Appendix

Key Studies of Pharmacological Interventions For COVID-19

REFERENCE	ORIGIN	STUDY DESIGN	POPULATION AND MAIN RESULTS	COMMENTS
Hydroxychloroquine				
Chen *et al*.[19]	China	Randomized clinical trial	30 patients were randomized to HCQ or SOC. No difference in negative conversion in nasopharyngeal samples at day 7.	Only abstract available in English. Small sample. No clinical endpoint.
Chen *et al*.[20]	China	Randomized clinical trial	62 patients were randomized to HCQ or SOC. Authors concluded the use of HCQ significantly shortens time to clinical recovery.	Did not include severe disease. Arms of the trial have important baseline differences. Variability in cointerventions (patients in both arms received other anti-infectives, IVIG and corticosteroids).
Gautret *et al*.[15]	France	Non-randomized clinical trial	14 patients treated with HCQ, 6 patients treated with HCQ and azithromycin, and 16 untreated patients used as controls. At day 6, 8/14 (57%) in the HCQ group, 6/6 (100%) in the HCQ and azithromycin group, and 2/16 (12.5%) in the control group had negative PCR results.	Best characterized as case series (small number of treated patients), lack of patients with severe illness, not designed to have control group, no clinical endpoint, loss to follow-up, conclusions not supported by the reported results. Co-author is Editor-in-Chief of the journal.
Gautret *et al*.[23]	France	Uncontrolled, observational	80 patients treated with HCQ and azithromycin. Favorable outcome was reported for 81.3%; 15% required O2; 3 patients transferred to ICU; 1 patient died; mean time to discharge from ID unit was 4.1 days. At day 8, PCR results were negative in 93% of those tested.	Preprint – no peer review. Almost all patients were considered low risk for clinical deterioration (4 asymptomatic patients included). No control group – impossible to tell if results are attributable to the intervention.
Mahevas *et al*.[24]	France	Retrospective, observational	84 patients with hypoxic pneumonia who received HCQ were compared with 97 similar patients who did not get the drug. The primary outcome — transfer to the ICU or death from any cause within 7 days — did not differ significantly between the groups.	Preprint – no peer review. Case-control methodology on a review of medical records.
Lopinavir/ritonavir				
Cao *et al*.[36]	China	Randomized clinical trial	199 patients with pneumonia, and an oxygen saturation of < 94% or a ratio of partial pressure of oxygen to fraction of inspired oxygen < 300 mmHg to receive SOC alone or with oral LPV/r. Trial arms did not differ significantly in time to clinical improvement (median, 16 days), duration of intensive care unit stay, duration in days of mechanical ventilation, or duration in days of oxygen support. Patients who received LPV/r had lower 28-day mortality (19% *vs* 25%), but the between-group difference was not significant.	Well-executed study, but did not demonstrate efficacy. Treatment interrupted in 14% due to adverse events. Possibly underpowered.

Remdesivir				
Grein *et al*.[40]	International	Observational	53 patients with severe disease that received intravenous remdesivir in the U.S., Canada, Europe, and Japan were evaluated. Need for oxygen support improved in 68%; 57% of patients on mechanical ventilation were extubated, and overall mortality was 13%. 60% had adverse events.	Without a comparison group, it is not possible to know whether the observed improvement was because of the drug.
Adaptive COVID-19 Treatment Trial[41]	International	Randomized clinical trial (interim analysis)	1063 patients with advanced COVID-19 and lung involvement that received intravenous remdesivir in 68 sites across the U.S., Europe, and Asia were evaluated. An interim analysis found that the median time to recovery was 31% faster with remdesivir than placebo (11 *vs* 15 days). The mortality rate was 8.0% with remdesivir and 11.6% with placebo (p = 0.059).	Good quality RCT. Interim analysis. More detailed information about the trial results are awaited.
Convalescent Plasma				
Shen *et al*.[44]	China	Uncontrolled case series	5 critically ill adults with ARDS. Following plasma transfusion, ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 were discharged from the hospital and 2 were in stable condition at 37 days after transfusion.	No control group. Variability in cointerventions (all received LPV/r, MP, interferon alfa b-1).
Duan *et al*.[45]	China	Observational (case series with historical controls)	10 patients with severe disease received convalescent plasma from recovered donors; historical control group of 10 patients in the same hospitals. All symptoms in all treated patients "disappeared or largely improved" within 1 to 3 days. No adverse events reported.	Small series. Variability in cointerventions (all received antivirals). Convalescent plasma therapy might be effective and safe for severely ill patients – RCT needed.
Methylprednisolone				
Wu *et al*.[48]	China	Retrospective, observational	In 201 patients with confirmed pneumonia, 84 developed ARDS. 30% of all patients received MP. In patients with ARDS, MP appeared to reduce the risk of death.	Small sample size. Confounding by intervention. Variability in cointerventions.

HCQ: hydroxychloroquine; SOC: standard of care; IVIG: intravenous immunoglobulin; PCR: polymerase chain reaction; ICU: intensive care unit; LPV/r: lopinavir/ ritonavir; NIH: National Institutes of Health; RCT: randomized clinical trial; ARDS: acute respiratory distress syndrome; MP: methylprednisolone