

## Article 2

# COVID-19 and the Rationale for Pharmacotherapy: A South African Perspective

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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 ( $\text{PaO}_2$ ) relative to the fraction of inspired oxygen ( $\text{FiO}_2$ ), i.e. a  $P/F$  ratio  $\leq 300$  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- $\gamma$  inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- $\alpha$ , 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 ( $P = 1.2 \times 10^{-5}$ ) and that a level >80 pg/ml during the disease predicted respiratory failure with high accuracy ( $P = 1.7 \times 10^{-8}$ , 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  $\geq 7$  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  $\geq 4$  (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.

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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 lopinivir/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 pneumonia 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 azithromycin 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 respiratory 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 initiation.(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 benefit may exceed risk and, in addition the Indian National Taskforce for CoVID-19 has authorized its use for prophylaxis.(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-1 $\beta$  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 single 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 clearing of pulmonary infiltrates.(34) No short-term adverse events were reported. All of the patients had deteriorated 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 intravenously once, with the option to repeat in 12 h (not exceeding 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 presentation with hypoxaemia or whether one should wait for evidence of the hyperinflammatory response as evidenced by a rising CRP, ferritin, D-dimer and worsening hypoxaemia. 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 currently 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 hyperinflammatory phase. IVIg is a blood product containing pooled polyclonal immunoglobulin G from healthy donors containing many bioactive moieties, which has been used in autoimmune or inflammatory diseases for many years.(38)

In previous studies of SARS-VoV-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 ventilated, were administered 0.4 g/kg IVIg. All became apyrexial 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://metaevidence.org/COVID19.aspx>.

### *Corticosteroids*

A systematic review of observational studies of corticosteroids administered to patients with SARS-CoV-1 reported

**Table 1:** Therapeutic Protocol for Managing COVID-19 infection

Clinical classification	Presentation	Supportive treatment	Antiviral treatment	Anti-inflammatory treatment
Asymptomatic		None: Monitor	None	
URT symptoms	Fever, sore throat, cough; no dyspnoea or tachypnea; saturation normal	Vitamin D 50,000 units stat Zinc 200 mg daily × 5 days Vitamin C 500 mg tds	None	Paracetamol
URT symptoms + age > 65± comorbidity		Symptomatic as above Vitamin D 50,000 units stat	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 <sup>2+</sup> and Mg <sup>2+</sup> ) + Zinc 200 mg BD± Lopinavir/ritonavir 200 mg/50 mg 2 BD Controversial Duration ~5 days dependent on clinical response	Paracetamol prophylactic anticoagulation
LRT symptoms ± pneumonia on CXR	Fever, dyspnoea, tachypnea, crackles saturation <90% P/F ratio <300 hypokalaemia	Supplemental oxygen therapy	As above:	Full anticoagulation if D-dimer >1 Methylprednisolone 40 mg BD OR Dexamethasone 20 mg daily × 5 then 10 mg daily × 5 Correct K <sup>+</sup>
Severe symptoms	Tachypnea, cyanosis, saturation <85%, P/F ratio <200; mechanical ventilation hypotension, hypokalaemia, organ dysfunction CRP >100 and rising; D-dimer rising; ferritin >1000	<b>Transfer to ICU</b> <b>Try to avoid mechanical ventilation</b> 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.

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;  $P = 0.003$ ).<sup>(7)</sup>

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

end-expiratory pressure of  $\geq 10$  cm H<sub>2</sub>O and FiO<sub>2</sub> of  $\geq 0.5$ , 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-ionophores 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.

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