INTRODUCTION
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the novel coronavirus first detected in Wuhan, China, that causes coronavirus disease 2019 (Covid-19) and pneumonia. Covid-19 pneumonia is defined by a positive result for SARS-CoV-2 on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a specimen collected from the upper or lower respiratory tract together with radiological features of pneumonia and clinical features of hypoxaemia and dyspnoea. Although more than 80% of patients with Covid-19 infection have mild disease and make a full recovery, a significant proportion of patients progress to pneumonia, and about half of these cases will develop severe acute respiratory syndrome (ARDS). Initial reports from China suggested that age >65 years and medical comorbidities are risk factors for poor outcomes.(1) The need for ICU admission and mechanical ventilation once ARDS develops is associated with a high mortality, ranging from 39% to 72%.(2,3) Current guidelines recommend that corticosteroids or immunosuppressive therapy should not be used in patients with Covid-19 pneumonia unless there are other indications, such as shock, asthma or exacerbation of chronic obstructive pulmonary disease.(4) However, the role of systemic corticosteroids is currently being re-evaluated in mechanically ventilated adults with ARDS, with some guidelines now suggesting their use.(5)

We describe a case of a patient with Covid-19 infection, progressive pneumonia, development of a hyperinflammatory state and cytokine release syndrome (CRS) who was successfully treated with steroids and tocilizumab.

CASE REPORT
In January 2020, a 53-year-old gentleman with a background of asthma on long-term low dose inhaled corticosteroid inhaler had an acute exacerbation of his asthma in February 2020 triggered by a viral upper respiratory tract infection and acute sinusitis and was managed with bronchodilator nebulization and a 7-day course of oral prednisone 30 mg daily. He made an uneventful recovery and proceeded to travel to Austria on 29 February 2020. During his stay in Austria, he had contact with a Covid-19 positive individual and started developing upper respiratory symptoms on 7 March. On his return to South Africa on 8 March he had a fever, sore throat, dry cough, severe wheezing and worsening dyspnoea. At that stage a commercial test for Covid-19 PCR was not yet available to the private pathology laboratories and blood tests showed a normal full blood count and a C-reactive protein (CRP) of 16 mg/L. He was advised to self-isolate at home and was managed telephonically with bronchodilator nebulization, oral prednisone 30 mg daily for 5 days and paracetamol. By 11 March he was not feeling any better and had ongoing fever and cough. The Covid-19 PCR test had become available at that stage and his initial test with a private pathology laboratory was negative.

Over the next 3 days his symptoms worsened, and on 16 March he was admitted to hospital to an isolation ward where blood tests showed a lymphopaenia and a rising CRP (Table 1). A high-resolution CT scan of his chest showed bilateral asymmetrical peripheral ground glass infiltrates in a subsegmental distribution, particularly in the lower
| Laboratory marker | Date              |                  |                  |                  |                  |                  |                  |                  |                  |
|-------------------|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                   | 2020-03-16 | 2020-03-17 | 2020-03-21 | 2020-03-23 | 2020-03-24 | 2020-03-25 | 2020-03-26 | 2020-03-27 | 2020-03-31 |
| White cell count (4–10 × 10^9/L) | 7.0 | 6.1 | 9.6 | 7.6 | 9.5 | 8.1 | 6.3 | 6.6 | 9.0 |
| Neutrophils abs (2–7 × 10^9/L) | 5.8 | 4.2 | 8.9 | 7.3 | 8.4 | 6.4 | 4.3 | 4.6 | 6.9 |
| Lymphocytes abs (1–3 × 10^9/L) | 0.6 | 1.2 | 0.4 | 0.2 | 0.6 | 1.1 | 1.3 | 1.2 | 1.4 |
| Neutrophil: Lymphocyte ratio | 9.6 | 3.5 | 22.3 | 36.5 | 14.0 | 5.8 | 3.3 | 3.8 | 5.1 |
| CRP (0–10 mg/L) | 56 | 73 | 98 | 169 | 94 | 43 | 22 | 12 | 4 |
| PCT (0–0.05 ng/L) | 0.05 | 0.04 | 0.03 | 0.02 | 0.04 |                  |                  |                  |                  |
| Ferritin (22–275 μg/L) |                  |                  |                  |                  |                  | 1900 | 1951 | 1164 |                  |
| LDH (125–220 U/L) | 185 | 161 | 340 | 259 | 235 |                  |                  |                  |                  |
| D-Dimer (0–0.225 mg/L) | 0.37 | 1.11 | 0.85 | 0.86 | 0.66 |                  |                  |                  |                  |
| Pro-BNP (<125 ng/L) | 338 | 297 | 173 | 115 | 98 |                  |                  |                  |                  |
| SARS-CoV-2 | Detected |                  |                  |                  |                  |                  |                  |                  | Not detected |

Arrows indicate treatment with tocilizumab 400 mg IV.
zones. A repeat Covid-19 PCR swab on this occasion was positive and he was diagnosed with Covid-19 pneumonia. His oxygen saturation was 86% on room air. He was haemodynamically stable and was kept in strict isolation, and treatment was commenced with supplemental oxygen via a nasal cannula, paracetamol, chloroquine, azithromycin and lopinavir/ritonavir. In keeping with national and international guidelines recommending against the use of systemic corticosteroids, prednisone was discontinued.

Over the next 5 days his clinical condition worsened despite antiviral therapy. His biomarkers, including lymphopaenia, CRP, pro-B-type natriuretic peptide (Pro-BNP), lactate dehydrogenase (LDH), D-dimers and ferritin all increased significantly (Table 1). His hypoxaemia worsened and he had increased bilateral chest infiltrates on follow-up radiology (Figure 1). His PaO2:FiO2 ratio decreased to 250. He was diagnosed as having Covid-19 hyperinflammatory syndrome, CRS and ARDS. After a discussion with the team he was treated with tocilizumab 800 mg IV, given as two doses of 400 mg 24 h apart on 23 and 24 March, as well as methylprednisolone 40 mg IV daily for 5 days. Chloroquine dose was reduced, and azithromycin and lopinavir/ritonavir were discontinued in view of QT prolongation (QTc > 500 ms).

Within 24 h following the tocilizumab infusion, there was an improvement in his fever, biomarkers (Table 1) and hypoxaemia. Mechanical ventilation was avoided and he was monitored for another 6 day in the isolation unit. His saturations on room air improved to 90%. He was discharged home on 27 March, where he continued to make an uneventful recovery. Follow-up blood tests as an outpatient showed normalization of his lymphocyte count and CRP (Table 1). His saturations on room air improved to 92%. A repeat nasopharyngeal and throat swab test for Covid-19 on 31 March was negative.

**DISCUSSION**

It has been postulated that there are three distinct but overlapping phases and pathological subsets of Covid-19 infection and subsequent Covid-19 disease in humans, the first two triggered by the virus itself and the third, by the host response.(6) Treatment recommendations differ depending on the stage of the Covid-19 disease: the viral response phase (about 1–6 days after start of symptoms), the pneumonic phase (about days 6–10) which may progress to acute lung injury and ARDS, and the hyperinflammatory phase which typically occurs after day 8 in a minority of patients. This last phase is associated with worsening ARDS, multi-organ dysfunction syndrome (MODS), coagulation abnormalities, myocarditis and death. Patients progressing to this last severe phase of Covid-19 have clinical and laboratory evidence of an exaggerated inflammatory response, similar to the CRS, with persistent fever, worsening ARDS, elevated inflammatory markers and proinflammatory cytokines and MODS.

The Covid-19 virus binds to alveolar epithelial cells, activating the innate and adaptive immune systems resulting in the release of pro-inflammatory cytokines. This can lead to the CRS which is characterised by a hyperinflammatory state with raised inflammatory cytokines and biomarkers such as interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumour necrosis factor-α, CRP, ferritin, Pro-BNP and D-dimer.(7) The clinical picture is one of progressive ARDS and fulminant MODS.

Although corticosteroids are not routinely recommended for the treatment of Covid-19-associated lung injury, CRS immunosuppression with corticosteroids and other therapies is likely to be beneficial. Although there are currently no controlled clinical trials on the use of corticosteroids in Covid-19 patients, several published reports

![Image](image-url)
of corticosteroid therapy in severe Covid-19 have shown a shorter duration of supplemental oxygen use, improved radiographic findings and lower mortality in patients with ARDS.(8,9) Tocilizumab, an IL-6 receptor blocker registered for CRS treatment, is being investigated for the treatment of patients with severe Covid-19, CRS and elevated IL-6 levels. IL-6 plays an important role in CRS and tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), inhibiting sIL-6R and mIL-6R-mediated signalling. Small observational studies support the concept that tocilizumab may be an effective drug for patients with severe Covid-19 and respiratory failure requiring mechanical ventilation.(10,11) In a study of 21 patients with Covid-19-related ARDS who received tocilizumab, the ICU mortality was less than 5%, all surviving patients became afebrile within 72 h, pulmonary infiltrates on follow-up CT scan improved in 90%, hypoxaemia resolved in the majority and 90.5% of patients were discharged from the ICU after a median of 13.5 days. (12) A large randomised, double-blind, placebo-controlled phase 3 clinical trial to evaluate the safety and efficacy of tocilizumab plus standard of care in hospitalised adult patients with severe Covid-19 pneumonia and ARDS has been being initiated.(13) Currently, tocilizumab is available in South Africa for patients with severe Covid-19 and ARDS under the Monitored Emergency use of Unregistered and Investigational Interventions framework.(14) This requires the treating physician to consult with an expert panel prior to enrolment, detailed patient data collection and ensuring that the patient meets the strict inclusion and exclusion criteria. Other immune modulating agents under investigation include siltuximab (IL-6 inhibitor), bevacizumab (vascular endothelial growth factor inhibitor), convalescent plasma from patients who have recovered from SARS-CoV-2 infection and intravenous immune globulin (Polygam).(15,16) This case study also highlights some of the many controversies and complications in managing patients with severe Covid-19:

• The use of inhaled or oral corticosteroids as a risk factor for severe Covid-19 is not certain. Individuals taking long-term corticosteroids for chronic conditions such as asthma, allergies and arthritis may be unable to mount an appropriate immune response and are generally considered high risk for severe disease if infected with Covid-19. (17) Corticosteroids can also result in increased viral replication and prolonged viral shedding. Even a short course of oral corticosteroids in the preceding month for an asthma exacerbation, such as in this case study, is a risk factor for ARDS and mechanical ventilation. (18) Conversely, in vitro studies with ciclesonide showed antiviral activity against Covid-19, and there have been reports of clinical effectiveness of inhaled ciclesonide in the treatment of Covid-19. (19) Studies are currently underway to investigate whether inhaled ciclesonide alone, or in combination with hydroxychloroquine, could eradicate SARS-CoV-2 from respiratory tract earlier in patients with mild Covid-19. (20)• Diagnosis of SARS-CoV-2 pneumonia is not always straightforward. Currently, the gold standard in clinical practice is the detection of Covid-19 RNA by RT-PCR in respiratory tract specimens. Nasopharyngeal and throat swabs are recommended over expectorated or induced sputum. Lower respiratory tract specimens, such as tracheal aspirates or bronchoalveolar lavage in intubated patients may have higher viral loads and be more likely to yield positive tests (up to 95% sensitive) but come with a higher risk of transmission of infection to health-care workers. (21) False-negative tests from upper respiratory specimens have been documented, as with this case study. If initial testing is negative in a patient with risk factors for infection and clinical or radiological features are highly suggestive of Covid-19 or determining the presence of infection is important for further management and infection control, repeat testing is recommended.

• Chloroquine, azithromycin and lopinavir/ritonavir can all cause QT prolongation and ventricular arrhythmia, in particular drug-induced torsades de pointes and sudden cardiac death. (22) Patients treated with any combination of these drugs should have 12–24 hourly ECG with QTc monitoring. If QTc > 500 ms (as in the case study), QTc increases > 60 ms from baseline after initiating drug therapy, discontinue azithromycin and lopinavir/ritonavir, and consider reducing dose of chloroquine. Frequent monitoring of QTc is mandatory and chloroquine should also be discontinued if QTc remains > 500 ms. The risk of serious ventricular arrhythmia may be reduced by performing a screening ECG prior to initiation of therapy, inquiring about a personal or family history of QT interval prolongation or sudden unexplained cardiac death, avoiding exposure to other medications known to affect QT interval, and aggressively treating hypocalcaemia, hypokalaemia and hypomagnesaemia. Hypokalaemia is especially common in patients with Covid-19 and is associated with a poorer prognosis. (23) The correction of hypokalaemia can be challenging due to continuous renal loss of potassium resulting from the degradation of angiotensin converting enzyme 2 by binding of SAR-CoV-2.

CONCLUSION

This case study of severe Covid-19 pneumonia and CRS illustrates some of the diagnostic and therapeutic challenges and controversies regarding the management of this novel and complex infection. Meticulous monitoring for and early treatment of the hyperinflammatory phase of the disease may be crucial in preventing progression to severe ARDS, MODS and death.
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REFERENCES

1. 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. Epub 2020 Mar 11.

2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020; 395(10223):497–506.

3. 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. doi:10.1016/S2213-2600(20)30079-5

4. Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed 2019 novel coronavirus (2019-nCoV) infection, <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html> [updated 12.02.20].

5. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med, 2020. Volume Online First Issue. doi:10.1097/CCM.0000000000004363.

6. Siddiqi H, Mehra M. 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.

7. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395(10229):1033–1034. doi:10.1016/S0140-6736(20)30628-0.

8. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv: 2020.2003.2006.20032342.

9. 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. doi:10.1001/jamainternmed.2020.0994.

10. Zheng C, Wang J, Lu Z, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 2020; 4(7):1307. doi:10.1182/bloodadvances.202000190716.

11. Zhang C, Wu Z, Li JW, et al. The cytokine release syndrome of severe COVID-19 and Interleukin-6 receptor antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020. doi:https://doi.org/10.1016/j.ijantimicag.2020.105954.

12. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. ChinaXiv. 2020. Available at <http://chinaxiv.org/abs/202003.00026>.

13. Hoffmann-La R. A study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (COVACATE). <https://clinicaltrials.gov/ct2/show/NCT04320615?term=tocilizumab&cond=COVID-19&draw=2&r&rank=2>; 2020.

14. http://www.who.int/ethics/publications/infectious-disease-outbreaks/en/ Chapter 9 MEURI.

15. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020. [e-pub]. <https://doi.org/10.1001/jama.2020.4783>.

16. https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=IL-6&entry=&state=&city=&dist.

17. Kaiser U, Mirmira R, Stewart P. Our Response to COVID-19 as endocrinologists and diabetologists. J Clin Endocrinol Metab. 2020; 105(5):dgaa148. <https://doi.org/10.1210/clinem/dgaa148>.

18. Bhatraju P, Ghassemieh B, Nichols M. Covid-19 in critically ill patients in the Seattle region – case series. NEJM. 2020. doi:10.1056/NEJMoa2004500.

19. Matsuyama S, Kawase M, Nao N. The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15. <https://doi.org/10.1101/2020.03.11.987016>.

20. A trial of ciclesonide alone or in combination with hydroxychloroquine for adults with mild COVID-19. ClinicalTrials.gov Identifier: NCT04330586

21. Wang W, Xu Y, Gao R. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020. doi:10.1001/jama.2020.3786.

22. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19 [published online ahead of print March 25, 2020]. Mayo Clin Proc. 2020. <https://doi.org/10.1016/j.mayocp.2020.03.024>.

23. Chen D, Li X, Song Q, et al. Hypokalemia and clinical implications in patients with coronavirus disease 2019. https://doi.org/10.1101/2020.02.27.20028530.
