Clinical management of COVID-19: Experiences of the COVID-19 epidemic from Groote Schuur Hospital, Cape Town, South Africa

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The SARS-CoV-2 pandemic has presented clinicians with an enormous challenge in managing a respiratory virus that is not only capable of causing severe pneumonia and acute respiratory distress syndrome, but also multisystem disease. The extraordinary pace of clinical research, and particularly the surge in adaptive trials of new and repurposed treatments, have provided rapid answers to questions of whether such treatments work, and has resulted in corticosteroids taking centre stage in the management of hospitalised patients requiring oxygen support. Some treatment modalities, such as the role of anticoagulation to prevent and treat potential thromboembolic complications, remain controversial, as does the use of high-level oxygen support, outside of an intensive care unit setting. In this paper, we describe the clinical management of COVID-19 patients admitted to Groote Schuur Hospital, a major tertiary level hospital at the epicentre of South Africa's SARS-CoV-2 epidemic during its first 4 months.

S Afr Med J 2020;110(10):Published online 26 August 2020. https://doi.org/10.7196/SAMJ.2020.v110i10.15157

The clinical management of COVID-19 is a rapidly evolving field, and one that has challenged clinicians across the world. Initially described as 'just like flu', we have come to appreciate marked differences and new challenges in managing this severe pneumonia, its complications and extra-pulmonary manifestations. Groote Schuur Hospital (GSH) is the 950-bed academic teaching hospital of the University of Cape Town, located at the epicentre of South Africa (SA)'s COVID-19 epidemic in its first 4 months. As of 6 August 2020, we have admitted 3 487 persons under investigation (PUIs), and 1 781 COVID-19 cases have been confirmed (Western Cape Provincial Health Data Centre, unpublished). In this paper, we share our experiences of developing a clinical service for COVID-19 in a tertiary centre in SA, and focus on new developments and areas of contention in clinical management of COVID-19 as well as practices implemented in our hospital.

Oxygen support outside of the ICU

About 20% of hospitalised patients with confirmed SARS-CoV-2 pneumonia will develop acute respiratory distress syndrome, and ~12% will meet conventional indications for intubation and mechanical ventilation.[1,2] In SA, the capacity to treat forecasted numbers of patients with acute hypoxaemic respiratory failure (AHRF) with ventilation in the intensive care unit (ICU) is severely constrained.[3] Furthermore, mechanical ventilation for COVID-19-associated AHRF is associated with variable, but often very high, mortality.[1] There has been considerable interest in strategies that improve oxygenation non-invasively, and that could be deployed in the non-ICU setting. High-flow nasal cannula (HFNC) is an oxygen delivery method capable of supplying high inspired partial pressures of warmed and humidified oxygen, while reducing anatomic dead space, work of breathing and respiratory rate, and increasing positive pressure and compliance. The device consists of a flow generator providing gas flow rates up to 60 L/min, an air-oxygen blender and a humidifier that saturates the gas mixture, markedly improving patient comfort, tolerance and compliance.[4]

In the non-COVID-19 setting, HFNC has been shown to avoid intubation compared with conventional oxygen supply devices,[5,6] and there are data to suggest that it may be useful in patients with COVID-19 pneumonia.[7-9] At GSH, in anticipation of severe pressure on ICU beds, we cohorted patients with laboratory-confirmed or highly suspected COVID-19 pneumonia and severe respiratory failure (ratio of arterial partial pressure of oxygen and fraction of inspired oxygen typically <100) in non-critical medical wards and treated them with HFNC and awake self-proning as a pre-ICU intervention. Despite the necessary compromises in offering this therapy in a less-monitored setting with a higher patient-to-nurse ratio as compared with ICU, we have found it to be a feasible strategy with lower overall intubation rates, less ICU resource utilisation and cost savings. HFNO may be considered as an appropriate mode of respiratory support where access to the infrastructure and/or expertise of ICU care is limited or, secondly, transport of clinically unstable patients to a facility with a designated ICU is potentially hazardous and undesirable. The two main disadvantages of HFNC relate to the risk of aerosolisation and the adequacy of oxygen supplies. Concerns about the former have not been substantiated,[10,11] but appropriate precautions (full personal protective equipment (PPE) including N95 respirator) should still apply. However, the scaling of any HFNC requires input from engineers and ongoing monitoring of local capacity and the oxygen supply chain. Based on our collective experiences, we have identified a number of important dos and don'ts relating to HFNC use for COVID-19 (Table 1).

The value of a dedicated intubation team

Early planning for the dramatic increased intubation requirement is critical, particularly in view of the high risk to staff from this aerosol-generating procedure (AGP). As routine and elective surgery de-escalated, the Department of Anaesthesia and Perioperative Medicine redeployed approximately half of its consultants and registrars to COVID-19 services and formed a dedicated COVID-19 Anaesthesia and Airway Team. We created a highly protocolised approach to safe intubation, which defined roles, checklists and systems (https://www.sasaCOVID19.com). We used our experience in simulation to provide open training sessions for all staff in appropriate use of PPE for AGPs, rapid intubation and patient transfers. We undertook *in situ* simulation in theatres, emergency departments and wards, and actively encouraged cross-disciplinary participation of staff in interchangeable roles. This strengthened interdepartmental collaboration and allowed systems testing and rapid improvement prior to the patient surge.

To date, the COVID-19 Anaesthesia and Airway Team have completed over 400 cases, including intubations for respiratory failure (particularly failure of high-flow nasal oxygen), anaesthesia for surgery, ICU tracheostomies and trauma/emergency intubations, in PUIs or COVID-19 patients, without any infections documented within our team. The use of reusable respirators with filters (allowing daily cleaning) by the team has practically eliminated the demand for the approximately 50 disposable N95 respirators that would have otherwise been required per day.

To counteract the exceptionally rapid and profound oxygen desaturation and the physical limitations of PPE, we adopted universal video laryngoscopy and routine use of tracheal tube introducers using a standardised technique.[12] This has maintained a rapid and high first-pass intubation success rate. Other pertinent lessons include the need for pre-induction fluid loading in patients who are often dehydrated to the point of hypovolaemia due to enhanced insensible fluid loss from high respiratory rates on oxygen for several days, and frequent need for induction dose adjustment and boluses of inotropes to support the transition to positive pressure ventilation. However, the greatest gains of instituting a COVID-19 intubation service have been breaking down silos of care, cross-discipline integrated training, systems strengthening through recursive testing of protocols and standardisation, and bridging the

Table 1. The dos and don'ts of delivering oxygen via HFNC

Dos	Don'ts
Ensure proper sizing, fitting and securement of nasal cannulae	To treat severe hypoxia, do not persist with conventional nasal cannulae at high flow rates (>6 L/min) or 'double oxygen' – rather use HFNC if available
Have patients wear a surgical mask over the HFNC to minimise risk of bioaerosolisation	If mechanical ventilation is an option, do not consider HFNC as first-line in hypercapnic, haemodynamically unstable or obtunded patients or those with imminent respiratory arrest
Monitor patients with continuous pulse oximetry and observe closely for any malposition or displacement of nasal interface	Do not initiate HFNC without regular clinical assessments of its efficacy (especially during the first few hours of treatment)
Allow patients to eat and drink while on HFNC	Do not delay intubation if there is a decline on HFNC (consistent or rapid increase in respiratory rate, consistently or rapidly declining SpO_2, or exhaustion)
Combine HFNC with awake self-proning to improve oxygenation	Do not offer a scalable HFNC service without first consulting with engineers about local oxygen capacity

HFNC = high-flow nasal cannula.

safe transfer of patients from the emergency department or wards to the ICU.

Antimicrobial stewardship

At the time of writing, no single antimicrobial has been shown to reduce mortality from SARS-CoV-2 infection. The broad-acting antiviral remdesivir has been shown to reduce duration of illness, but not directly affect mortality.[13] Results from larger randomised controlled trials are awaited. Despite being much vaunted, hydroxychloroquine has been shown to have no beneficial effect, and has been observed to trend towards worse outcomes in hospitalised patients.[14] The antiretroviral combination of lopinavir/ritonavir also showed no benefit.[15]

The existing epidemic of antibiotic-resistant bacterial infections in SA has been one of many entrenched public health crises, such as diabetes and obesity, to collide with COVID-19. The primary driver of antibiotic resistance is antibiotic consumption, historically fuelled by inappropriate prescribing for respiratory viral infections. Influenza pandemics characterised by bacterial co-infections begged the question of an equal impact from SARS-CoV-2. However, pooled prevalence of laboratory-confirmed bacterial infections was 7% throughout the course of hospitalisation in the largest systematic review and meta-analysis conducted to date.[16] Bacterial coinfection at the time of presentation to hospital is likely much lower. Despite this extremely low level, between 56 and 95% of patients in these and other studies received empirical antibiotics.[17]

Our approach is to withhold antibiotics in patients with a clinical or laboratory-confirmed diagnosis of COVID-19, and stop antibiotics in those treated empirically, even though clinical and radiological differentiation from bacterial pneumonia is difficult. Biomarkers are unhelpful in optimising antibiotic use in COVID-19, as high levels of C-reactive protein (CRP) are common, and no good data exist for procalcitonin (PCT), despite it being an indicator of severity, with a 5-fold increase in odd ratio of severe COVID-19 if PCT is raised.[18] We do not advocate measuring CRP or PCT as biomarkers for COVID-19 infection.

For patients who deteriorate during their hospital stay, hospital-acquired infection (HAI) should always be considered. HAIs are predominantly seen in ICU patients, and may be multi-drug resistant, especially when selected out by empirical broad-spectrum antibiotics used earlier. Empirical antibiotic choice will depend on local resistance patterns. If antibiotics are to be given, blood and site-directed specimens should be sent for culture prior to starting antibiotics, and the first dose should not be delayed. Oral medications should always be used in preference to intravenous whenever possible to reduce venous catheter-associated infections.

Corticosteroids

To date, only the anti-inflammatory therapy of 6 mg IV or oral dexamethasone daily for 10 days has been shown to reduce mortality in COVID-19 patients requiring oxygen – the largest gains were observed in those who were mechanically ventilated, with one-third reduction in death at 28 days v. one-fifth reduction in non-ventilated hospitalised patients requiring any level of oxygen support.[19] There was no benefit in patients not requiring oxygen support. We use intravenous dexamethasone in ventilated patients and, wherever possible, 40 mg oral prednisolone to negate the need for a venous catheter.

Anticoagulation

International cohorts report the incidence of confirmed venous thromboembolism (VTE) as between 20 and 60% among critically ill COVID-19 patients,[20,21] and >5% (up to 22% in one cohort) in those less severely hypoxic, despite heparin prophylaxis,[22-24] much higher rates than general medical patients.[25,26] Even in the absence of overt VTE, microvascular thrombosis in the pulmonary circulation may also contribute to hypoxaemic respiratory failure in COVID-19.[27]

The recognition and diagnosis of VTE is more challenging in the context of COVID-19: patients with severe COVID-19 pneumonia often have fluctuating oxygen requirements that may mask a new thrombotic event; they may be too unstable for transfer to undergo investigation; and IPC concerns may restrict access to diagnostic testing. We follow international guidelines to not screen routinely for VTE with lower-limb Doppler ultrasound or computed tomography pulmonary angiography.[21,28] Our indications for testing are clinically guided and include suspected symptomatic lower limb deep vein thrombosis, sudden unexplained respiratory deterioration and persistent or refractory hypoxia. We have recognised VTE across this clinical spectrum in our COVID-19 service.

All inpatients with suspected or confirmed COVID-19 pneumonia receive VTE prophylaxis unless there is a contraindication. Low-molecular-weight heparin is preferred due to ease of use (subcutaneous injection), predictable pharmacokinetics and limited monitoring requirements. Our practice has recently changed to provide enhanced or 'intermediate' dose enoxaparin prophylaxis for patients with hypoxic pneumonia (Table 2). This is to overcome putative heparin resistance[29] in COVID-19 due to increased circulating fibrinogen, factor VII and von Willebrand factor levels.[30,31] We have also witnessed incident VTE despite standard heparin prophylaxis,[20] and intermediate dose enoxaparin may ensure better protection for obese patients who may be underdosed because of failure to do accurate weight-based dosing. The intermediate dosing strategy is based on expert opinion and does not comply with current national guidance, which recommends the use of standard dose heparin prophylaxis in COVID-19; however, several international hospital groups[32] have instituted this practice, and a there is support in published consensus documents by major international societies.[28,32,33] Major bleeding events appear to be uncommon with anticoagulant use in COVID-19, but a recent retrospective study from Italy reported substantially increased bleeding risk with high doses of heparin in a cohort with a median age of 71 years.[34] Therefore, we are cautious with using non-standard-dose heparin prophylaxis in patients >70 years and those who have other bleeding risk factors.

D-dimer elevation[35,36] and obesity[37,38] are both common in severe COVID-19, and independently correlate with increased VTE risk and with mortality. Retrospective studies suggest improved survival for

Table 2. Enoxaparin dosing for VTE prophylaxis

Total body weight (kg)	Dose (subcutaneous)	Renal impairment (eGFR <30 mL/min)
<80	1 mg/kg daily	Reduce total daily dose by 50%
80 - 100 >100	0.5 mg/kg 12-hourly	Reduce to once-daily dosing

eGFR = estimated glomerular filtration rate.

Table 3. Enoxaparin dosing for therapeutic anticoagulation

Total body weight (kg)	Dose (subcutaneous)	Renal impairment (eGFR <30 mL/min)
<100	1 mg/kg 12-hourly	
100 - 150	1 mg/kg 12-hourly; up to 150 mg 12-hourly*	Reduce to once-daily dosing
>150	0.75 mg/kg 12-hourly*	

eGFR = estimated glomerular filtration rate.
*Suggest anti-Xa monitoring (if available) for doses >120 mg 12-hourly.

therapeutic anticoagulation in critically ill patients requiring mechanical ventilation[39] and those with very high *D*-dimer levels.[40] Because of greatly increased VTE risk in these groups (particularly in our population with a high prevalence of obesity) and limited diagnostic testing, we empirically prescribe therapeutic anticoagulation (Table 3) for the following patients in our service: those requiring high flow nasal cannula oxygen or mechanical ventilation (considered to be critically ill); *D*-dimer levels >1.5 × upper limit of normal or rising on serial measurement; and those with clinically suspected VTE. Major bleeding events appear to be uncommon with anticoagulant use in COVID-19, but we are cautious with this approach in patients older than 75 years and those who have other bleeding risk factors.

Arterial thrombosis occurs much less frequently than VTE,[41] but we have seen major events including critical limb ischaemia, thrombosis of the aorta, mesenteric and femoral arteries and several patients complicating with stroke and myocardial infarction. Prophylaxis with anti-platelet agents is not recommended and is not part of our practice.

Diabetes stewardship

The association between diabetes and increased morbidity and mortality from COVID-19 has been well-described globally.[1,42,43] We have seen large numbers of people living with diabetes (PLWD) and diagnosed with COVID-19 admitted with severe disease and/or diabetic ketoacidosis (DKA), as well as a large number of people diagnosed with COVID-19 presenting with new onset diabetes or first-time DKA.

To enable practical and consistent inpatient management of diabetes and COVID-19, we disseminated protocols for achieving glycaemic control and managing DKA in these patients (Fig. 1). The use of a single diabetes monitoring chart that included advice on the prescription and titration of insulin as well as the management of hypoglycaemia allowed for a unified approach in managing hyper- and hypo-glycaemia.

In-hospital management of diabetes in patients with SARS-CoV-2 infection

Problems

1. Patients living with diabetes have an increased risk of morbidity and mortality from infection with SARS-Cov-2
2. Poorly-controlled diabetes is a risk factor for increased morbidity and mortality from SARS-CoV-2 infection
3. Data from an observational study to show that morbidity and mortality from SARS-CoV-2 infection may be improved with better diabetes control
4. Acute hyperglycaemia has been shown to upregulate ACE2 expression on cells which might facilitate viral cell entry
5. In-hospital hypoglycaemia increases morbidity and mortality
6. Patients with diabetes and severe COVID-19 have marked insulin resistance disproportionate to the critical illness caused by other conditions and this may require very high doses of insulin to maintain euglycaemia
7. Good diabetes control in the hospital requires frequent fingerprick blood glucose testing (at least before each meal and at 22h00) and administration of insulin thereby increasing exposure of healthcare workers to the infected patient
8. There are no robust studies to guide the in-patient management of diabetes in patients with diabetes that are infected with SARS-CoV-2
9. Limited time available to stabilise on longterm treatment regimens and, at the moment, limited options for outpatient follow-up

Recommendations

1. HbA1c measurement on admission (unless HbA1c available within past 1 month)
2. INITIAL management of diabetes will depend on the HbA1c and disease severity
   a. HbA1c < 9% plus mild disease (no pneumonia or mild pneumonia with respiratory rate < 30 breaths/min and O_2 saturation ≥ 94%)
      - continue pre-admission medication
        - stop metformin if eGFR<45 ml/min
        - stop sulphonylureas (glimepiride, glibenclamide) if eGFR<90 ml/min
        - stop SGLT2 inhibitors

   b. HbA1c < 9% plus severe disease (respiratory rate > 30 breaths/min and/or O_2 saturation < 94%) OR HbA1c > 9% with any severity of illness
      - Stop all oral diabetes medications
      - Continue with pre-admission insulin regimen OR commence insulin as per Diabetes Chart, preferably using a basal bolus regimen
      - Use insulin correction doses as per Diabetes Chart

   c. **Patients may have other reasons (another infection, on steroids, etc) apart from COVID-19 that may change your INITIAL management so good and usual clinical judgement is required at all times**
   d. Encourage self-monitoring of fingerprick blood glucose by the patient if clinical status allows
   e. Encourage self-administration of insulin by the patient if clinical status allows
   f. Monitor fingerprick glucose twice daily if on oral therapy and 4 times daily if on insulin
   g. Review glycaemic control and management daily
   h. Aim for a fingerpick blood glucose between 5.0 mmol/L to 10 mmol/L at all times but preferably closer to 8.0 mmol/L
   i. Very important to avoid hypoglycaemia (glucose <4.0 mmol/L) and manage hypoglycaemia as per Diabetes Chart
   j. Nursing staff and doctors must please regularly educate patients on monitoring of fingerprick blood glucose, injection technique and diet, especially those with newly-diagnosed diabetes
   k. **Important to review the long-term management regimen prior to discharge**
   l. All patients with diabetes must please be given an appointment to attend the GSH Diabetes Clinic 1 month after discharge from hospital or 1 month after their self-isolation ends (please contact the Endo-on-call who will immediately give an appointment)

Glucose target
less than 10 mmol/L
avoid level < 5 mmol/L

Division of Endocrinology, Groote Schuur Hospital 08 May 2020

Fig. 1. In-hospital management of diabetes in patients with COVID-19. (eGFR = estimated glomerular filtration rate.)

Despite these measures, the inpatient management of PLWD diagnosed with COVID-19 proved challenging. Deployment of doctors and nurses inexperienced in diabetic management was a challenge and required rapid upskilling. Optimal inpatient glycaemic control requires frequent fingerprick glucose monitoring and injection of insulin, thereby increasing exposure of HCWs to infectious patients. To combat this, we encouraged the use of simple treatment regimens requiring less exposure, whenever clinically possible.

To simplify management on discharge, training was given to the patient on fingerprick glucose

Patients with COVID-19 and NEW Diabetes Mellitus

Discharge process

- Try and discharge patients on the simplest regimen that will keep their fingerprick blood glucose in the range 6.0-9.0 mmol/L
- All patients admitted in diabetic ketoacidosis (DKA) must be discharged on insulin
- Whilst the patient is in the ward the nursing staff and doctors should instruct the patient on fingerpick blood glucose monitoring and insulin administration
- As much as possible encourage self-monitoring of fingerprick blood glucose and self-administration of insulin
- Dietary advice: dietician, GSH Diabetes Stewardship dietary handout, COVID Ward handout
- Before discharge please ensure that the following have been entered into the patient's notes: HbA1c, weight, height, mid-upper-arm circumference
- Patients on a basal bolus regimen
    - A few days before discharge review the need for this regimen and the ability of the patient to comply with this regimen, it is an intense regimen and many patients are unable to comply
    - To convert to a more simple regimen using a pre-mix insulin (such as Actraphane or Humulin 30/70) twice-daily follow these steps:
        - Work out the total amount of insulin per day that the patient is needing (i.e., the total daily dose, TDD)
        - Give two-thirds of the TDD before breakfast and one-third of the TDD before supper
- Patients must monitor their fingerpick blood glucose before giving insulin and must use the following correction doses:

Meal-time insulin correction doses		
Blood glucose level (mmol/L)	Less than 4.0	**Eat and re-check blood glucose in 20 minutes**
	4.1 to 4.9	Decrease the prescribed dose of insulin by 4 units
	5.0 to 8.5	Give the prescribed dose of insulin
	8.6 -12.0	Increase the prescribed dose of insulin by 2 units
	Greater than 12.1	Increase the prescribed dose of insulin by 4 units

- After discharge patients can phone the Help Line, weekdays between 09h00 and 13h00 to discuss any problems with a doctor
- Patients must be please given an appointment for the GSH Diabetes Clinic for 2 weeks after the end of the patient's self-isolation (please contact the Endo SR-on-call for an appointment date, this is the only way of getting an appointment so please do it this way)

Division of Endocrinology, Groote Schuur Hospital, June 2020

Fig. 2. Discharge process for diabetics with COVID-19.

monitoring and the administration of insulin, and a handout was provided describing basic dietary advice as well as glycaemic management principles, including insulin correction doses and glucose targets (Fig. 2). Furthermore, a telephonic helpline was established for the patient to contact should (s)he require guidance.

Mental health – supporting staff and patients alike

Many HCWs have reported that mental health conditions linked to their work have been made worse by the COVID-19 epidemic. Working long hours in unfamiliar settings and in PPE, fear of contracting SARS-CoV-2 and passing it to their loved ones, seeing many patients die and breaking bad news to bereaved families are all having an impact on wellbeing. At the same time, the lockdown has meant that many have been unable to recharge their batteries. There is no socialising, and some have isolated themselves from their families to protect them.

Working closely in an established partnership between our hospital and Metropolitan Health, we developed a GSH Wellness Team to prioritise employee health and wellness during the crisis. We support on-site individual and group counselling to provide a containing and supportive space wherein HCWs are able to share their anxieties and fears and the traumas that they have experienced within the hospital context as a result of severe patient morbidity and mortality.

We perform daily mental health ward rounds to screen for patients who require mental health assessment, management and treatment. Common reasons for referral are agitated delirium (Fig. 3), bereavement, anxiety and behavioural problems. Smartphones have enabled us to FaceTime families within the high-risk COVID-19 wards to address the isolation and trauma that many patients experience.

Palliative care for COVID-19 patients

The World Health Organization (WHO) strongly recommends that palliative care should be accessible in all institutions that provide care for persons with COVID-19.[44] The Palliative Care Practitioners Association of SA (PalPrac) has created clinical guidelines on palliative care management for COVID-19 in SA (Fig. 4),[45] and has been supported by the provincial operational guide for implementation, with provincial training and mentorship by PalPrac.[46] Despite this, misconceptions around palliative care remain, and the lack of awareness, training and dedicated staff has hampered the integration of palliative care into healthcare facilities.

We strengthened the established team at GSH with family medicine registrars and by building strong relationships with the psychiatry, psychology, oncology and social work departments. Three main categories of patients are referred: firstly, the known palliative care patients whose care has been compromised in the time of COVID-19. Social isolation, complex advanced decision-making and downscaling of community palliative care resources have led to intensified palliative care for these patients in the hospital setting. Secondly, known patients in the COVID-19 wards requiring palliative care for an existing condition that has been complicated by the infection. The third group are the end-of-life patients dying from COVID-19-related complications because they were not candidates for ventilation. Terminal agitation, dyspnoea and delirium are the main symptoms requiring management. Pre-bereavement and bereavement care with families are essential components of palliative care, and psychiatry, psychology, spiritual care and social work colleagues worked alongside the palliative care team to broaden the reach for patients and their families.

Management of Agitated Delirium
Non-pharmacological or environmental support strategies should be instituted wherever possible. These include co-ordinating nursing care, preventing sensory deprivation and disorientation, and maintaining competence.

Pharmacological treatment should be directed first at the underlying cause (if known) and then at the relief of specific symptoms of delirium.

General principles of delirium management
ONLY USE ANTIPSYCHOTICS IF THE PATEINT IS DISTRESSED OR AGITATED

- Keep the use of sedatives and antipsychotic medications to a minimum.
- Use one drug at a time.
- Tailor doses according to age, body size and degree of agitation.
- Titrate doses to effect.
- Use small doses regularly, rather than large doses less frequently.
- Review at least every 24 hours.
- Increase scheduled doses if regular 'as needed' doses are required after the initial 24-hour period.
- Maintain at an effective dose and discontinue 7–10 days after symptoms resolve.

Antipsychotics
Use lower doses especially in patients who are elderly. Discontinue these medications as soon as possible. Attempt a trial of tapering the medication once symptoms are in control. Antipsychotics can be associated with adverse neurological effects such as extrapyramidal symptoms, neuroleptic malignant syndrome, and tardive dyskinesia. Longer term use is also associated with metabolic syndrome.

Haloperidol-Considered first-line agent. No trial data has demonstrated superiority of other antipsychotics over haloperidol; however, care must be taken to monitor for extrapyramidal and cardiac adverse effects. Avoid in Lewy body dementia and Parkinson's disease, Avoid intravenous use where possible. However, in the medical ICU setting, IV is often used with close continuous ECG monitoring

1) Start with either Haloperidol po or Risperidone po 0.5mg 12-hourly. Can increase to up to 0.5mg 6-hourly
2) If poor response to Haloperidol or Risperidone OR if patient is VERY agitated try Olanzapine 2.5mg po 12 hourly. Can increase to up to 2.5mg 8-hourly

Benzodiazepines- AVOID and stop if already in use
Reserved for delirium resulting from seizures or withdrawal from alcohol or sedative hypnotics OR Terminal delirium. Benzodiazepines are preferred over neuroleptics for treatment of delirium resulting from alcohol or sedative hypnotic withdrawal. Use special precaution when using benzodiazepines because they may cause respiratory depression, especially in patients who are elderly, those with pulmonary problems, or debilitated patients.

Terminal agitated Delirium
Midazolam 2.5 mg subcutaneously and increase or provide continuously through a syringe driver. (See Palprac guidelines – Figure 5)

Fig. 3. Management of agitated delirium in COVID-19 patients. (ICU = intensive care unit; IV = intravenous; ECG = electrocardiogram.)

Radiology services for COVID-19

Chest radiography is the mainstay of imaging, and it was planned as a mobile service for all COVID-19 suspects and patients using the two-radiographer technique. High demand caused strain on the service; however, this was somewhat offset by clustering patients whenever possible.

Within the Radiology Department one machine was a 'designated COVID-19 scanner' wherever possible. Magnetic resonance (MR) and CT scanning is performed with two radiographers in attendance; one remains clean in the console room, planning and executing the scan. The second wears full PPE and assists with positioning the patient in the room, remaining with the staff transporting the patient until the patient leaves the department. After every PUI or COVID-19 patient, the room is deep-cleaned by the housekeeping team and allowed to stand empty for an hour to ventilate. Ventilation and air flow must be checked by engineers to ensure it is adequate. The risk of transmission from asymptomatic or incorrectly categorised patients was offset by consistent PPE and IPC protocols.

We reserved the use of CT chest (high resolution CT and CT pulmonary angiography) for complications and for inpatients not improving on treatment. Indications for CT imaging have evolved, now including in some instances patients who are persistently reverse transcriptase polymerase chain reaction (RT-PCR)-negative with an abnormal chest X-ray.

A COVID-19 radiology meeting (initially held daily, then weekly) has been critical for discussing diagnostic challenges in imaging of COVID-19 patients.

Ensuring rapid turnaround times for SARS-CoV-2 diagnostic tests

Rapid turnaround time (TAT) for the SARS-CoV-2 RT-PCR diagnostic test is a critical factor in the clinical management of COVID-19 and triage through the hospital. Inpatient and HCW samples were prioritised from the start. Major challenges around supply chain management and a shortage of qualified staff for the shift system created a stressful environment and affected the quality and productivity of our virology laboratory service.

While direct communication with the laboratory to expedite urgent samples may be tempting, this adds further work and pressure on the already strained system. Eventually, we identified three key factors that improved TAT of urgent hospital samples. Firstly, a separate testing stream was established where samples were marked with a clearly visible red dot on the outside of the sample bag. Secondly, we identified the main bottleneck in testing as the nucleic acid extraction process, and developed an alternative extraction-free method, overcoming reagent shortages and saving precious processing time. Finally, work volumes were reduced by establishing additional testing laboratories – at the Greenpoint National Health Laboratory Service that tested community screening samples, and later, research laboratories at the University of Cape Town, allowing us to focus on serving the hospital population, and ultimately to improve quality and sample TAT.

Developing research as part of the COVID-19 response

Three broad priority areas for research were identified: Establishing a clinical and laboratory data repository; undertaking local studies to understand clinical epidemiology in our population and to directly inform our practice; and contributing data to global observational and trial protocols. Early in our epidemic,

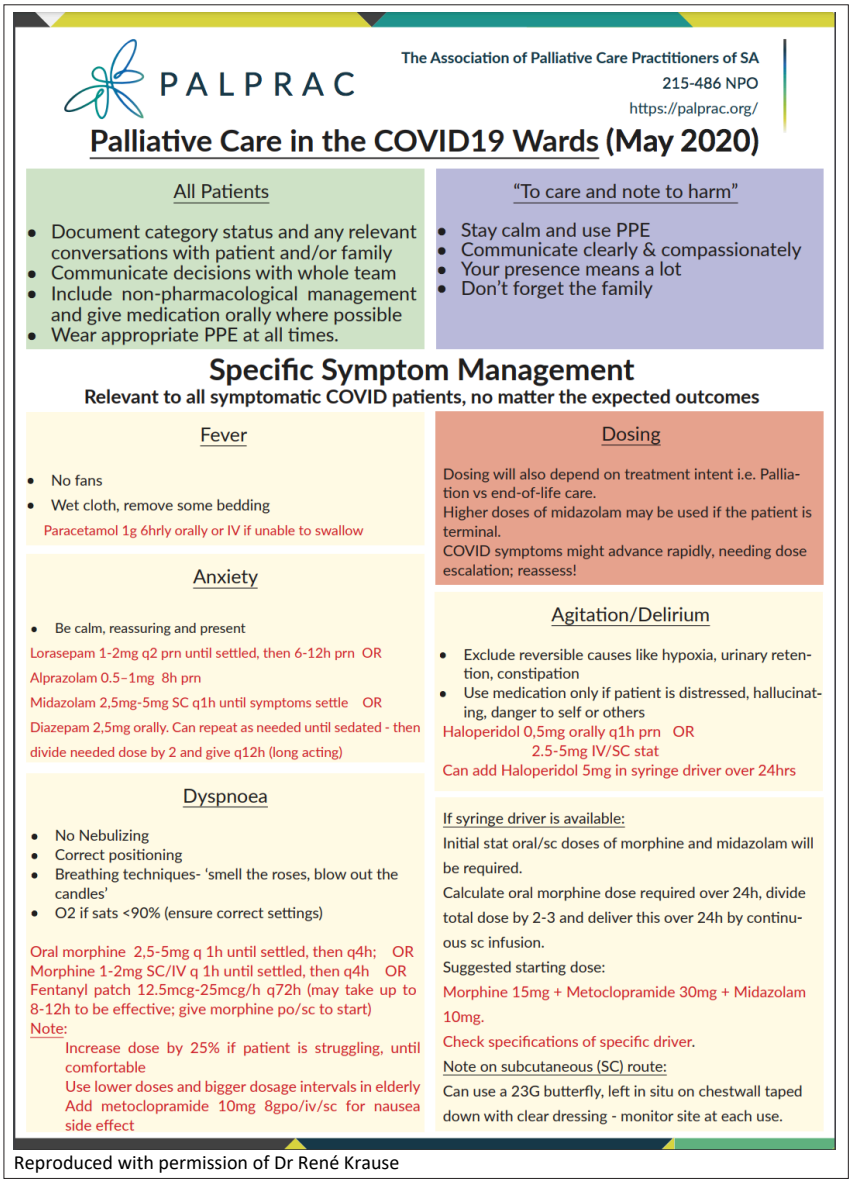

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Fig. 4. Palliative care in the COVID-19 wards. (PPE = personal protective equipment.)

the Department of Medicine, with ethics approval, implemented a protocol for collection and storage of clinical data linked to electronic records systems, a virtual repository for all clinical samples obtained from all COVID-19-related research, and a governance structure developed by a Departmental COVID-19 Research Steering Committee, which evaluates requests from investigators to access the data under approved protocols. This aims to ensure that no single research group has 'ownership' over data from COVID-19 patients, and avoids duplication in informed consent, study procedures and data reporting.

Local studies are focusing on main areas of clinical presentation and management, i.e. the COVID-19 and HIV interaction, impact of diabetes on clinical outcomes, use of HFNC oxygen, respiratory co-infections and optimising anticoagulation. Our hospital is also a participating centre for the WHO's SOLIDARITY trial,[47] and the ICU contributes to the International Severe Acute Respiratory and Emerging Infection Consortium database.[48]

A guiding principle of our efforts is that research conduct should contribute directly to the clinical service and not place additional burdens on staff or PPE, and that study procedures should not increase transmission risk in the hospital, e.g. through the use of paper-based records or performance of AGPs. Close engagement with ethical and regulatory bodies for the institution of rapid review processes for COVID-19-related projects and oversight in this challenging research environment is highly recommended.

Conclusion

Clinical management of COVID-19 improves with experience, and we now have a suite of interventions that we believe improve clinical outcomes (Fig. 5). Notable developments have been the use of corticosteroids, HFNC outside of the ICU, a dedicated intubation team to support management of these challenging patients, rigour in relation to antibiotic and diabetic stewardship and the provision of strong mental health and palliative care services to benefit distressed patients and staff. The challenge continues, with the only certainty being that we still have much more to learn.

Declaration. None.

Acknowledgements. We acknowledge with immense gratitude the tremendous contribution to the success of the COVID-19 response at GSH from our nurses, allied medical professionals, hospital and provincial managers, as well as every last porter, cleaner, caterer, volunteer and all other support staff who have contributed to our service. We also acknowledge that we would have been unable to provide the care we have to COVID-19 patients were it not for the partnership of other colleagues working across the hospital on non-COVID-19 wards. We dedicate this article to all the patients who have passed on and to those who have left our hospital to return to friends and family.

Author contributions. MM conceived and co-ordinated the manuscript. All authors wrote parts and/or led the clinical/laboratory/radiology services described, and all authors edited and approved the final manuscript for submission.

Funding. None.

Conflicts of interest. None.

1. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5 700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323(20):2052-2059. https://doi.org/10.1001/jama.2020.6775
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061-1069. https://doi.org/10.1001/jama.2020.1585
3. GroundUp. COVID-19: Groote Schuur on the brink. https://www.groundup.org.za/article/covid-19-groote-schuur-brink/ (accessed 13 July 2020).
4. Mauri T, Galazzi A, Binda F, et al. Impact of flow and temperature on patient comfort during respiratory support by high-flow nasal cannula. Crit Care 2018;22(1):120. https://doi.org/10.1186/s13054-018-2039-4
5. Li J, Jing G, Scott JB. Year in review 2019: High-flow nasal cannula oxygen therapy for adult subjects. Respir Care 2020;65(4):545-557. https://doi.org/10.4187/respcare.07663
6. Rochwerg B, Granton D, Wang DX, Einav S, Burns KEA. High-flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: Author's reply. Intensive Care Med 2019;45(8):1171. https://doi.org/10.1007/s00134-019-05658-2
7. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708-1720. https://doi.org/10.1056/NEJMoa2002032

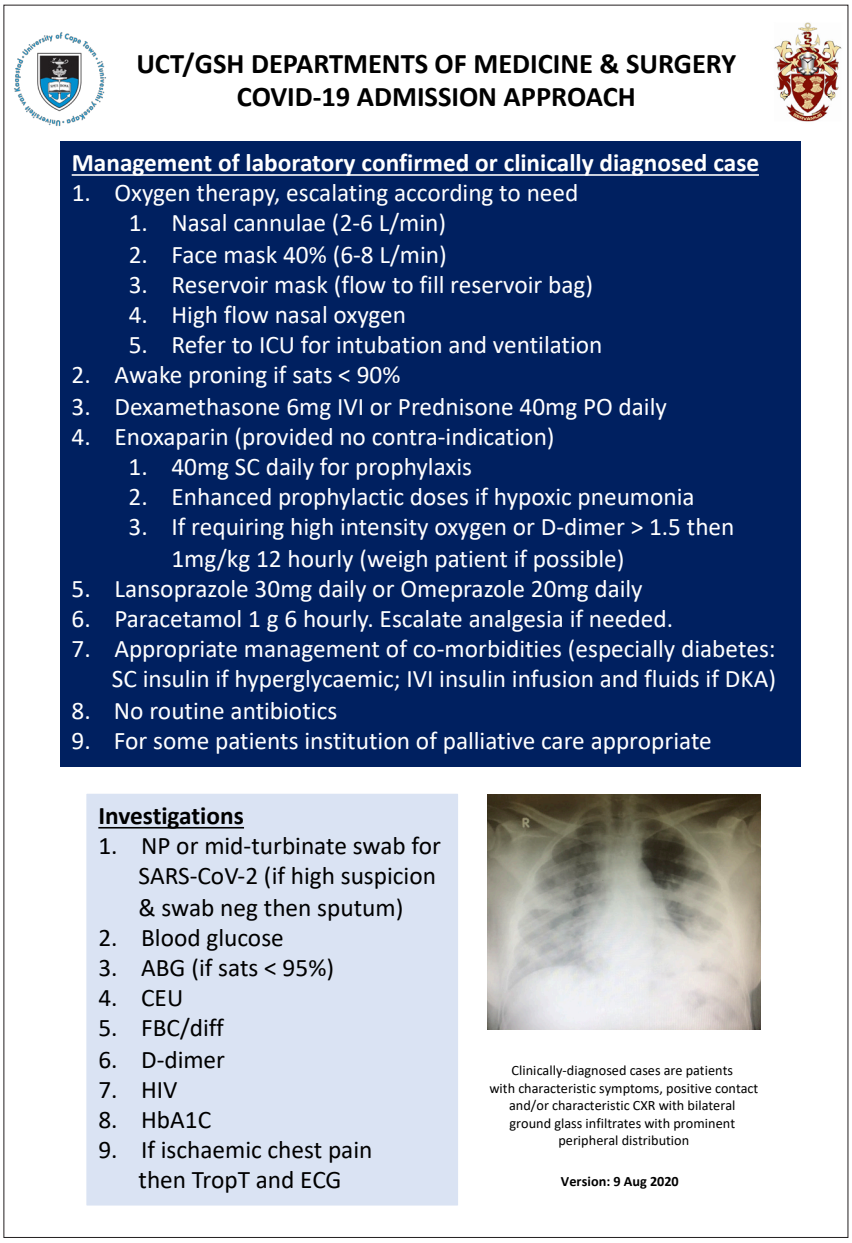

Fig. 5. Groote Schuur Hospital (GSH)/University of Cape Town (UCT) approach to admissions with COVID-19. (ICU = intensive care unit; IVI = intravenous infusion; PO = per os; SC = subcutaneous; DKA = diabetic ketoacidosis; NP = nasopharyngeal; ABG = arterial blood gas; CUE = creatinine, urea and electrolytes; TropT = troponin T; ECG = electrocardiogram; CXR = chest X-ray.)

8. Lalla U, Allwood BW, Louw EH, et al. The utility of high-flow nasal cannula oxygen therapy in the management of respiratory failure secondary to COVID-19 pneumonia. S Afr Med J 2020;110(6):432. https://doi.org/10.7196/SAMJ.2020.v110i6.14882
9. Geng S, Mei Q, Zhu C, et al. High flow nasal cannula is a good treatment option for COVID-19. Heart Lung 2020;S0147-9563(20)30113-8(epub 13 April 2020). https://doi.org/10.1016/j.hrtlng.2020.03.018
10. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. Eur Respir J 2019;53(4):1802339. https://doi.org/10.1183/13993003.02339-2018
11. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: Low risk of bio-aerosol dispersion. Eur Respir J 2020;55(5):2000892. https://doi.org/10.1183/13993003.00892-2020
12. Kingma K, Hofmeyr R, Zeng IS, Coomarasamy C, Brainard A. Comparison of four methods of endotracheal tube passage in simulated airways: There is room for improved techniques. Emerg Med Australas 2017;29(6):650-657. https://doi.org/10.1111/1742-6723.12874
13. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19 – preliminary report. N Engl J Med. 2020 (epub 22 May 2020). https://doi.org/10.1056/NEJMoa2007764
14. Horby P, Mafham M, Linsell, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRxiv 2020 (epub 15 July 2020). https://doi.org/10.1101/2020.07.15.20151852
15. Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on lopinavir-ritonavir, 29 June 2020. https://www.recoverytrial.net/files/lopinavir-ritonavir-recovery-statement-29062020_final.pdf (accessed 17 July 2020).
16. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: A systematic review and meta-analysis. J Infect 2020;81(2):266-275. https://doi.org/10.1016/j.jinf.2020.05.046
17. Rawson TR, Moore LSP, Zhu N. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020;ciaa530 (epub ahead of print). https://doi.org/10.1093/cid/ciaa530
18. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta 2020;505:190-191. https://doi.org/10.1016/j.cca.2020.03.004
19. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19 – preliminary report. N Engl J Med 2020 (epub 17 July 2020). https://doi.org/10.1056/NEJMoa2021436
20. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18(7):1743-1746. https://doi.org/10.1111/jth.14869
21. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in patients With COVID-19: CHEST guideline and expert panel report. Chest 2020 (epub 2 June 2020). https://doi.org/10.1016/j.chest.2020.05.559
22. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9-14. https://doi.org/10.1016/j.thromres.2020.04.024
23. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;18(8):1995-2002. https://doi.org/10.1111/jth.14888
24. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of *D*-dimer as predictive factors. J Thromb Thrombolysis 2020;50(1):211-216. https://doi.org/10.1007/s11239-020-02146-z
25. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999;341(11):793-800. https://doi.org/10.1056/NEJM199909093411103
26. Malato A, Dentali F, Siragusa S, et al. The impact of deep vein thrombosis in critically ill patients: A meta-analysis of major clinical outcomes. Blood Transfus 2015;13(4):559-568. https://doi.org/10.2450/2015.0277-14
27. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 2020;383(2):120-128. https://doi.org/10.1056/NEJMoa2015432
28. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75(23):2950-2973. https://doi.org/10.1016/j.jacc.2020.04.031
29. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J Thromb Haemost 2020;18(7):1747-1751. https://doi.org/10.1111/jth.14854
30. Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. Int J Lab Hematol 2020;42(S1):19-20. https://doi.org/10.1111/ijlh.13230
31. White D, MacDonald S, Bull T, et al. Heparin resistance in COVID-19 patients in the intensive care unit. J Thromb Thrombolysis 2020;50(2):287-291. https://doi.org/10.1007/s11239-020-02145-0
32. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135(23):2033-2040. https://doi.org/10.1182/blood.2020006000
33. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: Interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis 2020;50(1):72-81. https://doi.org/10.1007/s11239-020-02138-z
34. Pesavento R, Ceccato D, Pasquetto G, et al. The hazard of (sub) therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: The Padua province experience. J Thromb Haemost 2020 (epub 21 July 2020). https://doi.org/10.1111/jth.15022
35. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: Incidence and role of *D*-dimer as predictive factors. J Thromb Thrombolysis 2020;50(1):211-216. https://doi.org/10.1007/s11239-020-02146-z
36. 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
37. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. Clin Infect Dis 2020;71(15):896-897. https://doi.org/10.1093/cid/ciaa415
38. Rocha AT, de Vasconcellos AG, da Luz Neto ER, Araújo DM, Alves ES, Lopes AA. Risk of venous thromboembolism and efficacy of thromboprophylaxis in hospitalized obese medical patients and in obese patients undergoing bariatric surgery. Obes Surg 2006;16(12):1645-1655. https://doi.org/10.1381/096089206779319383
39. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76(1):122-124. https://doi.org/10.1016/j.jacc.2020.05.001
40. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18(5):1094-1099. https://doi.org/10.1111/jth.14817

41. Cantador E, Nunez A, Sobrino P, et al. Incidence and consequences of systemic arterial thrombotic events in COVID-19 patients. J Thromb Thrombolysis 2020 (epub 9 June 2020). https://doi.org/10.1007/s11239-020-02176-7
42. 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(13):1239-1242. https://doi.org/10.1001/jama.2020.2648
43. The OpenSAFELY Collaborative, Williamson E, Walker AJ, et al. OpenSAFELY: Factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv 2020 (epub 7 May 2020). https://doi.org/10.1101/2020.05.06.20092999
44. World Health Organization. Clinical management of COVID-19: Interim guidance, 27 May 2020. WHO reference number: WHO/2019-nCoV/clinical/2020.5. Geneva: WHO, 2020.
45. The Association of Palliative Care Practitioners of SA. Providing Palliative Care in South Africa during the COVID-19 pandemic. Cape Town: PALPRAC, 2020.
46. Arendse J. Operational guide to implementing palliative care during COVID-19. In: Department of Health Western Cape, ed. Palliative Care Position Statement. Cape Town, 2020.
47. World Health Organization. 'Solidarity' clinical trial for COVID-19 treatments. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments (accessed 17 July 2020).
48. International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). COVID-19 clinical data report. https://isaric.tghn.org/covid-19-clinical-research-resources/ (accessed 6 August 2020).

Accepted 12 August 2020.