SARS-CoV-2 is a pathogen phylogenetically similar to two previous zoonotic coronaviruses: severe acute respiratory syndrome coronavirus 2002 (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus 2012 (MERS-CoV), the case fatality rates (CFRs) of which were 7%–10% and 30%, respectively. (1,2) While the CFR of the current pandemic is considerably less than these prior epidemics (approximately 1%–2% of confirmed cases), the sheer numbers of patients globally that have contracted the disease has meant that the overall mortality has far outstripped that of the other coronavirus infections. This mortality seems to considerably vary from country to country, and this has not been fully explained. The real-time numbers infected and the mortality rates can be accessed at the following site: https://www.worldometers.info/coronavirus/. The low rates in areas such as South Korea are probably due to the extensive testing that has been performed to date, increasing the denominator by including asymptomatic or mildly symptomatic patients; however, other factors may be involved such as the overall age of the populations concerned and possibly the effect of vitamin D (i.e. sunlight) on the viral receptor ACE2 in the lung. (2,3)

Whatever the cause is, it is incumbent upon society to reduce the impact of the pandemic by social distancing, i.e. restriction of movement and mandatory isolation (which are more difficult to achieve in societies that are less authoritarian and the populace less obedient), effective therapies and vaccination. As far as the therapy is concerned, there have been, as of 6 April 2020, 1,277,248 documented cases with 69,570 deaths. Of the 941,217 active cases, 95% are mild and 5% are serious or critical, and it is the latter group that requires therapy beyond pure supportive measures.

It appears that there are three phases to the disease that merge into each other although it is difficult to predict whether or when progression will occur (4) – first, the viral response phase in which mild constitutional symptoms predominate and associated laboratory features such as lymphopaenia, increased prothrombin time, increased D-dimer and a mild increase in LDH occur. This merges over a variable time period in a proportion of patients into a phase in which pulmonary symptoms begin to emerge with dyspnoea and mild hypoxaemia with a partial pressure of arterial oxygen (PaO₂) relative to the fraction of inspired oxygen (FiO₂), i.e. a $P_{\text{a}}O_2/F_{\text{i}}O_2 \leq 300$ and a rising C-reactive protein (CRP) with a low procalcitonin. An even smaller proportion then progresses to the hyperinflammatory phase in which a “cytokine storm” characterized by increased interleukin (IL)-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, tumour necrosis factor and possibly most importantly IL-6 results in organ dysfunction, including the acute respiratory distress syndrome (ARDS), renal dysfunction, hypotension and cardiac failure. (5)

The aim of any therapy would be to intervene at a point that could prevent the need for mechanical ventilation (MV) and the occurrence of significant organ dysfunction, as the mortality for patients receiving MV exceeds 50% in most studies. (6) In order to do so, patients must be assessed for features denoting the phase of the illness. Clinical markers of severity include older age, comorbidity (particularly diabetes and hypertension), hypoxaemia, requirement for MV and evidence of organ dysfunction, including myocardial ischaemia or heart failure. (5,7,8) These factors were confirmed in a large retrospective case series of 1099 patients, which demonstrated that higher age and any comorbidity were associated with more severe diseases. Overall, severe pneumonia occurred in 15.7%, and mortality in this study...
was 1.36%, which was lower than the other estimates at that time.(9,10)

The INARC data from the United Kingdom summarizing those patients with severe disease found the following to be significant:(6)

Men are more likely to be admitted to ICU compared with other viral pneumonias (70.5% vs 54.3%) and men with CoVID-19 are more likely to die than women (53.2% vs 37.5%). The overall death rate for CoVID-19 for patients admitted to critical care is also much higher than for other viral pneumonias (47.9% vs 22.2%); 22.4% of patients admitted to ICU are young (<50 years old), but the death rate increases dramatically with age; 16–49 years (24.3%), 50–69 (40.3%) and >70 (73.2%). The death rate was higher in people who are overweight (BMI 30+ = 60.9% vs BMI 25 to <30 = 41.7%).(6)

Laboratory parameters associated with the development of ARDS and progression from ARDS to death include neutrophilia (HR, 1.14; 95%CI, 1.09–1.19; and HR, 1.08; 95%CI, 1.01–1.17, respectively), higher lactate dehydrogenase [HR, 1.61; 95%CI, 1.44–1.79; and HR, 1.30; 95%CI, 1.11–1.52] and D-dimer [HR, 1.03; 95%CI, 1.01–1.04; and HR, 1.02; 95%CI, 1.01–1.04, respectively].(5) In another study, an absolute D-dimer value >1 μg/l (18.42, 2.64–128.55; P = 0.0033) was particularly significant.(11)

Hyperferritinaemia (mean 1297.6 ng/ml in non-survivors vs 614.0 ng/ml in survivors; P < 0.001) was highly discriminatory as were IL-6 levels (P < 0.0001), suggesting that mortality might be due to virally driven hyperinflammation and may also be a marker of virally induced haemophagocytic lymphohistiocytosis.(12,13)

With reference to the above, possibly the most important marker of the hyperinflammatory state and worse outcome is the IL-6 level. A study that examined 40 patients admitted to a single hospital found that the 32.5% that required MV did not differ with regard to epidemiological factors such as age, comorbidities, radiological findings, respiratory rate or qSofa score. However, an elevated IL-6 was strongly associated with MV (P = 1.2 × 10−8) and that a level >80 pg/ml during the disease predicted respiratory failure with high accuracy (P = 1.7 × 10−8, AUC = 0.98) with a rate of 22 times higher vs those with lower levels.(14)

Cardiac disease and thrombotic episodes appear to contribute to mortality. With regard to thrombosis, in a study of 449 patients with severe CoVID-19, 99 received heparin (mainly low molecular weight heparin (LMWH) for ≥7 days). As seen in previous studies, in multivariate analysis, D-dimer, prothrombin time and age were positively, and platelet count negatively correlated with 28-day mortality. However, it appeared that heparin was only of benefit in those with more extensive thrombosis as evidenced by a sepsis-induced coagulopathy score ≥4 (40.0% vs 64.2%, P = 0.029), or D-dimer >6 fold of upper limit of normal (32.8% vs 52.4%, P = 0.017).(15,16)

In another study in patients receiving conventional antiviral treatment, LMWH reduced hypercoagulability, inhibited IL-6 release and counteracted IL-6 biological activity potentially blocking the cytokine storm.(17) This hypercoagulability may predispose to pulmonary embolism.

With regard to cardiovascular disease (CVD), a recent study described the relationship between troponin levels and prior cardiac disease and outcome. Of 187 confirmed CoVID-19 patients, 23% died. Sixty-six (35.3%) had underlying CVD which included hypertension, coronary heart disease and cardiomyopathy, and of these and 52 (27.8%) had elevated troponin T (TnT) levels. There was an exponential increase in mortality according to the presence of CVD and or elevated TnT; 7.62% (no CVD; normal TnT), 13.33% (CVD; normal TnT), 37.50% (no CVD; elevated TnT) and 69.44% (CVD; elevated TnT).(18)

Patients with underlying CVD were more likely to develop myocardial injury with increased TnT levels, and the high-sensitivity CRP positively correlated with the rise in TnT and N-terminal pro–brain natriuretic peptide levels. Interestingly, the mortality of patients with and without use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was 36.8% and 25.6%, respectively; however, this may just be due to a correlation between the use of these agents and underlying CVD.

THERAPIES FOR COVID-19

Therapy should be administered according to disease severity. In the first phase, symptomatic therapy would be utilized consisting of paracetamol and possibly vitamin D 50,000 units weekly or 4000 units daily.(3)

Antiviral therapy

Antiviral therapy may be of value although a recent trial of lopinivar/ritonavir proved to be negative when used as a single agent.(19) Other agents that are being studied are remdesivir, an agent devised for the therapy of Ebola, and there is promising evidence that this agent, which binds to RNA-dependent RNA polymerase and acts as an RNA-chain terminator, may be of value in treating CoVID-19 as well. There are currently four ongoing clinical trials utilizing this agent.(20,21)

There are also numerous other ongoing studies utilizing a variety of antiviral agents. These can be found at http://metaevidence.org/viewTreatment.aspx?exposition=545.

Chloroquine

Chloroquine (CHQ) is another potential antiviral agent and although evidence for or against its use and with or without azithromycin is accumulating, whether or not it is effective is still controversial.

Potent in vitro activity of CHQ has been demonstrated against SARS-CoV-2 and as a consequence, small observational studies in vivo have suggested that viral clearance
is more rapid and that it inhibits progression to pneumo-
nia when compared with controls.(22–24) In a study by
Gautret et al., 6 of their 20 patients (there were 16 controls)
on hydroxychloroquine (HCHQ) were prescribed azithro-
mycin as well as prophylaxis for bacterial infection, and this
appeared to enhance the activity of the HCHQ in terms
of viral eradication, leading to a recommendation that they
should be used together.(25)

There is, however, uncertainty as to the correct dose that
would be effective particularly since there are two main
forms of the drug: the CHQ phosphate and HCHQ, both
of which have very long half-lives.(21)

More recently, an extension of the previous French study
was published, which suggested an efficacy of HCHQ.(26)
In this study, a rapid fall of nasopharyngeal viral load tested
by polymerase chain reaction was noted, with 83% negative
at Day 7, 93% at Day 8, and virus cultures from respira-
tory samples were negative in 97.5% at Day 5. There were
numerous problems with this study, the most important
of which was a lack of outcome data and some confusion
as to patient numbers with some dropping out and others
only just starting therapy after the 6-day period ended.
In a journal pre-proof, another group of French investigators
repeated the study in 10 patients and 80% were still positive
for SARS-CoV-2 RNA at Days 5–6 after treatment initia-
tion.(27) Finally, in a Chinese pilot study of 30 patients, 15
received CHQ, 13 tested negative for SARS-CoV-2 after a
week of treatment vs 14 of the controls.(28)

Despite this, the FDA has authorized the use of
unproven therapies, including CHQ on the basis that ben-
et may exceed risk and, in addition the Indian National
Taskforce for CoVID-19 has authorized its use for prophy-
axis.(29,30)

Anti-inflammatory agents

Tocilizumab

Tocilizumab (Tmab) is a humanized monoclonal antibody
that has been approved for the therapy of patients with
rheumatoid arthritis. It inhibits IL-6, which is secreted by
monocytes and macrophages, and which is significantly
increased in patients who have developed the “cytokine
storm” described above.(12)

In a study of the MERS-CoV syndrome, IL-6, IL-8 and
IL-1β were significantly elevated and, similar to the picture
in CoVID-19, there was a delayed phasic cytokine response
with the development of hypoxaemia and ARDS.(31–33)
A small study (21 patients) from China looked at a sin-
gle dose of 400 mg (1 patient received a second dose) in
21 patients. All were confirmed cases and had markedly
elevated IL-6. All patients improved over the next few
days with an initial resolution of fever, improvement in gas
exchange, normalization of the CRP by Day 5 and clear-
ing of pulmonary infiltrates.(34) No short-term adverse
events were reported. All of the patients had deterio-
rated despite routine therapies in the previous week, and

the agent is now listed as a treatment option for severe or
critical cases with elevated IL-6 in the National Health
Commission of the People’s Republic of China COVID-
19 Diagnosis and Treatment Guide.(35) A very recent
case study has described the successful use of Tmab in a
patient on maintenance therapy for multiple myeloma who
had received bortezomib, thalidomide and dexamethasone
therapy approximately 4 years previously and had been on
thalidomide maintenance since then. He presented with a
shortness of breath only but responded rapidly to Tmab
after having deteriorated despite the oral antiviral therapy,
umifenovir 200 mg/8 h.(36)

The recommended dose is 4–8 mg/kg or 400 mg intrave-
nously once, with the option to repeat in 12 h (not exceed-
ing a total dose of 800 mg). There are two ongoing trials in
China and one study in the USA of sarilumab, a different
IL-6 inhibitor.(37)

The difficulty is of knowing precisely when to administer
Tmab, whether it should be administered at the first pre-
sentation with hypoxaemia or whether one should wait for
evidence of the hyperinflammatory response as evidenced
by a rising CRP, ferritin, D-dimer and worsening hypox-
aemia. We are initiating a study evaluating the use Tmab
in patients with hypoxaemia, elevated CRP, ferritin and
D-dimers, which will hopefully contribute more data to
the body of evidence regarding therapy, including its safety,
particularly regarding secondary infections. There are cur-
cently four ongoing randomized clinical trials of Tmab, as
well as studies on numerous other biologicals which can be
viewed at http://metaevidence.org/COVID19.aspx.

Immunoglobulins

It is possible that high-dose intravenous immunoglobulin
(IVIg) may have a beneficial effect in the hyperinflamma-
tory phase. IVIg is a blood product containing pooled pol-
clonal immunoglobulin G from healthy donors containing
many bioactive moieties, which has been used in autoim-
mune or inflammatory diseases for many years.(38)

In previous studies of SARS-CoV-1 and MERS-CoV,
IVIg showed clinical benefit with good tolerance, and small
case series have suggested a possible benefit in CoVID-19.
(39–41) In one, three patients who had deteriorated despite
standard therapy, but had not yet been mechanically venti-
lated, were administered 0.4 g/kg IVIg. All became apyrex-
ial in 1–2 days and pulmonary manifestations improved in
3–5 days.(42) Currently, two randomized controlled trials
evaluating the efficacy of high-dose IVIg therapy in severe
CoVID-19 have been initiated, which will provide more
evidence for use. These can be viewed at http://metaevi-
dence.org/COVID19.aspx.

Corticosteroids

A systematic review of observational studies of corticoster-
oids administered to patients with SARS-CoV-1 reported
Richards et al.

no survival benefit and possible harm and increased mortality and secondary infections were noted with severe influenza A; however, the evidence quality was low.(43) A subsequent study noted in the WHO guidelines found no effect on mortality.(43) Similarly in patients with MERS-CoV, corticosteroids had no effect on mortality but a delayed lower respiratory tract clearance of virus.(43)

In contrast, in the study by Wu described above, methylprednisolone was associated with increased survival in patients with ARDS specifically (HR, 0.38; 95%CI, 0.20–0.72; \( P = 0.003 \)).(7)

In a recent multicentre, randomized controlled trial in 17 Spanish ICUs in patients with established, moderate-to-severe ARDS (\( P/F < 200 \) mm Hg) with a positive

| Clinical classification | Presentation | Supportive treatment | Antiviral treatment | Anti-inflammatory treatment |
|--------------------------|--------------|----------------------|--------------------|---------------------------|
| Asymptomatic             | None: Monitor| Vitamin D 50,000 units stat | None               | None                      |
| URT symptoms             | Fever, sore throat, cough; no dyspnoea or tachypnea; saturation normal | Vitamin C 500 mg tds | None               | Paracetamol |
| URT symptoms + age > 65± comorbidity | Symptomatic as above | Plasmoquine 400 mg BD × 1 day then 400 mg daily, 5 days± Azithromycin 500 mg IVI stat then 250 mg daily Watch QT interval (replace Ca\(^{2+}\) and Mg\(^{2+}\)) + Zinc 200 mg BD± Lopinavir/ritonavir 200 mg/50 mg 2 BD | Paracetamol prophylactic anticoagulation |
| LRT symptoms ± pneumonia on CXR | Supplemental oxygen therapy | As above: Full anticoagulation if D-dimer >1 | Methylprednisolone 40 mg BD OR Dexamethasone 20 mg daily × 5 ± Azithromycin 500 mg IVI stat then 250 mg daily Over controversial: Polygam 24 g × 3 days review with expert group before use of these agents |
| Severe symptoms | Transfer to ICU Try to avoid mechanical ventilation Try Sequential: high-flow nasal with surgical mask or polymask CPAP: (adequate staff PPE) Mechanical ventilation ECMO if resources allow | Therapy as above: Consider: as above: add tocilizumab (Actemra) 400 mg IVI over 60 min × one dose Or controversial: Polygam 24 g × 3 days review with expert group before use of these agents |
| Cardiac failure/myocarditis | Gallop Reduced EF Troponin elevated | As above | As above | Polygam 24 g daily × 4 Methylprednisolone 250 daily × 3 |

URT: Upper respiratory tract infection; LRT: Lower respiratory tract infection.
end-expiratory pressure of ≥10 cm H2O and FiO2 of ≥0.5, 24 h after ARDS onset, patients were randomized to IV dexamethasone 20 mg daily (Days 1–5), then 10 mg daily (Days 6–10) or to continued routine care. Of 277 patients, 139 were assigned to the dexamethasone group. Ventilator-free days were higher in the dexamethasone group (4.8 days [95% CI 2.57–7.03]; \( P < 0.0001 \)) and 60-day mortality was 21% vs 36% in the controls: difference −15.3% (−25.9 to −4.9); \( P = 0.0047 \)). Adverse events did not differ significantly between groups.(44)

There are numerous randomized trials ongoing utilizing corticosteroids of different types and differing doses. These can be found at http://metaevidence.org/viewPathology2.aspx?exposition=522.

**Vitamin D**

SARS-CoV downregulates ACE2 protein expression with increased inflammation and injury from neutrophil infiltration in the lung from unbalanced activation of the renin angiotensin aldosterone system.(45) Vitamin D appears to be a negative endocrine regulator of the RAAS and can lower RAAS activity via a suppression of renin expression and as such has potential for benefit.(46)

**Zinc and vitamin C**

There is evidence that the damage that occurs to the lungs occurs through the binding of the virus surface proteins to haemoglobin releasing free iron. The virus surface proteins ORF8 and surface glycoprotein bind to porphyrin, while other proteins orf1ab, ORF10 and ORF3a could coordinate an attack on the heme on the 1-beta chain of haemoglobin to dissociate iron. This results in decreased ability to carry oxygen and carbon dioxide and oxidant-mediated injury in the lung.(47)

Vitamin C is an effective extracellular nutritional antioxidant. If injury occurs due to an increase in iron then vitamin C may be an effective quencher of free radicals induced by iron.(48)

CHQ has the potential to prevent some viral proteins to attack the heme and also inhibits binding of ORF8 and surface glycoproteins to porphyrins, which might reduce the extent of the pulmonary injury.

The relationship of the pulmonary manifestations to the effects of the virus on iron may lead to new therapies involving sequestration of iron and use of antioxidants. Increasing intracellular zinc (Zn\( ^{2+} \)) with zinc-ionsophores like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses, including poliovirus and influenza virus. The combination of Zn\( ^{2+} \) and PT at low concentrations (2 mM Zn\( ^{2+} \) and 2 mM PT) inhibits the replication of SARS-CoV in cell culture.(49)

**Therapeutic protocols (Table 1)**

In the first phase of the disease with mild upper respiratory symptoms, age <65 years, no comorbid conditions, not hypoxaemic (saturation normal as monitored by pulse oximetry): isolate at home if possible; paracetamol 1 g PO 6–8 hourly as required; vitamin D (calciferol) 50,000 IU PO STAT; zinc 100–200 mg PO daily for 5 days. It is possible that CHQ may be helpful at this stage but resource limitations preclude this.

In the second phase of the illness in which pulmonary infiltrates and hypoxaemia begin to occur, it is reasonable to try agents such as CHQ, azithromycin, colchicine and zinc as combinations or singly; however, the aim would be to use anti-inflammatory therapies early in the pulmonary phase to reduce progression to MV.

In conclusion, we are dealing with a pandemic unprecedented in the era of modern health-care technology. We are as yet hamstrung by a lack of an effective vaccine or of effective therapies to halt spread of disease and progression to the potentially lethal hyperinflammatory phase of this illness. Some agents appear promising in this regard and in particular those that inhibit IL-6, which frequently appears to be the driver of the inflammatory process. Given the high mortality of those in this phase of the disease, therapy with these agents and potentially other anti-inflammatory agents such as pooled immunoglobulin would appear to be justified.

**REFERENCES**

1. Paules CI, Marston HD, Fauci AS. Coronavirus infections – more than just the common cold. JAMA. 2020. <https://doi.org/10.1001/jama.2020.0757>.

2. Kwok KO, Tang A, Wei VWI, et al. Epidemic models of contact tracing: systematic review of transmission studies of severe acute respiratory syndrome and Middle East respiratory syndrome. Comput Struct Biotechnol J. 2019; 17:186–194. Published online January 26, 2019.

3. Garami A. Rapid response: Re: preventing a Covid-19 pandemic – is there a magic bullet to save COVID-19 patients? We can give it a try!. BMJ. 2020. <https://www.bmj.com/content/368/bmj.m810/rr-24 accessed 1/4/20>.

4. Siddiqu HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant. 2020. doi:10.1016/j.healun.2020.03.012.

5. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020. doi:10.1001/jamaitnmed.2020.0994.

6. ICNARC. Report on 775 patients critically ill with COVID-19. <https://www.icnarc.org/About/Latest-News/2020/03/27/Report-On-775-Patients-Critically-Ill-With-Covid-19>.

7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. NEJM. Published Online January 24, 2020 <https://doi.org/10.1016/S0020-7624(20)301835>.

8. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. Published Online February 21,
9. Guan W, Ni Z, Hu Y, et al, on behalf of China Medical Treatment Expert Group for 1029-nCoV. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med. 2020. Posted online February 9, 2020 New England Journal of Medicine doi:10.1056/NEJMoa2002032.

10. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(12):1239–1242. Published online February 24, 2020. doi:10.1001/jama.2020.2648 [accessed 09.03.20].

11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229):1054–1062. <https://doi.org/10.1016/S0140-6736(20)30566-3>.

12. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020. Published online March 3. doi:10.1007/s00134-020-05991-x.

13. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, and the HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229):1033–1034. <https://doi.org/10.1016/S0140-6736(20)30628-0>.

14. Herold T, Jurinovic V, Arreich C, et al. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. medRxiv preprint doi:https://doi.org/10.1101/2020.04.01.20047381.

15. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020. doi:10.1111/jth.14817.

16. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. J Thromb Haemost. 2020. doi:10.1111/jth.14781.

17. Shi C, Wang C, Wang H, et al. Clinical observations of low molecular weight heparin in relieving inflammation in COVID-19 patients: a retrospective cohort study. medRxiv preprint doi:https://doi.org/10.1101/2020.03.28.20046144.

18. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017.

19. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020. doi:10.1056/NEJMoa2001282 [accessed 02.04.20].

20. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. mBio. 2018; 9:e00221-18. <https://doi.org/10.1128/mBio.00221-18>.

21. McCreary EK, Pogue JM. COVID-19 treatment: a review of early and emerging options. Open Forum Infect Dis. 2020; 7:ofaa105. <https://academic.oup.com/ofid/advance-article-abstract/doi/10.1093/ofid/ofaa105/5811022> [accessed 03.04.20].

22. Rolain JM, Colson P, Raoul D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents. 2007; 30:297–308. doi:10.1016/j.ijantimicag.2007.05.015.

23. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 [Epub ahead of print]. doi:10.1038/s41422-020-0282-0.

24. Keyaerts E, Vlijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004; 323:264–8. doi:10.1016/j.bbrc.2004.08.085.

25. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial. Int J Antimicrob Agents. 2020;105949. doi:10.1016/j.ijantimicag.2020.105949.

26. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. Int J Antimicrobial Agents. 2020. <https://www.mediterraneainfection.com/wp-content/uploads/2020/03/Hydroxychloroquine_final_DOI_IJAA.pdf> [accessed 04.04.20].

27. Molina JM, Delaughter C, Goff JL, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect. 2020. <https://doi.org/10.1016/j.medmal.2020.03.006>.

28. Chen J, Liu D, Lui L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci). 2020; 49(1):0–0. doi:10.3785/j.issn.1008-9292.2020.03.03.

29. FDA authorize s widespread use of unproven drugs to treat coronavirus, saying possible benefit outweighs risk. <https://www.washingtonpost.com/business/2020/03/30/coronavirus-drugs-hydroxychloroquin-chloroquine/> [accessed 02.04.20].

30. Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-Cov-2 infection. <https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARS-CoV2infection.pdf> [accessed 02.04.20].

31. Li Y, Chen M, Cao H, Zhu Y, Zheng J, Zhou H. Extraordinary GU rich-rich single strand RNA identified from SARS coronavirus contributes an excessive innate immune response. Microbes Infect. 2013; 15:88–95. doi:10.1016/j.micinf.2012.10.008.

32. Lau SK, Lau CC, Chan KH, et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel middle east respiratory syndrome coronavirus: implications for pathogenesis and treatment. J Gen Virol. 2020; 94:2679–2690. doi:10.1099/jgv.0.008734-0.

33. Zhou Y, Fu B, Zheng X, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. BioRxiv. 2020. <https://doi.org/10.1101/2020.02.12.945576>.

34. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Pre Print. Available online: <http://chinaxiv.org/abs/202003.00026> [accessed 15.03.20].
35. National Health Commission (NHC) of the People's Republic of China. The diagnosis and treatment guide of COVID-19 pneumonia caused by new coronavirus infection. 7th ed. Published March 3, 2020. Translated to English. <http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm>.

36. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 2020; 4(7):1307–1310. doi:10.1182/bloodadvances.2020001907.

37. Sanofi, Regeneron launch trials of arthritis drug Kevzara for COVID-19. <http://www.pmlive.com/pharma_news/sanofi_regeneron_launch_trials_of_arthritis_drug_kevzara_for_covid-19_1329326> [accessed 04.04.20].

38. Galeotti C, Kaveri SV, Bayry J. IVIG-mediated effector functions in autoimmune and inflammatory diseases. Int Immunol. 2017; 29:491–498. doi:10.1093/intimm/dxx039.

39. Khanna N, Widmer AF, Decker M, et al. Respiratory syncytial virus infection in patients with hematological diseases: single-center study and review of the literature. Clin Infect Dis. 2008; 46:402–412.

40. Wang JT, Sheng WH, Fang CT, et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. Emerg Infect Dis. 2004; 10:818–824.

41. Arabi YM, Arif AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med. 2014; 160:389–397.

42. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease. Open Forum Infect Dis. 2019. <https://academic.oup.com/ofid/article-abstract/7/3/ofaa102/5810740> [accessed 05.04.20].

43. WHO. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. <https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf> [accessed 04.04.20].

44. Villar J, Ferrando C. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet. 2020; 8(3):267–276. <https://doi.org/10.1016/S2213-2600(19)30417-5>.

45. Dijkman R, Jebbink MF, Deijs M, Milewska A, Pyrc K et al. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. J Gen Virol. 2012; 93:1924–1929.

46. Yuan W, Pan W, Kong J, et al. 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem. 2007; 282(41):29821–29830. doi:10.1074/jbc.M705495200.

47. Liu W, Li H. COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. 2020. ChemRxiv. Preprint. <https://doi.org/10.26434/chemrxiv.11938173.v5>.

48. Mariak PE, Hooper MH. Doctor—your septic patients have scurvy!. Crit Care. 2018; 22:23. doi 10.1186/s13054-018-1950-z.

49. te Velthuis AJW, van den Worm SHE, Sims AC, et al. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog. 2010; 6(11): e1001176. doi:10.1371/journal.ppat.1001176.
