this preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in the patients' clinical status.The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**

Zhang et al., 2020	Type of study: Retrospective observational study Setting: Description of cases that were admitted to different Chinese hospitals Country: China Source of funding: Not described	N=4 Important characteristics: 1. female, 69y, history of hypertension 2. male, 55y, history of chronic obstructive pulmonary disease 3. male, 73y, history of hypertension and chronic renal failure 4. female, 31y, pregnant	Supportive care and convalescent plasma transfusion *[see manuscript for other pharmaceuticals that were administered, including viral drugs, human albumin, zadaxin and immunoglobulin, antibacterial and antifungal drugs]*	Length of follow-up: Up to 23 days (discharge from hospital) Loss-to-follow-up: n/a	Observations: Day-to-day description of treatment and symptoms, up to discharge from hospital	Remarks: -clear description of day-to-day treatment -dosage of pharmaceutical described -patients were admitted to different hospitals, had different medical history and different day-to-day pharmaceutical treatment -1 pregnant female Authors conclusion: Our results indicated convalescent plasma might be a potential therapy for critically ill patients infected with SARS-CoV-2. We observed no serious adverse reactions associated with the transfusion of convalescent plasma. However, the relative contributions of supportive care, investigational therapies, and patient's immune response on survival could not be determined. Whether convalescent plasma and/or supportive care provide any clinical benefit is unknown. The safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients should be studied within the context of a well-designed clinical trial.

Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**

Ahn et al., 2020	Type of study: Case study Setting: Dep. of Internal Med., Severance Hospital, Seoul Medical Center &National Medical Center, and Dep. of Laboratory Med., Severance Hospital, Seoul, Korea Country: Korea Source of funding: This study was supported by research grants for deriving the major clinical and epidemiological indicators of people with HIV (Korea HIV/AIDS Cohort Study, 2019-ER5101-00), and a grant from the Ministry of Health & Welfare, Republic of Korea (grant No. HI14C1324).	N total at baseline: N = 2 1.male, 71y 2. female, 67y	Convalescent plasma (CP) transfusion: 1. day 10: 500ml convalescent plasma from male donor in 20s, recovered from COVID-19 for 21 days *Patient earlier received amongst others hydroxy-chloroquine, lopinavir/ ritonavir.* 2. day 6: 500ml convalescent plasma from male donor in 20s, recovered from COVID-19 for 18 days *Patient earlier received amongst others hydroxy-chloroquine, lopinavir/ ritonavir.*	Length of follow-up: 1. 26 days 2. 20 days	Described: Day-to-day treatment, laboratory results and clinical symptoms	Remarks: Authors conclusion: Both patients presented severe pneumonia with acute respiratory distress syndrome and showed a favorable outcome after the use of convalescent plasma in addition to systemic corticosteroid. Our cases suggest that convalescent plasma from patients who have recovered from COVID-19 infection might be an additional option to treat patients without causing any severe adverse effects.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Pei et al., 2020	Type of study: case series (N=3) Setting: "1. Hunan Engineering Research Center of Obstetrics and Gynecological Disease 2. Department of Dermatology, Hunan Engineering Research Center of Skin Heath and Disease, Xiangya Hospital, Central South University, Changsha, Hunan Province, China 3. Department of Blood Transfusion of Xiangya Hospital, Central South University, Changsha, Hunan Province, China 4. Department of Blood Transfusion Laboratory of Changsha Blood Center, 509 Wanjiali North Road, Changsha 410001, Hunan Province, China" Country: China Source of funding, conflict of interest: No conflict of interests were reported in the article. No funding.	Inclusion criteria patients: Severe and critically COVID-19 patients, and patients suffering advanced stages of the disease. 1. Duration of the disease is within three weeks, novel coronavirus virus nucleic acid test is positive with viremia. 2. Severely and critically ill COVID-19 patients assessed by clinicians. It is made available under a CC-BY-NC 4.0 International license . author/funder, who has granted 3. Patients with long-term (more than 4 weeks) positive of novel coronavirus nucleic acid test (for details please refer to patient 2 in Fig.2). Exclusion criteria patients: 1. Congenital IgA deficiency. 2. A history of allergy including plasma infusion, human plasma protein products, sodium citrate. Plasma inactivated by methylene blue virus is strictly prohibited in patients with methylene blue allergy. Other history of severe allergies and contraindications. 3. At the end of critical illness with irreversible multiple organ failure. Other conditions that are not suitable for	Convalescent plasma (CP) transfusion: The infusion dose is dependent on the clinical status and the patient's weight. Usually the infusion dose is 200-500ml (4-5ml/kg). According to the principle of cross-matching of blood, ABO homogenous plasma is preferred. A slow infusion is required in the first 15 minutes to pay attention to adverse reactions. Inclusion criteria donors for CP transfusion: "1. More than 3 weeks after the onset of symptoms of the COVID-19 and complete resolution of symptoms at least 14 days prior to donation. 2. In accordance with relieved isolation and discharge standards following the latest version of the therapeutic schedule.	Length of follow-up: until hospital discharge Loss-to-follow-up: none	*Improvement of clinical symptoms* The first two patients improved in clinical symptoms, the third patient developed an anaphylactic shock after the infusion. *Reduction of pulmonary lesions on chest CT examinations* Not reported. *Outcome of patients treated with CP as compared to a recent historic control group* 2 successfull cases and one unsuccessful case (longer hospital duration) due a an anaphylactic shock.	Remarks: Study goal was mainly to describe the protocol for CP transfusion to health care practitioners. Authors conclusion: CP transfusions are safe and can improve treatment outcomes in critically ill patients and patients with a long disease duration (>4 weeks). Selection of plasma donors should be strictly in accordance with the inclusion criteria.

		infusion assessed by clinicians. N total at baseline: 3	3. Age: 18 -55 years old. 4. Weight: male≥50kg, female≥45kg. 5. No history of blood-transmitted diseases. 6. Eligible donors must be assessed by clinicians according to treatment."			
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Ye et al., 2020.	Type of study: case series (6 cases) Setting: the COVID-19 hospital Huoshenshan in Wuhan. Country: China Source of funding, conflict of interest: "The authors reported no conflicts of interest." "The study was partially funded by the National Natural Science Foundation of China and Jiangsu Provincial Key Research and Development Program. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the	Inclusion criteria patients: "(1) laboratory confirmed cases; (2) patients with abnormalities in chest CT (Case #5 was an exception); (3) patients with deteriorated symptoms after standard treatment; (4) patients with persistent positive result of throat swab; (5) critically ill patients." Exclusion criteria patients: (1) patients allergic to plasma contents; (2) patients positive for HBV, HCV and HIV; (3) patients with uncontrolled bacterial mixed infection; (4) patients with malignant tumors; (5) patients who developed multiple organ dysfunction syndrome N total at baseline: 6 Characteristics patients: Sex, age, comorbidities: 1: Male, 69, no comorb. 2. Female, 75, no comorb.	Convalescent plasma (CP) transfusion: At least one cycle of 200 ml ABO-compatible CP transfusion, each cycle administered over a 30-minute period. Inclusion criteria donors for CP transfusion: 1. Recovered from COVID-19, defined as: 1) afebrile status for at least 3 days, 2) alleviation of respiratory symptoms, 3) negative for SARS-COV-2 nucleic acid for at least two RT-PCR tests and at least 3 weeks following disease onset.	Length of follow-up: Up to hospital discharge Loss-to-follow-up: None	*Improvement of clinical symptoms* All 6 patients experienced a relieve of clinical symptoms such as fever, shortness of breath, non-productive cough, fatigue and myalgia. *Reduction of pulmonary lesions on chest CT examinations* Radiologic findings improved rapidly and dramatically in 3 patients with bad lung conditions. *Outcome of patients treated with CP as compared to a recent historic control group* Not reported.	Remarks: patients with distinct radiologic, laboratory and clinical features were included, representative of the COVID-19 population in Wuhan. The main limitation was the sample size (N=6). Authors conclusion: "Since more and more patients have recovered from the infection of SARS-CoV-2, voluntary donation of convalescent plasma would be definitely encouraged and appreciated. Taken together, COVID-19 is becoming a global health threat, reliable treatment is crucial for reducing mortality and preventing disease outbreak. SARS-CoV-2-specific therapies, including convalescent plasma from recovery patient, would be highly effective weapons to win the war against COVID-19."

	study and had final responsibility for the decision to submit for publication.”	3. Male, 56, bronchitis 4. Female, 63, Sjögren’s disease 5. Female, 28, no comorb. 6. Male, 57, no comorb.	2. Seronegative for anti-HBV, HCV and HIV. 3. Seropositive for antiSARS-COV-2.			

Siltuximab						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Gritti et al., 2020	Type of study: Retrospective observational study Setting: This study retrospectively analysed data collected on patients with pulmonary infection by SARS-CoV-2 (confirmed by clinical and radiological assessment) and ARDS (in accordance with the Berlin 2012 criteria) (Definition Task Force ARDS, 2012) who were admitted to the hospital between 11 March 2020 and 24 March 2020. Country: Italy, Bergamo Source of funding: Not reported	Inclusion criteria: Not reported Exclusion criteria: Not reported N total at baseline: N = 21 Important characteristics: Mean age: 64 (range 48 – 75 years) Male gender: 18 (85.7%) Disease characteristics: • Fever: 90.4% (19/21) • Dry cough: 61.9% (13/21) • Dyspnea: 71.4% (15/21) • CRP levels: median 23.4 (range 9.5 - 43.1 mg/dL) • IL-6 levels: median 139.5 (range 113 - 239 pg/mL) • PaO2/FiO2: median 127 (range 69 -291) Comorbidities: Hypertension 42.8% (9/21) Diabetes: 23.8% (5/21) Cardiovascular disease: 19.0% (4/21)	Patients were treated according to the hospital standard of care, and received treatment with siltuximab administered intravenously at a dose of 11 mg/kg/day over 1 hour. Five patients received a second dose of siltuximab; for three of these five patients the infusions were two days apart, and for two of these patients the infusions were three days apart. Patients were treated with siltuximab within two days after initiating ventilation with either CPAP or NIV.	Length of follow-up: Median follow-up: 8 days Loss-to-follow-up: N/a	Clinical outcome: • Improvement (released from CPAP/NIV): 7 (33%) • No clinically relevant change (continuous use of CPAP/NIV): 9 (43%) • Worsening of condition (intubation or death): 5/24% Serum CRP levels reduced in all 16 patients with available data following treatment	Remarks: • Compassionate-use program not specified • Limited number of patients • Short-follow-up period • A cohort study matching patient treated with siltuximab to those treated with standard therapy at our hospital is ongoing and will report full clinical outcome upon completion. Author's conclusion: This analysis is presented to inform the medical community of the potential role of siltuximab in treating patients with ARDS secondary to SARS-CoV-2 infection, and a cohort study with patients treated with standard therapy in our hospital is ongoing, and will report the 30-day mortality rates upon completion.

Tocilizimab						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Michot et al., 2020	Type of study: Case-study Country: France Source of funding, conflicts of interest: Authors reported several sponsored research from pharmaceutical companies.	N=1 Male, 42-year-old Recently diagnosed with metastatic sarcomatoid clear cell renal cell carcinoma, had been hospitalized for fever, symptomatic bone metastases pain management and first-line systemic treatment decisions	D7: lopinavir-ritonavir (400mg-100mg, orally), maintained for 5 days D8: two doses of tocilizumab (8mg/kg, IV, 8 hours apart)	Length of follow-up: Twelve days	**D8:** sudden dyspnea and saturation drop required oxygen supplementation increase to 6 l/min, without the need for artificial ventilation **D8**: after treatment witn tocilizumab rapidly afebrile and with gradually decreased oxygen consumption. **D12:** improvement by showing partial regression of the pulmonary infiltrates and ground glass appearance. Creactive protein idecreased from 225 mg/L to 33 mg/L in 4 days	Remarks: The patient was immunosuppressed because of his medical history, and this case is therefore not generalizable to the non-cancer population Authors conclusion: This study suggests that anti-IL6 receptor inhibitor treatment could decrease the risk of progression toward SARS by mitigating the cytokine storm in the lungs with Covid-19.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Ferrey et al., 2020	Type of study: Case-study Setting: Country: USA Source of funding, conflicts of interest: Funding sources specified, no conflicts of interest reported	N = 1 • Male, 56-year old • end-stage renal disease secondary to biopsy-proven IgA nephropathy on hemodialysis since late 2016	Treatment: Descriptive information; no details provided. • In-patient clinic: antimicrobial therapy with ceftriaxone and azithromycin. • ICU: no candidate for remdesivir trial (end-stage renal disease), started on hydroxy-chloroquine and on hospital day 6 started on tocilizumab given continued hemody-namic instability with elevated inflammatory markers including interleukin (IL)-6.	Length of follow-up: retrospective and day-to-day description	Reported: • Day-to-day test results, symptoms and treatment • Timeline including location, facility and symptoms	Remarks: This is a case-study Authors conclusion: Our case is unique in its atypical initial presentation and highlights the importance of early testing.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Xu et al., 2020	Type of study: Retrospective observational study Setting: All patients enrolled met the severe or critical criteria defined by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (6th interim edition) and were treated with tocilizumab between February 5 to February 14 Country: China Source of funding: supported by Department of Science and Technology of Anhui Province and Health Commission of Anhui Province (grant	Inclusion criteria: • Positive diagnosis COVID-19 by detection who were treated with tocilizumab • Severity was defined if any of the following conditions was met: (1) respiratory rate ≥ 30 breaths/min; (2) SpO2 ≤ 93% while breathing room air; (3) PaO2/FiO2 ≤ 300 mmHg. A critical case was diagnosed if any of: (1) respiratory failure which requiring mechanical ventilation; (2) shock; (3) combined with other organ failure, need to be admitted to ICU.	Treatment: All patients received standard care, including lopinavir, methylprednisolone, other symptom relievers and oxygen therapy, and added with tocilizumab (Roche Pharma (Schweiz) prescribing 400 mg once through an intravenous drip.	Length of follow-up: Five days of follow-up at the time of the present analysis Loss-to-follow-up: N/a	Observations: Clinical features including body temperature, oxygen saturations, etc, were recorded. A whole blood white cell count was performed repeatedly. All patients had been spiral computerized tomography (CT) scanned on admission and a week later after the beginning of tocilizumab treatment, using a 64-row spiral Optima CT680 Clinical outcome: Discharge from hospital 19/21 (90.5%)	Remarks: • The number of patients were rather limited. • It was a single observation study and a significant bias could possibly be existed. • To confirm the conclusions of the observation, a randomized controlled trial and a study on the mechanism of IL-6 in COVID-19 is needed. Authors conclusion: Tocilizumab effectively improves clinical symptoms and repress the deterioration of severe COVID-19 patients. Therefore, tocilizumab is an effective treatment in severe patients of COVID-19, which provided a new

	number: 202004a07020001) and the China National Center for Biotechnology Development 175 (grant number: 2020YFC0843800).	Exclusion criteria: • Not specified N total at baseline: N = 21 Important characteristics: Mean age: 56.8 ± 16.5 (range 25 – 88) Male gender 18 (85.7%)			Laboratory tests before and after Tocilizumab: Before White-cell count: 6.30 ± 2.77 Lymphocyte percentage, %: 15.52 ± 8.89 C-reactive protein, mg/L: 75.06 ± 66.80 Procalcitonin, ng/ml: 0.33 ± 0.78 Day 1 White-cell count: 8.05 ± 4.39 Lymphocyte percentage, %: 11.78 ± 11.36 C-reactive protein, mg/L: 38.13 ± 54.21 Procalcitonin, ng/ml: 0.21 ± 0.35 Day 3 White-cell count: 6.02 ± 3.05 Lymphocyte percentage, %: 16.93 ± 13.59 C-reactive protein, mg/L: 10.61 ± 13.79 Procalcitonin, ng/ml: 0.09 ± 0.13 Day 5 White-cell count: 5.25 ± 2.11 Lymphocyte percentage, %: 22.62 ± 13.48 C-reactive protein, mg/L: 2.72 ± 3.60 Procalcitonin, ng/ml: 0.12 ± 0.15	therapeutic strategy for this fatal infectious disease.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**

Cellina et al., 2020	Type of study: Case-study Country: Italy	**N = 1** • Male, 64-year old, without significant clinical history	Day 7 and 8: patient received 2 doses of tocilizumab (8 mg/kg), 12 hours apart	14 days	Repeated CT results, laboratory results and clinical outcomes	Authors' conclusion: Favorable changes of CT findings were observed in a patient with COVID-19 pneumonia after treatment with tocilizumab. It is likely that in a near future, chest CT will become a pivotal tool for monitoring disease progression and effec-tiveness of experimental therapies in patients affected by COVID-19 pneumonia.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**		**Comments**
Mihai et al., 2020	Type of study: Case-study Country: Switzerland	N = 1 • Women, 57-year old, diagnosed with systemic sclerosis, insulin-dependent type 2 DM and WHO grade I obesity	Treatment + dosage Tocilizumab, with 8 mg/kg body weight every 4 weeks intravenously, was started, leading to a good control of both arthritis and SSc-ILD, with gradual improvement of musculoskeletal and respiratory symptoms, lung function and high-resolution. Tocilizumab was continued at 5-week intervals.	4 weeks after the last tocilizumab infusion, the patient presented to the emergency department with cough, headache, and general malaise since about 1 week. She reported contact with a patient with COVID-19 2 weeks earlier. A follow-up nasopharyngeal swab for SARS-Cov2 performed on March 26 turned out negative. She was declared cured from the infection and scheduled to receive the next tocilizumab dose 4 days after the negative test.		Authors' conclusion: In this case, a patient with insulin-dependent type 2 diabetes mellitus and SSc-ILD treated with tocilizumab developed a mild form of COVID-19. Her pre-existing ILD and diabetes are WHO-defined risk factors for a more severe course of COVID-19,1 while immunosuppressive treatment is currently also regarded as a risk factor
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Luo et al., 2020	Type of study: Retrospective study Setting: Jan 27 to 5 March 2020, at Zhongfaxincheng campus, Tongji Hospital in Wuhan Country: China Source of funding: Not reported	Inclusion criteria: • Patients infected with COVID-19 • treated with Tocilizumab Exclusion criteria: • not reported N total at baseline: 15 patients Important characteristics: Age: median 73 [range 62-80y]	Treatment: Tocilizumab (TCZ) (80 to 600 mg per time)	Length of follow-up: 7 days	Described: Day-to-day Serum levels CRP and IL-6, before and after TCZ administration. Clinical outcome: evaluated within 1 week after TCZ therapy. (death / clinical stabilization / disease aggravation)	Remarks: • This is a retrospective descriptive study and a significant bias could have occured. Authors conclusion: TCZ appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storms. And for these critically ill patients with elevated IL-6, the repeated dose of the TCZ is recommended.

		Sex: 12/15 male Disease severity: Critically ill: n=7 Seriously ll: n=6 Moderately ill: n=2 <u>Other:</u> Co-morbidities				
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
De Luna et al., 2020	<u>Type of study:</u> Case report <u>Country:</u> France	N = 1 • Male, 45-year old, with homozygous sickle cell disease (SCD); presence of multifocal vaso-occlusive crises for the past 24 hours, Severe Acute Chest Syndrome	<u>Day 1:</u> Antibiotic treatment; Hydroxy-chloroquine (200mg orally every 8 hours) <u>Day 2:</u> one pulse Intravenous tocilizumab (TCZ, 8mg/kg)	5 days	Pharmaceutical treatment, clinical assessments, RT-PCR	<u>Authors conclusion:</u> Covid-19 and the associated ARDS, represent a significant mortality risk for SCD patients. For our patient, given the prior history of severe SCD and the potential risks, treatment with hydroxychloroquine and TCZ were initiated, with a positive resolution. More studies are needed to determine the proper therapy for COVID-19 in patients affected by SCD.
Di Giambenedetto et al., 2020	<u>Type of study:</u> Case-study <u>Setting:</u> III level Italian Hospital <u>Country:</u> Italy <u>Source of funding:</u> This study was performed as part of our routine work.	<u>N total at baseline:</u> N=3 1. Male, 71y, hypertensive 2. Male, 45y 3. Male, 53y, hypertensive	<u>Treatment:</u> 1. Two doses of tocilizumab 12 hours apart 2.Two doses of tocilizumab 3. Three doses pf tocilizumab	<u>Length of follow-up</u>: Up to 16 days	<u>Observations:</u> Day-to-day description of treatment and symptoms, up to discharge from hospital	<u>Remarks:</u> This is a case study <u>Authors conclusion:</u> Our observations highlight the efficacy of tocilizumab in the treatment of COVID-19 even after a short time and seem in line with the work of Pan et al1. Rapid relief of respiratory symptoms, resolution of fever and reduction in CRP were the first effects following tocilizumab administration. Of note, no adverse events were

						registered during the follow-up of our three patients. Despite the lack of IL-6 levels determination for selecting the best candidates to tocilizumab therapy at the time of our case series, our work gives further evidence that tocilizumab may represent an effective and safe option in the treatment of SARS-CoV-2-infected patients with severe pneumonia. Randomized trials are urgently needed to confirm our findings.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Morisson et al., 2020	Type of study: Case-study Setting: - Country: Detroit, US Source of funding: -	N=2 • Case 1: 65 year old male • Case 2: 43 year old female • Both had elevated inflammatory markers, and severe acute respiratory distress syndrome (ARDS) with no alternative diagnosis.	Treatment: • Case 1: lopinavir/ritonavir, ribavirin, and hydroxychloroquine Tocilizumab (TCZ) was administered on day 9 and 10 (dosage not reported). • Case 2: lopinavir/ritonavir, ribavirin, and hydroxychloroquine. TCZ was initiated on day 13 (dosage not reported).	Length of follow-up: Not reported	Observations: Description of serum TG levels, biomarkers for acute pancreatitis (AP), hemophagocytic lymphohistiocytosis (HLH), enteral feeding (yes/no).	Remarks: This is a case study Authors conclusion: TCZ is progressing as a viable and promising treatment option in patients with severe COVID-19. Given the paucity of robust clinical trial data for most COVID-19 pharmacotherapies at this time, clinicians should continue to remain steadfast in recognition of interventions that improve clinical outcomes and vigilant in monitoring for acute adverse effects that are difficult to detect in clinical trials with small sample sizes. The observations from our two cases highlight the complex, not fully elucidated interrelationship between elevated IL-6 and pharmacologic interventions impacting this pathway. Clinicians should consider monitoring for hypertriglyceridemia described with chronic TCZ use in patients with COVID-19 treated with TCZ.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Radbel et al., 2020	Type of study: Case report (n=2) Setting: Not reported Country: Not reported Source of funding: Not reported. One of the authors reported paid research support to the institution, and internal funding for research.	Inclusion/exclusion criteria: Patients with COVID-19 CRS after treatment with tocilizumab. Exclusion criteria: not reported. N total at baseline: 2 Important characteristics: Age, sex 1. 40 year, male 2. 69 year, female Comorbidities 1. no medical history 2. type 2 diabetes mellitus, rheumatoid arthritis, and aplastic anemia	Treatment: 1. one dose of tocilizumab (400 mg IV) (9 days after symptom onset) 2. one dose of tocilizumab (560 mg IV) (7 days after symptom onset), second dose of tocilizumab (700 mg IV) (9 days after disease onset)	Length of follow-up: 6 and 4 days of hospital admission Lost to follow up: NA	Described variables: Day-to-day report of disease development is described, clinical laboratory trends are described for 1 patient, and chest images are shown.	Remarks: This is a case study, reporting detailed poor outcomes of patients with COVID-19 CRS after treatment with tocilizumab. Authors conclusion: Both patients progressed to sHLH despite treatment with tocilizumab, and one developed viral myocarditis, challenging the safety and clinical usefulness of tocilizumab in the treatment of COVID-19-induced CRS. Tocilizumab may have worsened the clinical course of the patients by adding to immunosuppression. We fear that tocilizumab may have been responsible for the development of viral myocarditis. This notion is further supported by decreased lymphocyte counts posttreatment in both the patients, suggesting decreased IL-6-mediated lymphocyte maturation. These cases highlight the need for clinical trials to determine optimal patient selection and timing for the use of tocilizumab during this disease process.

Study reference	Study characteristics	Study population (number, selection criteria)	Treatment (drug, dosage, frequency)	Follow-up	Description of variables (primary and secondary outcomes, other variables described)	Comments
Alattar et al., 2020	Type of study: Retrospective review Setting: 25 patients with confirmed severe COVID-19 who were treated at least 14 days with Tocilizumab in Qatar were included. All patients are treated with concomitant antiviral agents. Country: Qatar Source of funding: Not mentioned	Inclusion/exclusion criteria: Inclusion: - Patients in Qatar with laboratory confirmed SARS-CoV-2 infection - Patients who received one or more doses of tocilizumab and completed at least 14 days of follow up Exclusion: Not mentioned N total at baseline: 25 patients Important characteristics: Age, median (IQR): 58 (50-63) Male gender (n, %): 23, 92%	Treatment: Treatment with Tocilizumab: Median total dose per patient: 5.7 mg/kg (IQR, 4.8-9.5) Median number of doses per patient: 1 (IQR, 1-3) Treatment with concomitant investigational antiviral agents (n,%): Hydroxychloroquine (25, 100%) Azithromycin (24, 96%) Lopinavir/Ritonavir (24, 96%) Ribavirin (22, 88%) Interferon 1--a2a (15, 60%) Doses of these antivirals is not mentioned. Median number of antivirals administered to individual patients: 5.	Length of follow-up: 14 days Lost to follow up: n/a	Primary outcome: Discharge alive from ICU by day 14. Met by 9 patients (36%). Of remaining patients, 3 patients died (12%) and 13 patients (52%) were still at ICU. Secondary outcome: - Categorical ventilatory support status - Inflammatory markers over 14 days of administration of tocilizumab	Remarks: Confounding potentially present, as all patients are also administered concomitant antivirals. Also lack of a control group. Authors conclusion: Authors describe how in COVID-19 patients administered with Tocilizumab, they observe reduced requirements of ventilatory support, a decline in inflammatory markers an d radiological improvements. However, authors state that the study leads to assessment of the possible role of tocilizumab for COVID-19 patients, but it is impossible to draw any firm conclusions
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Sánchez-Montalvá et al, 2020	Type of study: Prospective cohort study Setting: Vall d'Hebron University Hospital, in Barcelona (Spain), including all	Inclusion/exclusion criteria: -Patients with laboratory-confirmed COVID-19 and radiologically confirmed	Treatment: Tocilizumab Patients over 75kg received 600mg, otherwise 400mg wasthe preferred	Length of follow-up: At least 7 days Lost to follow up:	Described variables: • Death at 7 days after first dose of tocilizumab • Admission to Intensive Care Unit	Remarks: • One patient died a few hours after receiving tocilizumab and was excluded from the primary endpoint analysis.

	consecutive patients who had a confirmed infection with SARS-CoV-2 and who were treated with tocilizumab from March 13th until March 25th <u>Country:</u> Spain <u>Source of funding:</u> Not reported	pneumonia who received at least one dose of tocilizumab -Tocilizumab was considered as additional treatment in patients with the following criteria: 1) respiratory failure; 2) interleukin-6 (IL-6) levels >40pg/mL (reference 0-4.3pg/mL) or a D-dimer levels > 1500 ng/mL <u>N total at baseline:</u> N = 82 <u>Important characteristics:</u> Age, mean (SD): 59.1 (19.8) years 63% male	dose.A second dose was considered in patients with a poor early response.	Not reported	• Acute Respiratory Distress Syndrome (ARDS) • Respiratory insufficiency progression. • Acute myocardial infarction • Septic shock • Acute kidney injury • Secondary infections. • Laboratory and radiologic findings on admission and during follow up • Microbiologic results <u>Results</u> At the end of the follow up period, of the 82 patients 34 (41.5%) had been discharged, 22 (26.8%) had died, 14 (17.1%) were hospitalized in ICU, 9 (11.0%) were hospitalized in medical wards, and 3 (3.7%) had been transferred to another institution. By 7-day follow-up, the mortality rate was 4.0% per person-day (95% confidence interval [CI], 2.4% to 6.2%) by Kaplan-Meier analysis. Mortality was more frequent in patients receiving tocilizumab once ARDS was present (hazard ratio for mortality 3.3; 95% CI, 1.3 to 8.5; age-adjusted hazard ratio for	• Patients also received other medical treatment (hydroxychloroquine, lopinavir/ritonavir, darunavir/cobicistat, azithromycin) • All patients were initially treated with antibiotic therapy, mainly ceftriaxone <u>Authors conclusion:</u> Our results show that a timely administration of immune-modulating therapies, before the onset of respiratory insufficiency or ARDS, can improve severe COVID-19 patients' outcomes with a threefold reduction in 7-day mortality. In summary, we found a mortality rate of 26.8% in this subset of patients with COVID-19 receiving tocilizumab for the treatment of inflammatory-related lung injury. Time from lung injury onset to tocilizumab administration may be critical to patient recovery. Our results may help front line physician to make evidence-based decisions in times of scarce resources and operationalized fair and transparent allocation procedures, maximizing the benefit of the intervention. Future and current host-directed clinical trials for patients with COVID-19 should consider our preliminary data in their design. All our patients were treated with a combination of antiviral drugs whose efficacy is yet to be demonstrated. Host-directed therapies in the absence of antiviral drugs needs further investigation.

					mortality 2.1; 95% CI, 0.8 to 5.8) or respiratory failure was present (hazard ratio for mortality 3.13; 95% CI, 1.3 to 7.8; age-adjusted hazard ratio for mortality 2.4; 95% CI, 0.9 to 6.4)	
Immunomodulerende middelen						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment & Follow-up** (drug, dosage, frequency)		**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Cao et al., 2020	Type of study: Case-study Setting: Single centre Country: China Source of funding: Not reported	N=3 Case 1 • 56-year-old man • Clinical diagnosis grading was modified from common to severe type. Case 2 • 34-year-old man, admitted on January 29, 2020, with fever and dry cough for 10 days. • Clinical diagnosis grade severe type Case 3 • 35-year-old woman Clinical diagnosis grading was modified from common to severe type	Case 1 Follow-up: 16 days • COVID_19, common type: Supportive care and empirical moxifloxacin • COVID-19, severe type: High dose IVIg from Jan 28th (hospital day 7) at 25 g/d for 5 days (body weight 66 kg). Moxifloxacin continued until Feb 2 Case 2: Follow-up: 6 days • COVID-19, severe type: IVIg was administered immediately at a dose of 25 g/d for 5 days (body weight 63 kg). Case 3: Follow-up: 15 days • COVID-19, common type: Oral lopinavir/ritonavir was continued to complete the 2-week course. • COVID-19, severe type: IVIg was administered from Jan 29th at 25 g/d for 5 days (body weight 56 kg). Meanwhile, methylprednisolone 40 mg/d for 3 days.		Observations: Description of naso- and oropharyngeal swab results, CT scan and clinical characteristics (body temperature, symptoms) and days of treatment.	Remarks: This is a case study Authors conclusion: Here we report a case series of patients with COVID-19, all of whom were successfully treated by high-dose IVIg at the early stage of clinical deterioration. Based on these observations, a high dose of IVIg administered at the appropriate point could successfully block the progression of the disease cascade and improve the outcome of COVID-19.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Zhong et al., 2020	Type of study: Case-studies	N=2; organ transplant recipients	Treatment:	• 57 days • 50 days	Observations:	Remarks: This is a case study

	Setting: Single centre Country: China Source of funding: National Natural Science Foundation of China, Grant Nos. 81970548, 81570079 and No. 81700657 and the Post-Doctoral Innovative Talent Support Program.	Case 1 • Male, 37 year-old • 19-year history of hepatitis B • Underwent liver transplantation Jan 21. • Day 9 after liver transplantation: fever (peak body temp 38.6°C); nasopharyngeal swab RT-PCR test positive. Case 2 • Male, 48 year-old • Living related donor renal transplantation 2003 • 2 days after confirmed COVID-19, hospitalization on February 6,	• Oral tacrolimus was also suspended, and low-dose intravenous methylprednisolone was administered (40 mg, q12h). • Oseltamivir, abidol, moxifloxacin, recombinant human interferon alpha (30 μg, qd), low-dose methylprednisolone (40 mg, qd), and human immunoglobulin for intravenous injection (IVIG) (10 g, qd), together with symptomatic supportive treatment		Description of of naso- and oropharyngeal swab results, bloodtests results, clinical characteristics (body temperature, symptoms) and pulmonary CT scan.	Authors conclusion: In conclusion, the clinical features and management of two COVID-19 cases in SOT recipients were reported above. From this experience, the regimen for COVID-19 positive SOT recipients should be adjusted after comprehensive evaluation, according to the infection level, immunosuppressant concentration, immune status, and side effects. A therapeutic regimen consisting of reduction of calcineurin inhibitors and MMF, combined with low-dose methylprednisolone, is recommended at present. Certainly, further data are needed to gain better understanding of the impact of immunosuppressive therapy on the clinical presentation, severity, and outcome of COVID-19 in SOT recipients.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Iwabuchi et al., 2020	Type of study: Case report Setting: 3 patients, previously attending the Diamond Princess, now admitted to hospital Country: Japan Source of funding: not reported	N=3 1. female, 73y 2. male, 78y 3. female, 67y	1. Ciclesonide inhalation, 200 μg, twice a day (also CTRX, AZM, Lopinavir/ Ritonavir) 2. Ciclesonide: Feb 20: 200 μg, twice a day; March 3rd: 1200μg/day (400μg, 3 times a day) 3. Ciclesonide inhalation, 200 μg, twice a day	Length of follow-up: • 2 weeks from admission to hospital are reported	Described variables: Day-to-day report of clinical results and adaptations in treatment	Remarks: Three single cases are described. All three were given Ciclesonide, a corticosteroid inhalation. Timing and dosage of this pharmaceutical differed, as well as other supportive or pharmaceutical components of treatment. Authors conclusion: We treated 3 cases of mild to mid-stage COVID-19 with ciclesonide, inhaled steroid, and obtained favorable results.
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**

Diurno et al., 2020	Type of study: Case studies Setting: Single centre Country: Napels, Italy Source of funding: Not reported	N=4 1: female; 54 years old No comorbidities on clinical history 2: male, 73 years old Hypertension 3: female, 82 years old Hypertension, chronic ischemic heart disease, chronic obstructive bronchopathy 4: male, 53 years old Hypertension	Treatment: Patients were treated with up to 4 infusions of eculizumab Patients were also treated with anticoagulant therapy with Enoxaparin 4000 IU/day via subcutaneous injection, antiviral therapy with Lopinavir 800 mg/day + Ritonavir 200 mg/day, hydroxychloroquine 400 mg/ day, ceftriaxone 2 g/day IV, vitamin C 6 g/day for 4 days, and were on Non-Invasive Ventilation (NIV)	Length of follow-up: 1: 15 days 2: 6 days 3: 16 days 4: Unknown	Observations: Four COVID-19 patients were admitted to the intensive care unit because of severe pneumonia or ARDS. All patients successfully recovered after treatment with eculizumab. Eculizumab induced a drop in inflammatory markers. Mean C Reactive Protein levels dropped from 14.6 mg/dl to 3.5 mg/dl and the mean duration of the disease was 12.8 days.	Authors conclusion: Eculizumab has the potential to be a key player in treatment of severe cases of COVID-19. Our results support eculizumab use as an off-label treatment of COVID-19, pending confirmation from the ongoing SOLID-C19 trial
Multiple treatment						
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Liu et al, 2020	Type of study: Case-study, data was retrospectively collected Setting: - Country: China Source of funding: -	N=1 • 50-year-old male • Resident of Wuhan • Received liver transplantation for hepatitis B cirrhosis on July, 2017 • Current immunosuppression (tacrolimus monotherapy at a mean dosage of 0.03 mg/kg/d) • The oropharyngeal swab tested positive for SARS-CoV-2.	Treatment: • Immunosuppression withdrawal • Umifenovir (0.2g three times daily) and lopinavir/ ritonavir (400 mg and 100 mg respectively, two times daily) for one week • Systemic methylprednisolone (initially 40 mg/d for a week, then tapered to 20 mg/d for a week) • Intravenous immunoglobulin (10 g/d for 12 days)	Length of follow-up: Until discharge (36 days)	Observations: Description of chest-CT results, oropharyngeal swab results, inflammatory markers, markers of liver function, clinical characteristics (fever, symptoms) and days of treatment.	Remarks: This is a case study Authors conclusion: Clinical data on COVID-19 infection in transplant population is still very limited. In present case, recovery after having severe COVID-19 pneumonia may depend on normalization of immunity. Temporary withdrawal of immunosuppression and administration of corticosteroid in low-dose might be principle components of therapeutic regime. Nevertheless, success of a single positive case indeed does not

			• Prophylactic antibiotic (cefoperazone, 2.0 g/d twice a day) • Alpha interferon (4 million units daily for 10 days, atomization inhalation) • *(nutritional supportive treatment and oxygen treatment)*			represent the rationality and necessity of complex strategy. Additional data from immunosuppressed cases need to be collected to further recognize the clinical features of COVID-19 in transplant recipients.
Novi et al., 2020	Type of study: Case report Setting: Hospital (not specified) Country: Italy Source of funding: No funding reported	Inclusion criteria: n.a. (case report) Exclusion criteria: n.a. (case report) N total at baseline: N=1 Important characteristics: Age: 58 years Gender: male Medical condition: primary progressive multiple sclerosis, diagnosed in 2009. Past medical history includes allergic rhinitis, asthma and peptic ulcer.	In January 2018 treatment with ocrelizumab (humanized anti-CD20 monoclonal antibody) was started. Periodic 6-month ocrelizumab infusions were performed until August 2019. A reinfusion was rescheduled in March 2020 but patient developed fever and cough in the beginning of March. Patient was treated with symptomatic therapy for high fever (paracetamol	Length of follow-up: Hospital admission at March 10, discharged at March 13, phone interview at March 28. Lost to follow-up: n.a. (case report)	*Resolution of symptoms* Resolution of symptoms within 2 days. Discharged after 4 days. No occurrence of symptoms, as reported during phone interview. *Inflammatory markers* Admission • Leukocyte count: 7.79×10^9 cells/L, range 4.90-9.80 • Lymphocyte count: 1.50×10^9 cells/L, range 1.10-4.80 • C-reactive protein levels: 63.1 mg/L, range 0-5 • IL-6 levels: 6 pg/ml, range 0-3.4 • IgG hypogammaglobulinemia: 6.5 g/L Discharge • Leukocyte count: 5.13×10^9/L cell/L • Lymphocyte count: 1.63×10^9/L • C reactive protein levels: 16.4 mg/L	Authors conclusion: We speculate that the persistence of B cells within secondary lymphoid organs, associated with a moderately reduced immune response due to lack of peripheral B cells might have played a favourable role in this patient. The lack of significant increase of IL-6 (that might be released by the peripheral B cells) seems to support our hypothesis. If confirmed by larger case series, our observation might indicate that patients who undergo B cell depletion could be protected from serious complications of COVID-19 and might support the use of selective immunosuppressant such as tocilizumab in serious COVID-19 cases.

					• Complete B-cell depletion: 1 CD19+ cell/mm^3	
Liu et al., 2020	Type of study: case report (N=3) Setting: Dazhou Central Hospital, Dazhou, Sichuan, China Country: China Source of funding: This study was funded by Sichuan City Science and Technology Bureau Key Research and Development Projects	Inclusion criteria: severe COVID-19 pneumonia who were managed by a multidisciplinary and personalized approach that included nutritional support, antiviral pharmacotherapy, active control of comorbidities, prevention of complication development and psychological intervention. Exclusion criteria: not reported N total at baseline: 3 Important characteristics: Age, sex 1. 32, male 2. 48, male 3. 84, female Disease characteristics: All had a severe COVID-19 pneumonia Current smoker: 1. No 2. Yes 3. No Comorbidities: 1. None 2. Diabetes and COPD 3. Osteoporosis	. - ceftazidime 2.0g twice daily for 13 days - levofloxacin 0.5g daily for 3 days - recombinant interferon α aerosol 500 x 10^6 U twice daily for 17 days - lopinavir ritonavir 0.2g twice daily for 5 days oral umifenovir 0.2g three times daily - intravenous esomeprazole 40mg/day q12h for 5 days - injectable Xuebijing for 13 days Besides CPAP ventilation ((Fi: 0.4e0.6) for 5 days), enteral nutritional support, psychological Intervention and traditional Chinese medicine. 2. - recombinant interferon a aerosol (500 x 10^6 U twice daily) - lopinavir-ritonavir, metformin (0.5 g twice daily) - intravenous ceftazidime (2 g twice daily) - oral glimepiride (2 mg once daily Besides oxygen supplementation (5 mL/min) and nutritional support.	Length of follow-up: Until discharge Loss-to-follow-up: None	Clinical outcome: 1. The patient showed clinical improvement until discharge. 2. The patient's condition worsened despite treatment, the patient needed mechanical ventilation. The patient received intravenous insulin (20IU/daily) and intravenous moxifloxacin (0.4 g once daily). The patient gradually improved until discharge. 3. The patient showed clinical improvement until discharge. Chest CT: 1. Improved chest CT 2. Improved chest CT 3. Improved chest CT	Remarks: The authors describe a multidisciplinary approach with early screening, early recognition, early diagnosis and early prevention of complications, rather than a single antiviral treatment. Author's conclusion: "In conclusion, our successful management of COVID-19 cases including severe cases and cases with mortality risk factors shows that early screening and prompt diagnosis and a multidisciplinary therapeutic approach that includes nutritional support, pharmacotherapy, and psychotherapy and tailors to the specific condition of the patient are critical to achieving a favorable clinical outcome."

			3. - recombinant interferon α aerosol (500 x 10^6 U twice daily) - intravenous methylprednisolone (40 mg twice daily) - intravenous esomeprazole (40 mg twice daily) - oral umifenovir (0.2 g, three times daily) Besides oxygen supplementation (4L/min.) and human immunoglobulin (10 g/day) for 6 days, nutritional support and traditional Chinese medicine.			
Study reference	**Study characteristics**	**Study population** (number, selection criteria)	**Treatment** (drug, dosage, frequency)	**Follow-up**	**Description of variables** (primary and secondary outcomes, other variables described)	**Comments**
Xiong et al, 2020	Type of study: Case-study, data was retrospectively collected Setting: - Country: China Source of funding: This study was funded by the Medical Science Advancement Program (Clinical Medicine) of Wuhan University (grant number TFLC2018002)	N=3 • 65-year-old male (father), history of hypertension and coronary heart disease • 61-yeard-old female (mother) • 38-year-old male (son) • Residents of Wuhan • Due to the initial shortage of testing kits for SARS-CoV-2, thecases were not diagnosed until day 9	Treatment: All received: • Oxygen through nasal canula (2L per minute) • 75 mg oseltamivir (2dd for 5 days) • 80 mg methylprednisolone sodium succinate (3dd first 3 days, followed by 40 mg dd for the following 3 days, 20 mg dd for another 3 days before being discontinued) Father received:	Length of follow-up: Until discharge (20 days)	Observations: Description of chest-CT results, oropharyngeal swab results, inflammatory markers, clinical characteristics (fever, symptoms) and days of treatment.	Remarks: This is a case study Authors conclusion: The fever disappeared in all three patients approximately 5–7 days following admission and their clinical conditions further improved thereafter. After approximately 3weeks of hospitalisation, lung inflammation had largely resolved, as indicated by CT scans, and two consecutive throat swab samples tested negative for SARS-CoV-2 with the RT-PCR test performed for each patient. The patients were discharged from hospital and were required to stay home for further recovery. They have reported

			• Methylprednisolone at a dose of 40 mg per day for 5 days and 20 mg per day for another 5 days. Mother and father administered: • Amoxicillin sodiumflucloxacillin sodium (6g, intravenous infusion every 12hours) for 2weeks. Son received: • Son received ceftriaxone-tazobactam (2g, intravenous infusion, every 12hours) for 3days, followed bybiapenem (0.3g, intravenous infusion every 8hours) for another 9days. Mother and son were administered: • Mother and the son were administered levofloxacin (0.4g, intravenous infusion, daily) starting on admission day 6 until day 14. Fahter received: • Moxifloxacin (0.4g, intravenous infusion, daily) for 2weeks starting on admission day 1.			no new symptoms.