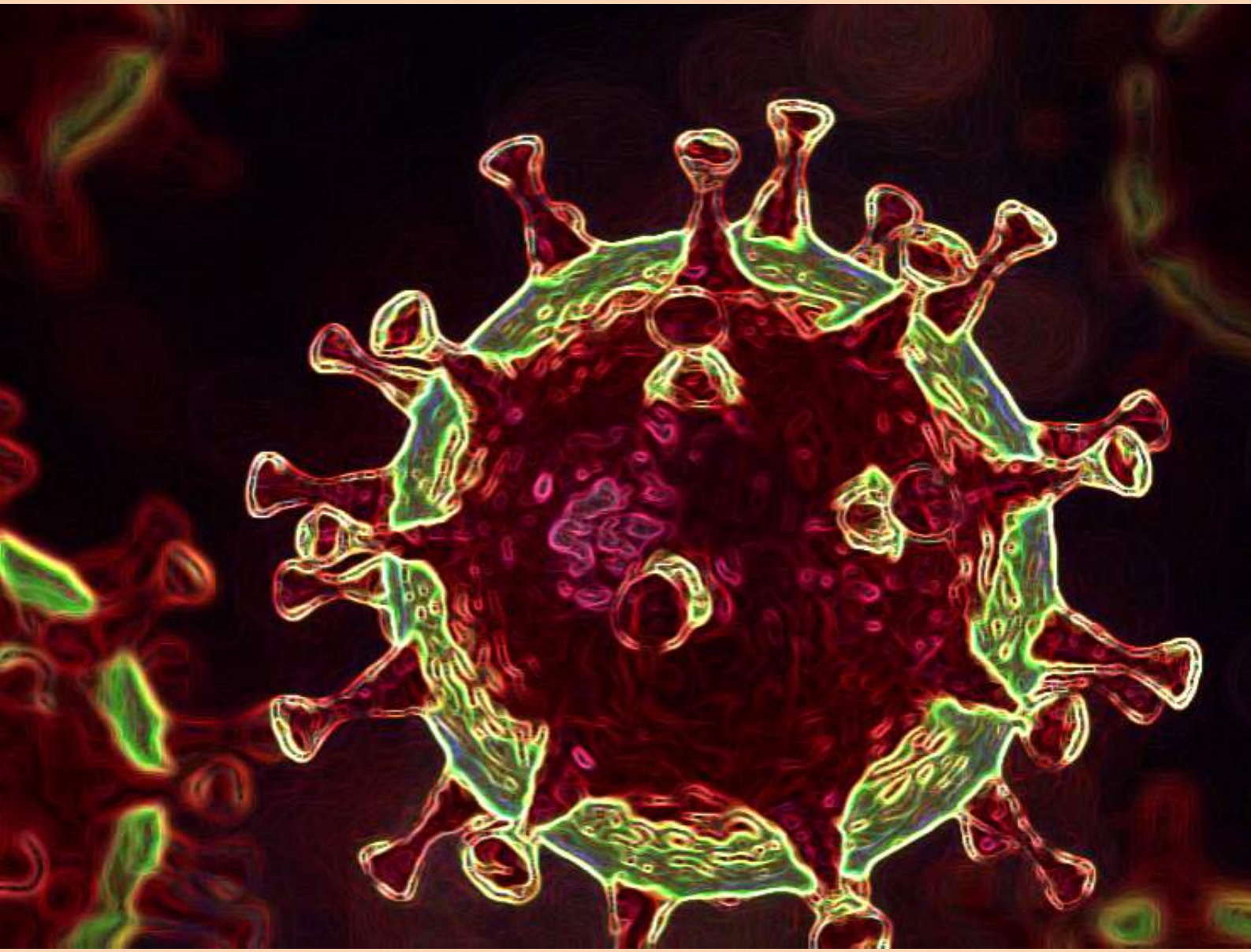
Ministry of Health
Republic of Zambia

Clinical Guidance for Management of Patients with Coronavirus Disease 2019 (COVID-19)



January 2023

Table of Contents

This page was intentionally left blank

List of Tables

List of Figures

Abbreviations and Acronyms

AIIR	Airborne Infection Isolation Room
ARDS	Acute Respiratory Distress Syndrome
ARI	Acute Respiratory Infection
ART	Antiretroviral therapy
COVID-19	Coronavirus Disease-19
CRP	C-Reactive Protein
D-DIMER	Fibrin Degradation Product
DHO	District Health Office
EMS	Emergency Medical Service
FBC	Full Blood Count
Hb	Haemoglobin
HCW	Healthcare Worker
HF	Health Facility
HIV	Human Immunodeficiency Syndrome
ICU	Intensive Care Unit
IPC	Infection Prevention and Control
MERS CoV	Middle East Respiratory Syndrome Coronavirus
MMD	Multi-Month Dispensing
MoH	Ministry of Health
PCR	Polymerase Chain Reaction
PEEP	Positive End-Expiratory Pressure
PLHIV	People Living with HIV
PPE	Personal Protective Equipment
RDT	Rapid Diagnostic Test
RsOC	Recipients of Care
RT-PCR	Real Time Polymerase Chain Reaction
SBP	Systolic Blood Pressure
SARI	Severe Acute Respiratory Infection
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
VTM	Viral Transport Medium
WHO	World Health Organisation
ZNPHI	Zambia National Public Health Institute

Acknowledgements

The Ministry of Health is committed to provide quality and effective Healthcare service to those who fall ill as clearly outlined through its legacy goals. The development of this interim guidance on the management of patients infected with the Novel Coronavirus (SARS-CoV-2) demonstrates the Ministry's resolve to have optimal clinical care for all diseases.

I am very thankful to the team of experts without whose effort this document could never have been developed. These include but not limited to the following institutions:

Ministry of Health
University Teaching Hospitals
Levy Mwanawasa University Teaching Hospital
Zambia National Public Health Institute
Zambia Medical Association
World Health Organization
Centre for Diseases Control and Prevention
University of Maryland
University of North Carolina
Centre for Infectious Disease and Research in Zambia

Special thanks to the Editorial Committee

Directorate of Clinical Care and Diagnostic Services

Prof. Lloyd Mulenga
Dr. Alex Makupe
Dr. Richard Nsakanya
Dr. Godfrey Phiri

Ministry of Health/University Teaching Hospitals

Dr. Consity Mwale
Dr. Duncan Chanda
Dr. Aggrey Mweemba
Dr. Mateyo Kondwelani
Dr. Suilanji Sivile
Dr. Sombo Fwoloshi
Dr. Khozya D. Zyambo
Dr. Aaron Shibemba
Dr. Grace Mwaka Monze
Mr. Matthews Mwale
Mr. Davies Kampamba
Mr. Boyd Mwanashimbala
Ms. Uchizi Chirwa
Mr. John Mutukwa
Dr. Nyakulira Kandiwo
Dr. Manoj Mathews
Dr. Musisye Luchembe
Dr. Agatha Lloyd
Dr. Danielle Engamba
Dr. Katongo Mutengo
Dr. Peter Matibula
Dr. Kenneth Kapolowe
Ms. Lily Besa
Mr. Robert Chirwa
Ms. Anitah Bhebhe-Moyo
Ms. Linda Musonda
Dr. Chitalu Chanda
Mr. Powell Choonga
Dr. Catherine Chunda
Dr. Chris Chanda

Zambia National Public Health Institute (ZNPHI)

Prof. Roma Chilengi
Dr. Nathan Kapata
Dr. Paul Zulu
Dr. Nyambe Sinyange
Dr. Kunda Musonda
Dr. Nyuma Mbewe
Dr. Naeem Dalal

Centre for Diseases Control and Prevention (CDC)

Dr. Paul Psychas
Dr. Annie Mwila
Dr. Nzali Kancheya
Dr. Omega Chituwo
Dr. Jonas Hines
Dr. Meg Itoh

University of Maryland

Dr. Lottie Hachaambwa
Dr. Cassidy Claassen

University of North Carolina

Dr. Michael Herce

World Health Organisation (WHO)

Dr. Peter Chipimo

Clinton Health Access Initiative (CHAI)

Ms. Hilda Shakwelele
Ms. Prudence Haimbe
Mr. Mwaba Mulenga
Mr. Felton Mpasela
Ms. Nawaka Mulenga
Ms. Lindiwe Nchimunya
Ms. Yucheng Tsai

Centre for Infectious Disease Research in Zambia

Dr. Monde Muyoyeta
Dr. Luunga Mandla Ziko
Dr. Lilungwe Mutti
Dr. David Singini

ICAP at Columbia University in Zambia

Dr. Job Mwanza
Dr. Chalomba Chitanika
Ms. Tamara Hatuma

Prof. Lackson Kasonka
Permanent Secretary – Technical Services
MINISTRY OF HEALTH

Chapter 1: Overview of COVID-19 Infection

Background

The respiratory disease caused by a novel severe acute respiratory coronavirus 2 (SAR-CoV-2) was first reported in China in December 2019. Since then, the disease has spread worldwide including Zambia. The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern (PHEIC) on 30th January 2020.

Since its discovery, knowledge about SARS-CoV-2 virus and COVID-19 transmission, clinical management, post-infection sequelae, and immunology has been rapidly evolving. Emerging clinical trial data improved the treatment of infected persons, but available information continues to change as the disease evolves.

Over the pandemic, the virus has undergone various mutations giving rise to different variants such as Variants of Interest (VoI), Variants of Concern (VoC), Variants being monitored, and possibly Variants of High Consequence (currently none). The variants have implications for treatment outcomes and the potential for immune "escape" (both natural and vaccine). Some variants have been shown to have higher transmissibility and some such as omicron has shown to be less virulent with a predilection for the upper airway as opposed to beta and delta variants that have a predilection for the lungs.

Transmission of the SARS-CoV-2

1. Animal-to-person transmission: this is based on the initial large number of infected individuals that were exposed to the wet animal market in Wuhan City, China. However, at this time, there is no evidence that animals, including household pets, play a significant role in the continued spread of the virus that causes COVID-19.[1]

2. Person-to-person transmission: when the infection spreads between individuals who had no exposure to animals. Person-to-person transmission is thought to occur primarily via respiratory droplets from infected persons during talking, coughing, or sneezing or by direct contact with surfaces contaminated with respiratory droplets from infected persons. Aerosol transmission is also suggested by multiple studies, but its role in transmission is unclear in the absence of aerosol-generating procedures in healthcare settings.[2]

[1] https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html

[2] WHO. Scientific Brief. July 9, 2020

Clinical Presentation

There is a growing body of literature describing the clinical presentation of patients with confirmed SARS-CoV-2 infection. The incubation period is thought to be up to 14 days, with a median of 4-5 days and the vast majority of infections occurring within 11 days of exposure.[1,2,3] Frequently reported signs and symptoms among hospitalised patients include fever (43–98%), cough (46%–82%), myalgia or fatigue (11–44%), and shortness of breath (31%) at COVID-19 illness onset.[3,5] Sore throat has also been reported in some patients early in the clinical course. Other commonly reported symptoms may include but are not limited to new onset loss of taste or smell, congestion or rhinorrhoea, sputum production, headache, haemoptysis, and anorexia. The loss of taste and smell has been reported less in patients infected with the Omicron variant[3]. Some patients have experienced gastrointestinal symptoms such as vomiting, diarrhoea, and nausea prior to developing fever and lower respiratory tract signs and symptoms. The fever course among patients with COVID-19 may be prolonged and intermittent but is absent in many infected persons with COVID-19. Truly asymptomatic infection, initially thought to be very rare, now appears to be a substantial driver of transmission, with recent systematic review and meta-analysis estimating that the proportion of total infections that are truly asymptomatic range from 6% to 41%. [6,4] Infectivity begins before symptoms develop and the virus can initially be detected 1-2 days before symptom onset.[6]

Clinical Course

Clinical presentation among reported cases of COVID-19 varies in severity from asymptomatic infection to pre-symptomatic infection to mild illness to severe or fatal illness. Some reports suggest the potential for clinical deterioration during the second week of illness.[3] In one report, among patients with confirmed COVID-19 and pneumonia, just over half of patients developed dyspnoea with a median of 8 days after illness onset (range: 5–13 days). Severe disease, which occurs in about 15-20% of patients includes severe pneumonia, Acute Respiratory Distress Syndrome (ARDS), sepsis, and septic shock.[3-5] Other reported complications include acute cardiac injury, arrhythmia, shock, large vessel strokes, venous thromboembolism, and acute kidney injury. SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children (Multisystem

[1] https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html
[2] WHO. Scientific Brief. July 9, 2020
[3] Boscolo -Rizzo BMJ 2022;378:e069503 doi: https://doi.org/10.1136/bmj.o1653
[4] Byambasuren. MedRxiv. 2020;[Preprint]. Note: this study has not been peer reviewed.

Inflammatory Syndrome in Children or MIS-C).[5,6] Overall mortality from COVID-19 ranges from 1-3%.

Older patients above the age of 50 and those with chronic medical conditions (including diabetes, hypertension, and cardiovascular disease, uncontrolled HIV, obesity, tuberculosis, chronic kidney, liver, lung diseases, cancer, etc) are at higher risk of progression to severe illness requiring hospitalisation.[1,3,4] *See **Box 1** below for other risk factors.*

The clinical course of COVID-19 in people living with HIV (PLHIV) has been described several studies, that have not shown worse outcomes for PLHIV and HIV infection was not independently associated with worse outcomes among patients hospitalised for COVID-19.[4],[6] However, those with severe HIV disease were more likely to develop severe COVID-19 or to die of COVID-19 compared with those with controlled HIV disease[5]. Additionally, persons with immunocompromising medical conditions like diabetes or cancer appear to have higher occurrences of severe disease and mortality.

Box 1: Risk Factors for Rapid Disease Progression and Hospitalization

- Age above 50 years*
- individuals not fully vaccinated against COVID-19*
- HIV positive individuals with uncontrolled diseases
- Other immunosuppression such as Chronic Steroid Use
- Cancer
- Diabetes
- Hypertension
- Heart Conditions
- Obesity or overweight (BMI >25 kg/m2)
- Pregnancy
- Chronic Lung, Kidney, or Liver Disease
- Tuberculosis
- Neurological and psychiatric conditions
- Current smoking and substance use disorders
- Patients dependent on medically related devices such as tracheostomy tubes, urinary catheters, intracardiac devices, nasogastric feeding tubes, extra-ventricular drainage devices, etc

* Individuals under the age of 50 and with no risk factor beyond status as unvaccinated still have low risk for hospitalization and hence vaccination status can be used to prioritize patients with at least one risk factor.

[5] Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case series. J Pediatric Infect Dis Soc. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32463092.
[6] Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32418446.

Earlier data suggested that pregnant women do not appear to be at higher risk of severe disease,[4] however, several recent studies demonstrated increased rate of hospitalizations, ICU care, and mechanical ventilation, but not death, in pregnant women vs age-matched non-pregnant controls.[4,5] Although there is limited data in children, infections appear to be generally mild, although severe disease has been reported in 2.5% (mortality was 0.2%).[6] The reason for this paradox is not known. Vertical (mother-to-child) transmission has not been confirmed although several case reports suggest this is possible. [5]

SARS-CoV-2 can affect other organ systems besides the lungs (see **Table 1**). Hypercoagulability, with venous or arterial thrombosis, has been described. These may manifest as pulmonary embolism, myocardial injury, stroke, or digital ischemia. Cardiac dysfunction is an emerging concern. Additional information about the effects of SARS-CoV-2 on the body continues to emerge every day.

Table 1: Extrapulmonary Manifestations of COVID-19

Neurologic	Headaches, Dizziness, seizures, Encephalopathy, Guillain-Barré, Ageusia, Myalgia, Anosmia, Stroke
Renal	Acute kidney injury, Proteinuria, Haematuria
Hepatic	Elevated Aminotransferases, Elevated bilirubin
Gastrointestinal	Diarrhoea, Nausea/vomiting, Abdominal pain, Anorexia
Thromboembolism	Deep vein thrombosis, Pulmonary embolism, Catheter-related thrombosis
Cardiac	Takotsubo cardiomyopathy, Myocardial injury/myocarditis, Cardiac arrhythmias, Cardiogenic shock, Myocardial ischemia, Acute cor pulmonale
Endocrine	Hyperglycaemia, Diabetic ketoacidosis
Dermatological	Petechiae, Livedo reticularis, Erythematous rash, Urticaria, Vesicles, Pernio-like lesions

Laboratory Findings

The most common laboratory abnormality reported among hospitalised patients with COVID-19 is lymphopenia. Other laboratory abnormalities have included elevated levels of **Procalcitonin, C-reactive Protein, D-dimer, Ferritin, fibrinogen, and Lactate Dehydrogenase**, and these may be associated with severe disease.

SARS-CoV-2 RNA can be detected from upper and lower respiratory tract specimens, bronchoalveolar lavage fluid, saliva, and stool specimens. Low viral loads are observed in the first couple of days but then peak around days three to six, tailing off at days seven to nine until no viable virus could be recovered by day ten. Viral RNA fragments may continue to be detected in various specimens for weeks. SARS-CoV-2 has been isolated from

respiratory, blood, urine, and stool specimens but only from respiratory tract specimens for MERS-CoV.[21-23]

Tests for SARS-CoV-2 antigens are available in Zambia (***see Table 2)***. These tests can diagnose SARS-CoV-2 infection.

The serologic tests are generally not recommended as the sole basis for diagnosing acute SARS-CoV-2 infection. Unlike molecular diagnostic and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic tests are intended to identify persons with recent or prior SARS-CoV-2 infection given it may take 21 days or longer after symptom onset for seroconversion or detection of immunoglobulin M and/or immunoglobulin G antibodies to SARS-CoV-2

Table 2: Types of Tests Available for SARS-CoV-2 and their Recommended Uses

	Molecular Test	Antigen Test	Antibody Test
Testing method	rt-PCR device-based	RDT or POC device-based	RDT or lab-based ELISA
When to use	To diagnose ***active*** coronavirus infection		To identify ***past*** infection
Use Case	Diagnosis, screening, infection clearance	Diagnosis, screening, surveillance	Surveillance & Seroprevalence studies only

SARS-CoV-2 Antigen Tests

These are immunoassays that detect the presence of specific SARS-CoV-2 viral infection. Below are their key characteristics:

- They imply current viral infection
- They can be used as a rapid point-of-care test
- They can be used for *diagnosis*, *screening* and for *epidemiological surveillance*
- They are currently authorised devices which return results in approximately 15 minutes leading to rapid initiation of treatment or isolation of positive individuals to prevent further transmissions
- Currently recommended RDT-Antigen tests are highly sensitive and hence confirmatory PCR testing is no longer recommended
- Antigen testing is recommended in most settings except for routine pre-operative testing, boarder testing and testing regulations for employment and travel. See ***Table 3*** for the rationale for recommendation of the SARS-CoV-2 Antigen Testing. Self-testing kits are

now available and recommended for symptomatic individuals with provision of linkage to care and treatment at their nearest health facility

Table 3: Recommended Scenarios for Rapid Antigen Tests to Diagnose COVID-19

Modality of testing Scenarios	Need to for rapid TAT	Antigen test recommended
In hospital symptomatic	High	Yes
In hospital Asymptomatic	High	Yes
High risk Exposed HCW	High	Yes
Pre-op testing	High	No
Mortuary Surveillance	Low	Yes
Index case in a suspected outbreak	High	Yes
Contacts of confirmed cases during outbreak investigations	High	Yes
General community testing	High/moderate	Yes
Self-testing	High/moderate	Yes
Border testing	High	No
Testing for regulations such as employment or travel	High	No

COVID-19 Antigen Rapid Test Device Specifications

- Diagnostic rapid test for qualitative detection of SARS-CoV-2 antigen
- Targets Nucleocapsid Proteins from SARS-CoV-2
- Storage: $2^{O}C$-$30^{O}C$
- Sample Type: Nasopharyngeal, Nasal swab, or Oral samples
- Test time: 15-20 Minutes

The below figure is one of the example Ag-test that are used in Zambia:

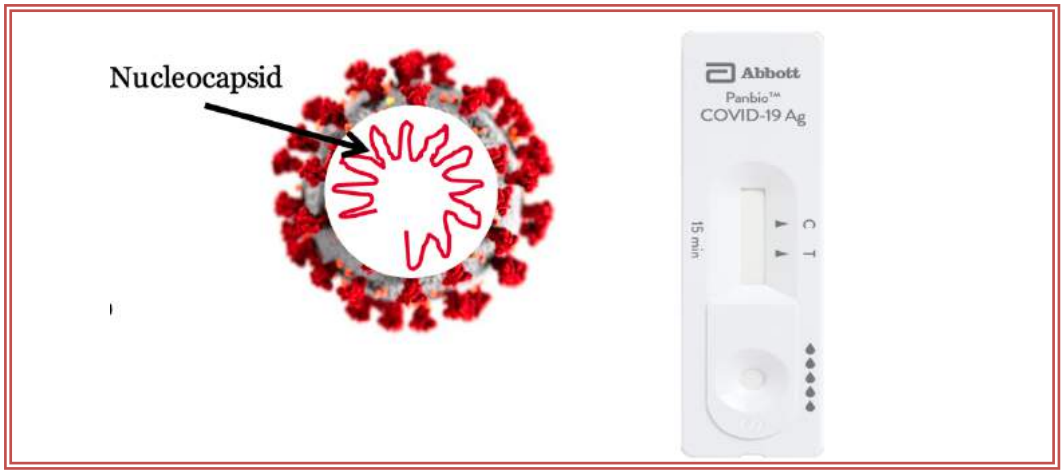
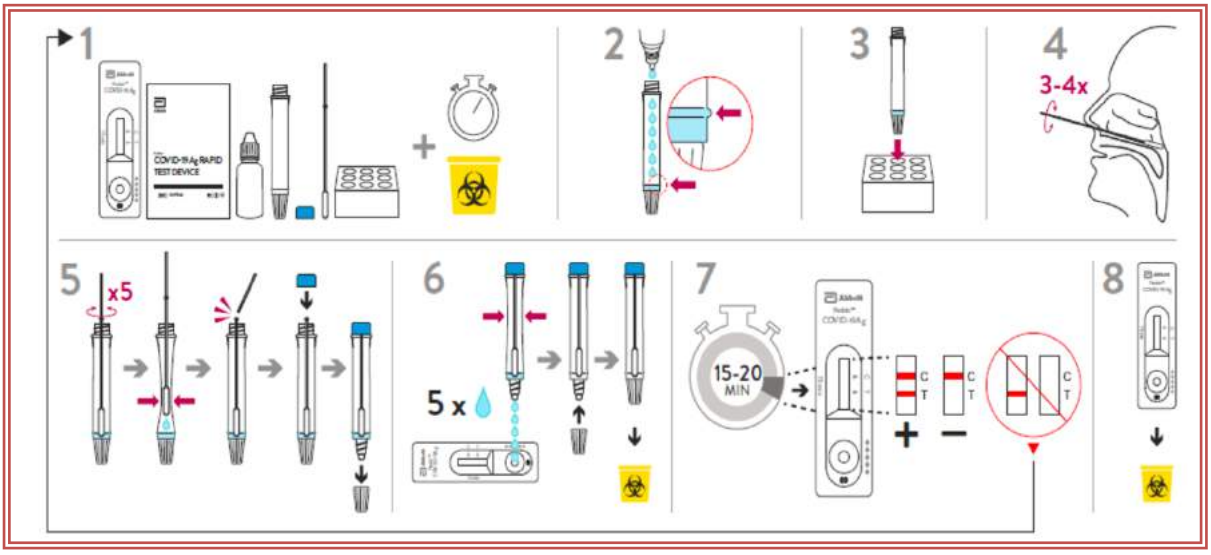
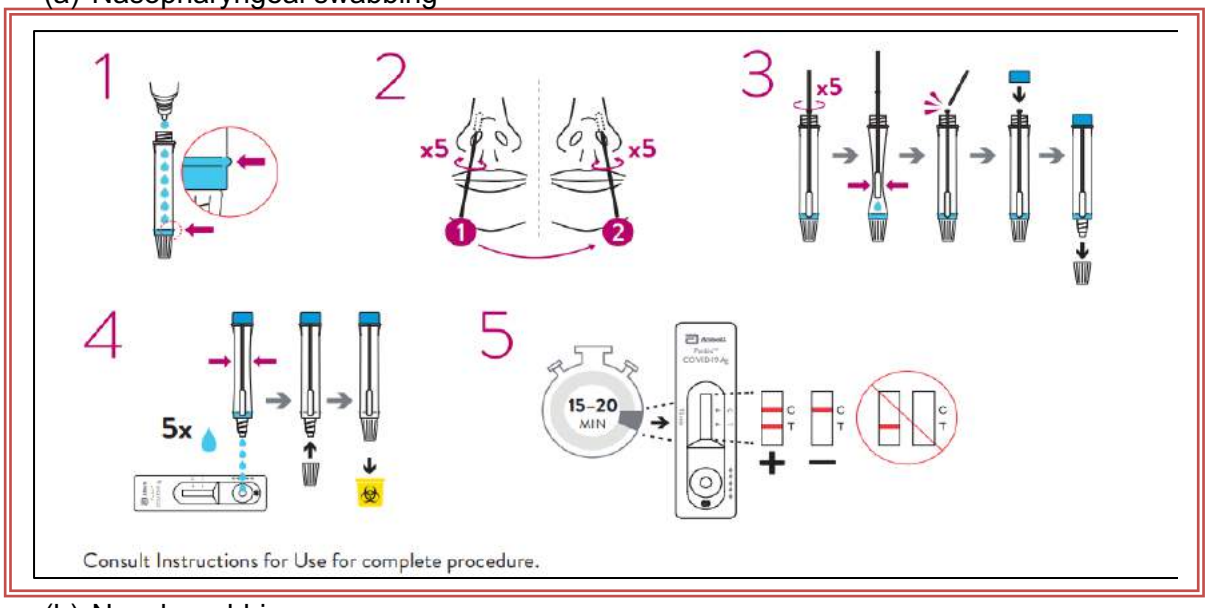


Figure 1: Abbott Panbio COVID-19 Antigen Rapid Diagnostic Test Device



(a) Nasopharyngeal swabbing



(b) Nasal swabbing

Figure 2: Panbio COVID-19 Rapid Test Procedure (a: Nasopharyngeal swabbing b: Nasal swabbing)

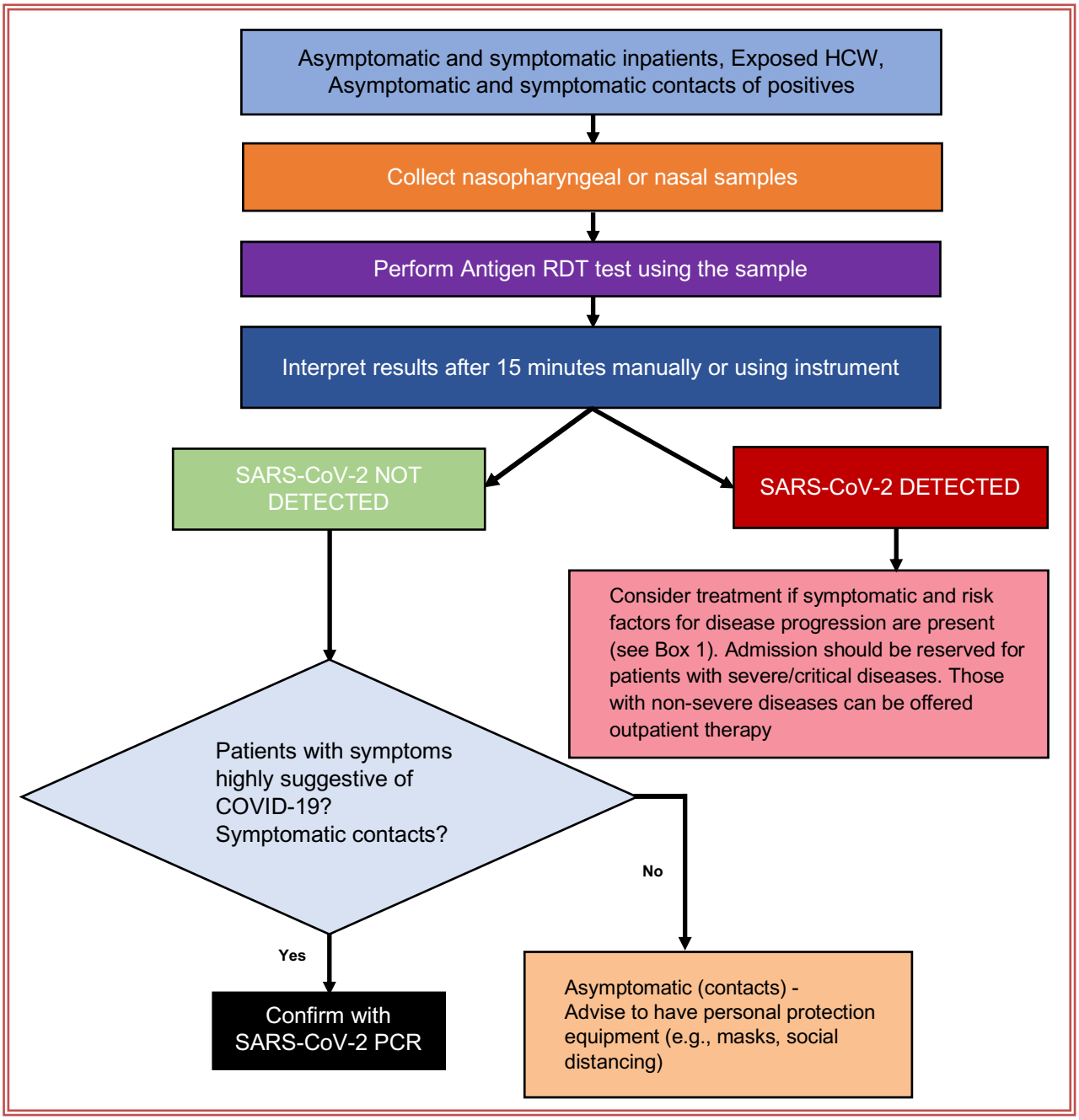


Figure 3: Algorithm for COVID-19 Antigen Testing

Recommendations for SARS-CoV-2 Rapid Antigen Test

- ☞ Should be the first line for COVID-19 testing
- ☞ Not recommended for individuals with a previous positive test result to assess negativity
- ☞ Not recommended to be used to assess discharge qualification from either facility or home isolation
- ☞ Positive results should be reported to surveillance

***For more details, please refer to COVID-19 Testing Guidelines (2022)**

Genomic surveillance

The primary objective of genomic surveillance of SARS-CoV-2 is to monitor the geographic and temporal distribution of genotypes using genomic sequencing in order to make quick and informed public health decisions.

Genomic sequencing is a method used to decipher the genetic material found in a pathogen or organism. Sequences from specimens can be compared to help scientists track the spread of a virus, how it is changing, and how those changes may affect public health.

Case definition when conducting genomic sequencing

Routine and Targeted Surveillance: The case definition for selection of samples is 'Samples tested SARS-CoV-2 positive using PCR or RDT,'

Testing categories

The current testing categories for SARS-CoV-2 are

1. Institutions/organisations such as Government Ministries, Church organisations, and Schools
2. 'Super Spreader Event (SSE)' cases – cases from clusters with 5 or more cases Healthcare workers are tested as part of routine screening
3. Outpatients tested at health facilities
4. Inpatients at health facilities
5. Screening at Points of Entry (PoE)
6. Community, or contacts of a positive case
7. Self-testing
8. Deaths – both individuals who die at health facilities, and brought-in-dead (BID)

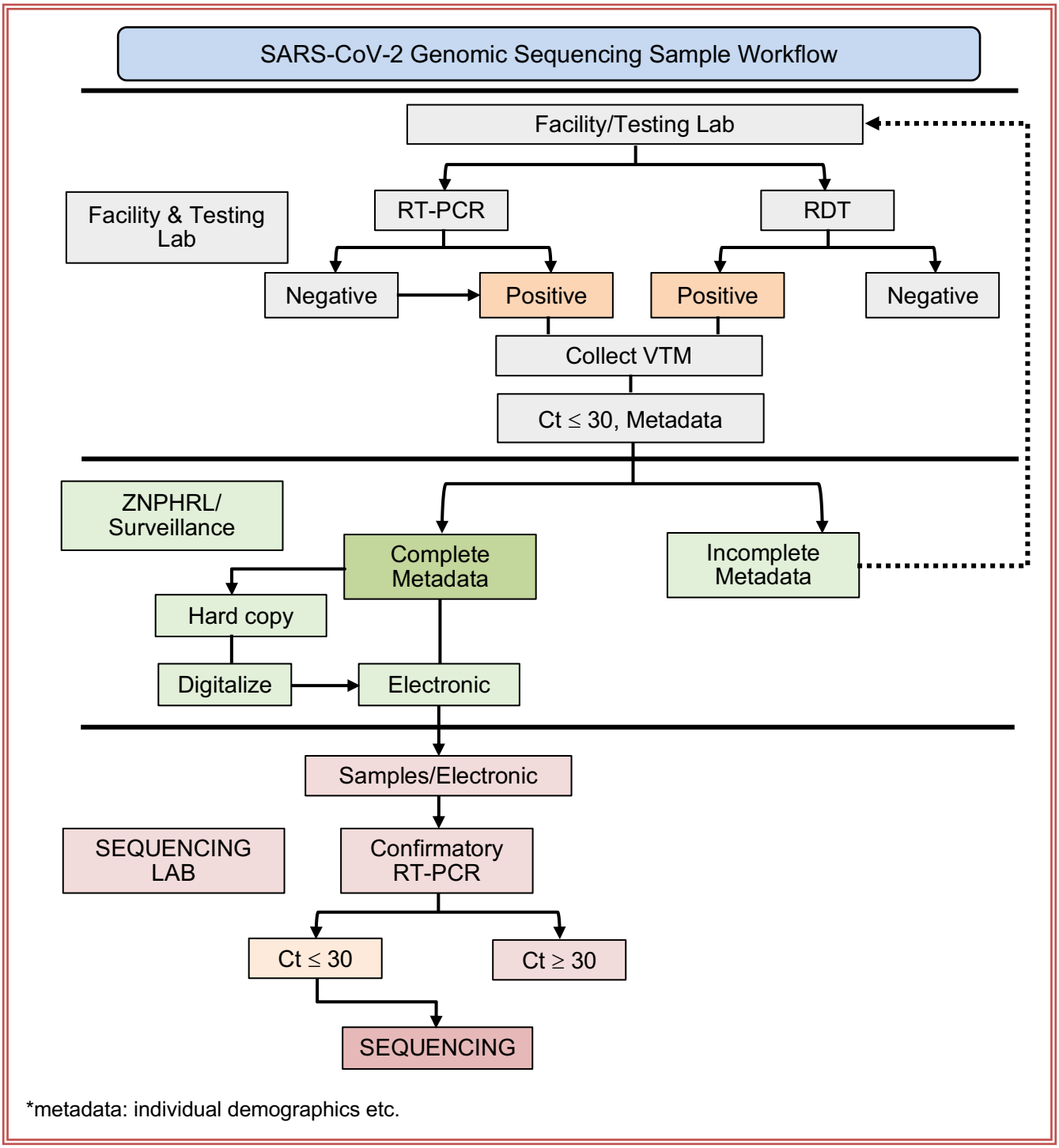


Figure 4: SARS-CoV-2 Genomic Sequencing Sample Workflow

Radiographic Findings

Chest radiography is abnormal in ~60% of patients.[2] Ground glass opacification is the typical findings in the early stages of the disease; usually diffuse bilateral, peripheral infiltrates in the lower zones and sparing the hila. Less frequently reported abnormalities include consolidations, upper zone opacities, nodules, and pleural effusion.

Images from Computer-aided Topography (CT scans) of the chest have shown bilateral involvement in most patients. Multiple areas of consolidation and ground-glass opacities are typical findings reported to date.[3-5,9-12]

In centres with easy access to Chest CT, it has been used to assign a level of suspicion in cases without available PCR results. The score used is known as the COVID-19 Radiological Score (CO-RADS), (*see Table 4)*.

Table 4: COVID-19 Radiological Score (CO-RADS)

CO-RADS		
	Chance of COVID-19	CT Findings
CO-RADS 1	Highly unlikely	Normal or non-infectious abnormalities
CO-RADS 2	Unlikely	Abnormalities consistent with infections other than COVID-19
CO-RADS 3	Equivocal	Unclear whether or not COVID-19 is present
CO-RADS 4	Probable	Abnormalities suspicious for COVID-19
CO-RADS 5	Highly likely	Typical COVID-19
CO-RADS 6	PCR proven	

Ultrasound, a point of care tool is another modality that can be utilised if available. Typical findings on Chest ultrasound for COVID-19 are Thickening of the pleural line with pleural line irregularity, B-lines in a variety of patterns including focal, multifocal, and confluent, consolidations, multifocal small, non-translobar, and translobar with occasional mobile air bronchograms during recovery.

Clinical Management of COVID-19

Patients with a mild clinical presentation may not initially require hospitalisation. However, clinical signs and symptoms may worsen in the **second week of illness**. Patients with severe infections (*see **Box 3**: COVID-19 Severity Classification, page 24*) should be hospitalised.

Possible risk factors for progressing to severe illness may include but are not limited to, older age, underlying chronic medical conditions such as lung disease, cancer, cardiac disease, renal disease, liver disease, diabetes, and immunocompromising conditions.

Supportive Management

WHO recommends for isolation of suspected/confirmed cases to contain SARS-CoV-2. isolation can occur at home or in a designated COVID-19 health or community facility. Treat symptoms (e.g., antipyretics for fever/pain, adequate nutrition, appropriate rehydration. Educate patients on signs and symptoms of complications that if developed should prompt pursuit or urgent care. Close monitoring is advised for older patients and those with underlying comorbidities due to the increased risk of disease progression. In non-hospitalized patients, do not initiate anticoagulants or antiplatelet therapy to prevent VTE or arterial thrombosis unless other indications exist.

Therapeutics

Aside from Oxygen, the following primary drug therapeutics Remdesivir (RDV), Heparin (Enoxaparin), Dexamethasone, Nirmatrelvir-r, and Molnupiravir have emerged most promising in clinical trials of COVID-19 patients. Newer oral Direct acting antivirals (Ritonavir-boosted Nirmatrelvir and Molnupiravir) have been shown to be highly effective in stopping viral replication and reducing the risk of admission if started early in patients highly at risk. These medicines have either WHO or FDA Emergency Use Authorization.

Treatment options using the different antivirals for COVID-19 are guided by the patient's clinical status and risk factors for disease progression (see ***Box 1**, page 3*). For patients with non-severe disease, Nirmatrelvir-ritonavir (Paxlovid) is the recommended therapy for patients with at least one risk factor and has been shown to reduce the risk of hospitalization. Alternative outpatient oral therapy for non-severe diseases is Molnupiravir, however caution remains for use in children and in women who are pregnant, breastfeeding of childbearing potential). Use of Remdesivir has been expanded beyond severe cases, to be given as outpatient intravenous therapy for 3 days in patients with non-severe disease who have other contraindications for oral therapies. Inpatient management for patients with severe

disease includes oral Janus kinase inhibitors such as Baricitinib, and monoclonal antibodies like Tocilizumab and Bamlanivimab.

Further details on the therapeutic options available in Zambia for the management of COVID-19 infection are outlined below.

Therapeutics for Non-Severe Disease

1. **Nirmatrelvir-ritonavir (NMV-r) is** an Oral antiviral for SARS-CoV-2 that inhibits the SARS-CoV-2 protease (3CLpro), thereby preventing cleavage of the viral polyprotein needed for viral proteins to become functional.

It is recommended treatment for adult and paediatric patients above the age of 12 years (or above 40kg) with non-severe COVID-19 at highest risk of progression to hospitalisation (see ***Box 1,*** *page 3*)

NMV-r should be administered as soon as possible after the onset of symptoms, ideally within 5 days. Patient is treated as an outpatient and reminded to return for review at the end of 5 day or if the symptoms progress prior to that.

Combination of NMV-r is given as 300mg of Nirmatrelvir (two tablets of 150mg each) plus Ritonavir (one tablet of 100mg). All three tablets are taken together twice daily for the 5 days. In renal insufficiency (CrCl 30–59 mL/min) the dose should be reduced to a single tablet of Nirmatrelvir (150mg) and one tablet of Ritonavir (100mg) taken together twice daily.

Nirmatrelvir-ritonavir is contraindicated among individuals with **severe renal impairment (CrCl < 30 mL/min**. Prescribers also need to be mindful of drug interactions (see list in Appendix). For children less than 40kg, or people coinfected with Tuberculosis, alternative therapy is recommended.[7][8]

Figure 5: Suggested Dosing Regimens for Nirmatrelvir-ritonavir

[7] FDA Fact Sheet - Emergency Use Authorization fo**r Nirmatrelvir-ritonavir**

[8] Arberl et al. 2022 NEJM Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge

Clinical "Rebound" of COVID-19 Symptoms after Nirmatrelvir-ritonavir

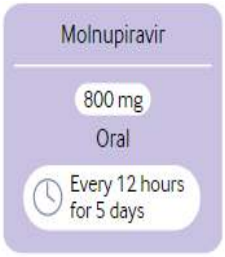
A brief return of symptoms may be part of the natural history of SARS-CoV-2 in some persons, independent of Nirmatrelvir-r treatment. Limited information is currently available from case reports suggesting that persons with rebound have mild illness; there are no reports of severe disease. There is currently no evidence that additional treatment is needed with Nirmatrelvir-r or other therapies.

Advise patients with COVID-19 rebound to re-isolate for at least 5 days, and they can end their re-isolation period after 5 full days if fever has resolved for 24 hours (without the use of fever-reducing medication) and symptoms are improving. The patient should wear a mask for a total of 10 days after rebound symptoms started. Consider clinical evaluation of patients who have COVID-19 rebound and symptoms that persist or worsen.

2. **Molnupiravir** is another newly approved orally available prodrug of ß-D-N4-hydroxycytidine (NHC) that Inhibits replication of SARS-CoV-2 similar to Remdesivir. It is a nucleoside drug, but the mechanism of action involves lethal mutagenesis of the virus

Note that WHO has given "weak or conditional" recommendations for Molnupiravir, to be used when other options are not available or possible. Specifically for populations not indicated for Nirmatrelvir-r such as people living with TB on Rifampicin, due to drug-drug interactions.

Avoid people under the age of 18, pregnant and breastfeeding women, or those trying to conceive due to potential embryo-foetal toxicity[9]. Advise cautious use coupled with effective contraception used correctly and consistently for the duration of treatment and for 4 days after last dose[10]. Breastfeeding not recommended during treatment and for 4 days after the last dose. Non-clinical studies to fully assess potential to affect offspring of treated males are not yet completed. Thus, if sexually active with individual of childbearing potential, contraception advised for at least 3 months after last dose. Pregnancy surveillance should be done.



- Taken orally twice daily at 800mg

[9] Source: https://www.cdc.gov/mmwr/volumes/71/wr/mm7125e2.html

[10] Pregnancy surveillance program https://pregnancyreporting.msd.com/

3. **Remdesivir** is now recommended for the treatment of non-severe cases at risk of progression and severe cases. Remdesivir should be administered as soon as possible after the onset of symptoms, ideally within 7 days.

It has been shown to delay progression to severe disease reduce time to clinical recovery in admitted patients[11],[12],[13]

- In non-severe It is given intravenously at 200mg stat then 100mg daily for two days in non-severe cases
- In severe cases for adults and children above 40kg, Remdesivir is given at 200mg Intravenous Infusion on day 1 followed by 100mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation). If a patient is otherwise ready for discharge prior to completion of the course, Remdesivir can be discontinued
- The suggested dose for paediatric patients with body weight between 3.5kg and < 40kg with severe/critical disease is a single loading dose of Remdesivir 5mg/kg IV (infused over 30 to 120 min) on Day 1 followed by Remdesivir 2.5mg/kg IV (infused over 30 to 120 min) once daily from day 2 to day 5
- Each infusion should be administered over 30 – 120 minutes. Patients should be observed for ≥ 1 hour after infusion as clinically appropriate
- Special consideration: can still be even in patients with renal failure with CrCl < 30mL/hr in consultation with a nephrologist
- The Remdesivir may be added to other drugs such as Dexamethasone, Baricitinib if indicated

[11] Horby et al 2020 RECOVERY doi:10.1056/NEJMoa2021436

[12] Gottileb N Engl J Med 2022;386:305-15. DOI: 10.1056/NEJMoa2116846

[13] Beigel et al 2020 ACTT-1. doi:10.1056/NEJMoa2007764

Therapeutics for Severe Disease

1. Tocilizumab and Sarilumab

Interleukin-6 (IL-6) inhibitors whose recent data indicates that it plays an important role in the COVID-19-related Cytokine Release Storm (CRS). Thus, most clinical guidelines, IL-6 inhibitors are recommended as one of the options available to severe or critically ill patients[14].

2. Baricitinib

A selective Janus kinase 1 and 2 inhibitor. The proposed benefits of Baricitinib in the management of COVID-19 may be two-fold as it has both anti-inflammatory and potential antiviral activity. Janus kinase mediates cytokine signalling, which contributes to inflammation; Janus kinase inhibitors, therefore, may decrease cytokine-mediated inflammation. Baricitinib may be used in combination with steroids and/or Remdesivir in severely ill patients

Baricitinib is given orally at a dose of 4 mg daily dose for 14 days or until discharge from hospital whichever comes first has been demonstrated to have a survival benefit in those with ***severe COVID-19*** requiring Oxygen compared to no Baricitinib. Dose adjustment should be done for those with renal and liver dysfunction.

3. Dexamethasone

Corticosteroid drug with anti-inflammatory effects and has been shown to reduce mortality in individuals requiring supplemental Oxygen or receiving mechanical ventilation. There was no benefit seen for those who did not need Oxygen to receive Dexamethasone

In early or non-severe disease corticosteroids tend to worsen outcomes, presumably by suppressing the immune response. However late or severe illness, when excess inflammation may become prominent, corticosteroids are beneficial

Before initiating Dexamethasone, clinicians should review the patient's medical history and assess the potential risks and benefits of administering corticosteroids to the patient. For example, patients with poorly controlled diabetes may not be appropriate for steroids. Additionally, it is necessary to screen for TB prior to initiation of steroids and consider TB preventative therapy if at additional risk of development of TB (e.g., PLHIV).

[14] WHO Clinical management of COVID-19: Living guideline, 23 June 2022

4. Heparin

Anticoagulants have been seen to have a crucial role in the management of patients of COVID-19. Several studies, including an autopsy study done in Zambia at the University Teaching Hospitals on patients who died from COVID-19, have shown micro and macro thrombi in various organs predominantly the brain, lungs, and kidneys[15].

5. Other modalities that have been promising and should be considered under specialist care with broader consultation include Plasma Exchange/Plasmapheresis, Convalescent Plasma, IVIG, and Haemo-adsorption

Therapeutics Shown not to Work

1. **Hydroxychloroquine (HCQ)** - shown to provide no additional benefit compared to placebo control for the treatment of COVID-19 in hospitalized patients. The Outcomes Related to COVID-19 treated with Hydroxychloroquine (HCQ) among In-patients with symptomatic Disease Study (ORCHID) was halted by the NIH in the UK as data from this study showed that the drug provided no additional benefit compared to placebo control for the treatment of COVID-19 in hospitalised patients [16] [17]

2. **Azithromycin -** The COALITION 2 trial showed no benefit of using Azithromycin in COVID-19 unless with underlying bacterial pneumonia[18].

3. **Ivermectin -** its use did not result in a lower incidence of hospitalisation or emergency room visits for COVID-19 in high-risk non-hospitalized patients) (add ref Together trial). Moreover, there was no additional benefit when the analysis was extended to safety endpoints, viral clearance, hospitalisation for any cause, mortality, or receipt of mechanical ventilation[19].

4. **Ivermectin + Fluvoxamine + Metformin -** were tested in phase III, a randomised, placebo-controlled trial to evaluate the effectiveness of this combination therapy in preventing severe COVID-19 illness in non-hospitalized adults with a confirmed diagnosis of SARS-CoV-2 infection. The results showed that early outpatient treatment with Metformin, Ivermectin, or Fluvoxamine failed to prevent hypoxemia, emergency department visit, hospitalisation, or death in adults with overweight or obesity and SARS-CoV-2 infection[20].

---

[15] Himwaze et al 2021 International Journal of Infectious Diseases 108 (2021) 363–369 doi.org/10.1016/j.ijid.2021.06.013 1201-9712

[16] Self W. ORCHID study *JAMA*. 2020;324(21):2165-2176. doi:10.1001/jama.2020.22240

[17] Avezum Lancet Regional Health- Americas 2022;11: 100243 https://doi.org/10.1016/j. lana.2022.100243

[18] Furtado et al COALITION II lancet 2022 DOI:https://doi.org/10.1016/S0140-6736(20)31862-6

[19] WHO Clinical management of COVID-19: Living guideline, 23 June 2022

[20] Bramante C et al. N. Engl. J. Med 2022 Aug 18;387(7)599-610

5. **Favipiravir -** Results of studies evaluating Favipiravir's efficacy, published and unpublished, are mixed and possibly misleading by supporting a favourable effect. One RCT was able to show that Favirpiravir lacked a mitigating effect on COVID-19 symptoms, measured as time to sustained clinical recovery, and did not decrease the progression of COVID-19, measured as the development of new moderate or severe symptoms or the need for emergency room visits and hospitalizations. In addition, the pace of cessation of viral shedding was not affected by Favipiravir treatment. This lack of Favipiravir effect was observed across analysis populations and patient subgroups[21].

6. **Colchicine** is an anti-inflammatory drug that is used to treat a variety of conditions, including gout, and recurrent pericarditis. It has several potential mechanisms of action, including reducing the chemotaxis of neutrophils, inhibiting inflammasome signalling, and decreasing the production of cytokines, such as interleukin-1 beta. When Colchicine is administered early in the course of COVID-19, these mechanisms were thought to potentially mitigate or prevent inflammation-associated manifestations of the disease. These anti-inflammatory properties coupled with the drug's limited immunosuppressive potential, favourable safety profile, and widespread availability prompted investigation of colchicine for the treatment of COVID-19. However, several large Randomised controlled trials, including RECOVERY, PRINCIPLE and have shown no benefit with regard to 28-day mortality or any secondary outcomes for hospitalised patients, and no shortening of clinical symptoms for outpatients.[222324] Aside from failing to add any clinical benefit, further studies have shown that the use of Colchicine instead increased the incidence of diarrhoea in treatment groups.

7. **Monoclonal Antibodies:**

   For non-severe COVID19, monoclonal antibodies are used as alternative only when Paxlovid or Remdesivir are not available, not feasible or not clinically appropriate. As of 30th November 2022, the FDA revoked emergency use authorization for the last monoclonal antibody Bebtelovimab because of lack of efficacy against newer viral variants. Hence these agents are no longer recommended for use in patients with COVID-19.

Treatments such as **Sotrovimab, Casirivimab and Imdevimab, Bamlanivimab (BAM) and Etesevimab (ETE)** are human monoclonal antibodies that bind to the SARS-CoV-2 spike protein and were used in non-severe, severe and critical COVID-19. These should be

[21] Bosaeed 2022 Clinical Microbiology and Infection doi.org/10.1016/j.cmi.2021.12.026

[22] RECOVERY GROUP *Lancet Respir Med*. 2021;9(12):1419-1426. ttps://www.ncbi.nlm.nih.gov/pubmed/34672950.

[23] Dorward J et al PRINCIPLE 2022 .

[24] Sandu T et al *Can J Infect Dis Med Microbiol*. 2020;2020:8865954

limited for use to patients in whom the variant of infection is responsive. The different monoclonal antibodies bind to specific epitopes of the SARS-CoV-2 spike protein, preventing the virus from entering but can be evaded in variants such as omicron which have mutations on the spike proteins. In patients with non-severe illness, Sotrovimab probably reduces hospitalisation, with little or no impact on infusion reactions[25]. Additionally, there is a substantial body of evidence demonstrating a lack of efficacy of Casirivimab-Imdevimab against the Omicron BA.1 variant. As a result, Casirivimab-Imdevimab is no longer recommended for COVID-19 treatment except in cases where rapid viral genotyping is available and confirms infection with a SARS-CoV-2 variant (such as Delta) that is susceptible. We suggest treatment with Casirivimab-Imdevimab for patients with seronegative status, and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e., excluding Omicron BA.1)[26],[27]

25 FDA Fact sheet for healthcare providers' emergency use authorization for Sotrovimab

26 WHO Clinical management of COVID-19: Living guideline, 23 June 2022

27 Horby et al 2020 RECOVERY doi:10.1056/NEJMoa2021436

Chapter 2: Triage and Diagnostics

Most patients with COVID-19 will have mild illness consisting of upper respiratory tract infection symptoms. However, even mild infections may be infectious to others, so it is important for Healthcare Providers to recognize potential COVID-19 at first contact with the healthcare system. Early recognition of suspected COVID-19 infection allows for timely initiation of Infection Prevention and Control (IPC) measures and guides clinical triage of patients.

Early identification of those with severe manifestations of COVID-19 allows for immediate implementation of optimised treatments and safe, rapid admission (or referral) to the intensive care unit when indicated.

Triage of Patients with Suspected COVID-19

The purpose of triage is to:

1) **Identify** and **isolate** patients who may have COVID-19
2) Test patients who meet clinical testing criteria for COVID-19
   (*see **Box 2**: Clinical Testing Criteria, page 21)*
3) Assess and determine the appropriate patient disposition depending on disease severity
4) Institute treatment and manage COVID-19 complications, where indicated
5) Immediately **notify** infection prevention and control teams

PPE and IPC for Healthcare Workers at Point of Contact:

Immediately implement IPC measures, including correct use of Personal Protective Equipment (PPE) by Healthcare Providers (*refer to Appendix 3*). For PPE recommendations for inpatient and outpatient settings, *refer to Appendices 4 and 5*

For the purpose of triage, appropriate PPE are gloves and a face mask with adequate physical distancing. For specimen collection, Healthcare Workers MUST at a minimum wear glove, N95, face shield/goggles, and an apron. This is also true for aerosol-generating procedures such as tracheal intubation, gastrointestinal tube insertion, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, and bronchoscopy.

Clinical Screening for COVID-19

Screening for COVID-19 testing should follow the National Testing guidelines. Because COVID-19 is a rapidly evolving situation, these may change over time. Healthcare providers should remain aware of the screening criteria set forth by the ministry. At the time of this guidance, the clinical testing criteria for COVID-19 in Zambia is:

Testing anyone with compatible symptoms or persons with close contact with a confirmed case. Testing has been decentralized and available at all levels of health care. All populations should have access to testing.

Box 2: COVID-19 Clinical Testing Criteria

1) Any person with signs or symptoms of respiratory infection such as fever, chest pain, cough and shortness of breath
2) Any person who is a close contact† in the past 14 days with a person with confirmed COVID-19 infection
3) Severe acute respiratory infection (SARI)‡ with no alternative aetiology (no epidemiological risk factor needed)

*The clinical screening criteria are deliberately broader than the WHO case definition for suspected case (*Appendix 6*) in order to identify mild cases that are still infectious

†Close contact is defined as: a) providing direct care without proper PPE for COVID-19 patients; b) Staying in the same close environment of a COVID-19 patient [including workplace, classroom, household, and gatherings]; c) Travelling together in close proximity [1 metre] with a COVID-19 patient in any kind of conveyance

‡SARI is defined as fever and a respiratory symptom requiring hospitalisation

Disposition Based on Disease Severity

For those with mild illness, hospitalisation is not required unless there is concern for rapid deterioration such as the elderly, those with underlying medical conditions like diabetes, cardiovascular disease, chronic lung disease, or immunocompromising conditions. If hospitalisation is not medically necessary, home care is preferable if the individual's situation allows it.

All cases under home care should be instructed on how to monitor for deterioration of symptoms and advise them to quickly seek medical attention if they notice worsening signs and symptoms. Home-based care is covered in *Chapter 6*.

Various antiretrovirals and monoclonal antibodies (mABs) are now available for use in outpatient clinics and home care. In both home-based and outpatient clinic settings, baseline investigations, if available, can be used as part of assessment and to monitor progression.

Triage and Diagnostics for Acute COVID-19

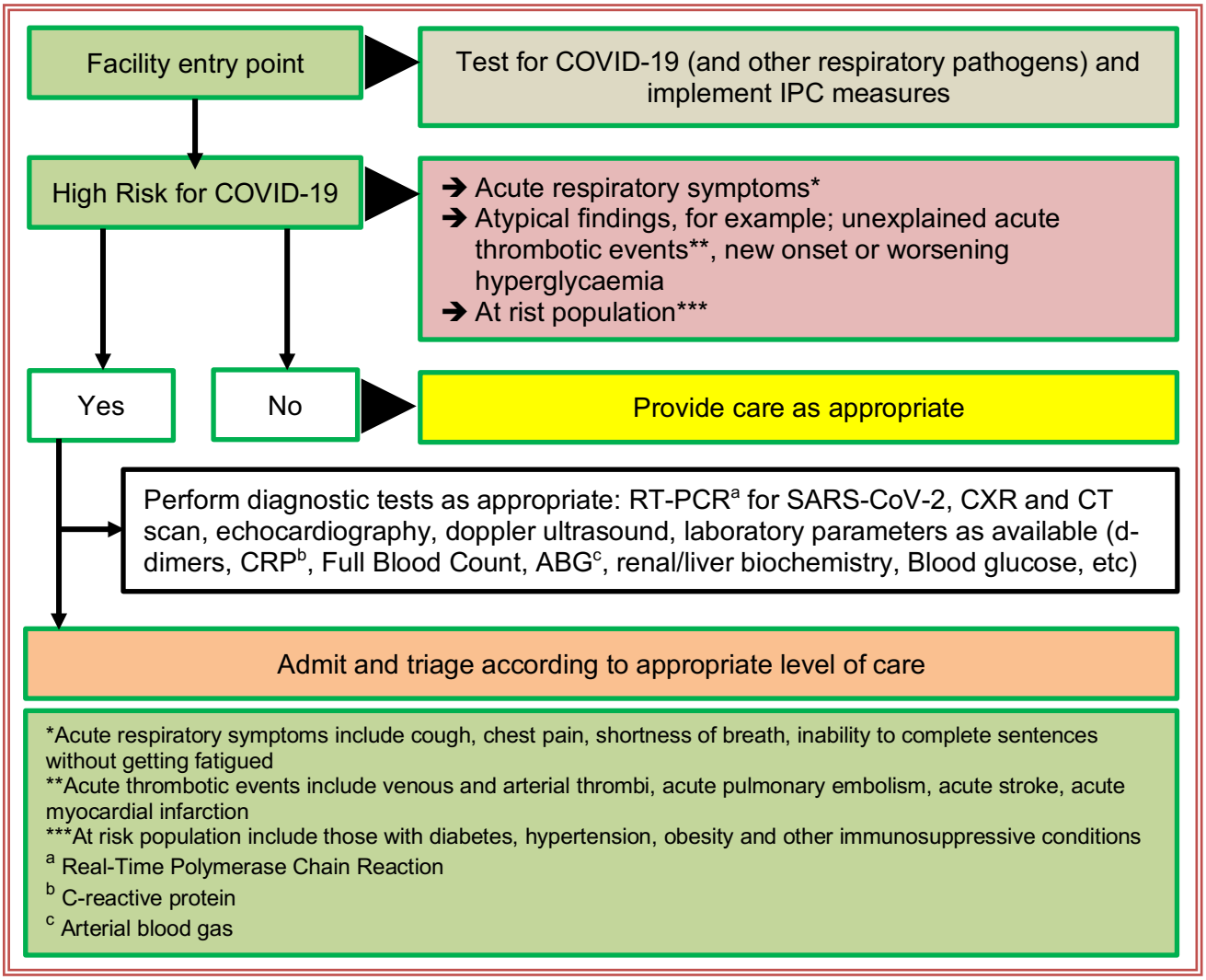


Figure 6: Flow Diagram for Testing and Diagnosis of COVID-19 at a Health Facility

Testing for COVID-19 at a Health Facility

The Ministry of Health recommends testing for all patients coming to the health facility with respiratory symptoms including fever, cough, difficulty breathing, sore throat, changes in smell, chest pains, myalgia, general weakness, and diarrhoea. It is recommended that all admitted patients with medical, paediatric, or oncological conditions are tested for COVID-19.

Healthcare Providers should note that COVID-19 can present with other extrapulmonary conditions such as stroke, myocardial infarction, incident diabetes mellitus, and rash. Therefore, they should practice a high index of suspicion in such individuals. We also recommended bi-directional screening of TB in patients suspected of COVID-19 and vice versa.

Testing for COVID-19 within the Community

Rapid tests for COVID-19 are available and could be used for self-testing within households. Linkage to care is very important for people who test positive in the home, regardless of symptoms. People who are asymptomatic should still seek medical advice at the facility even though the test is negative to allow assessment for risk of progression and eligibility for oral antiviral therapy.

Primary and Community Health Services should integrate the provision of self-testing strategies and oral antiviral therapy such as NMV-r and Molnupiravir to complete the “test and treat” strategy for COVID-19.

COVID-19 Severity Classification

Once the diagnosis and decision to treat for COVID-19 is made either by a test result or clinically, disease severity must be classified to provide the appropriate care for the patient (*see **Box 3**: COVID-19 Severity Classification, page 24*).

- Asymptomatic and non-severe patients can be managed from home
- Severe and critical patients must be managed from health facilities
- Critical patients should only be managed in facilities with Intensive Care Units and disease must be transferred to a health facility with ICU capabilities

Clinicians must note that patients who have mild or asymptomatic disease can rapidly deteriorate to severe disease especially those with **risk factors for disease progression** listed in **Box 1** (*page 3*) and should be assessed for eligibility for outpatient therapy such as oral antivirals (Paxlovid) or Remdesivir.

Asymptomatic or mild patients with abnormal inflammatory markers or radiological markers must be managed in the health facility as these could be markers of the cytokine storm and are at risk of disease progression.

Box 3: COVID-19 Severity Classification	
Asymptomatic infection	• Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., Polymerase Chain Reaction) or antigen test, but have no symptoms • Note that symptoms may be mild, and the clinician will need to probe
Non-severe COVID 19	• Defined as the absence of any criteria for severe or critical COVID-19
Severe COVID 19	• Defined by any of: ◦ oxygen saturation < 90% on room air ◦ signs of pneumonia ◦ signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis, or presence of any other general danger signs including the inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness)
Critical Illness	• Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy

The COVID-19 severity is further illustrated by the infographic below[28]:

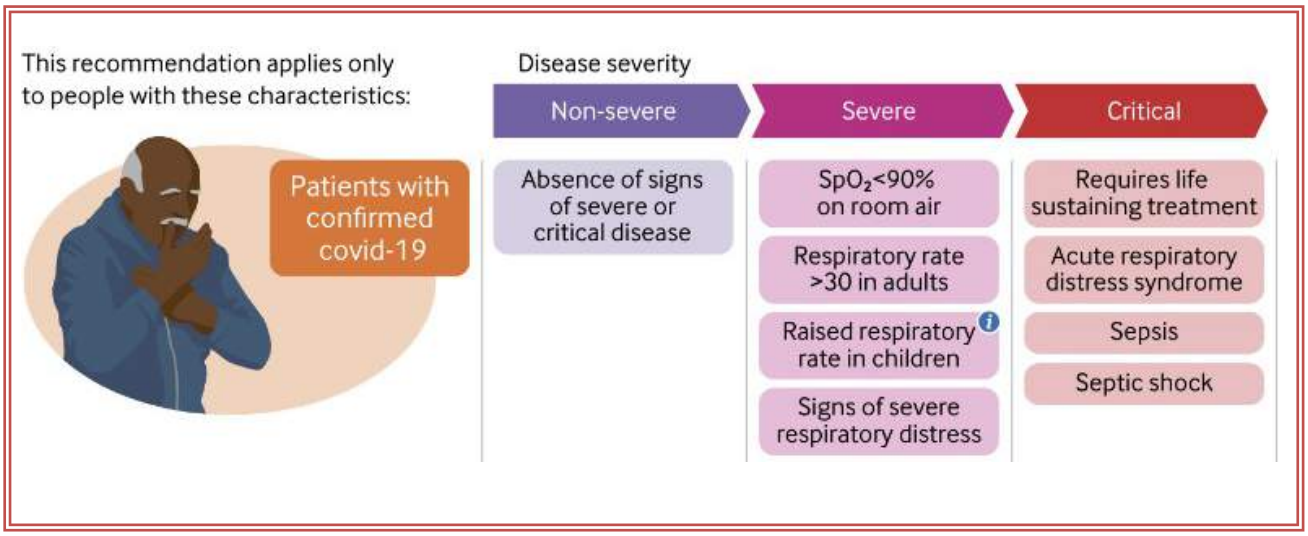


Figure 7: Disease Severity Infographic

[28] Infographic co-produced by the BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ recommendations)

Conducting Triage at a Health Facility

The initial triage should be quick and efficient. All health facilities should set up triage stations at the entry point(s) to screen for COVID-19 symptoms in all individuals entering the facility.

Patients suspected to have COVID-19 following screening (i.e., patients with fever, cough, or shortness of breath/difficulty breathing,) should be provided with a surgical mask and directed to a designated isolation room or designated “respiratory waiting area” where a healthcare worker (HCW) in appropriate PPE will conduct further history and examination. They will then collect specimens for COVID-19 testing as appropriate. If it is determined that a patient is not a suspect case, they may be managed routinely.

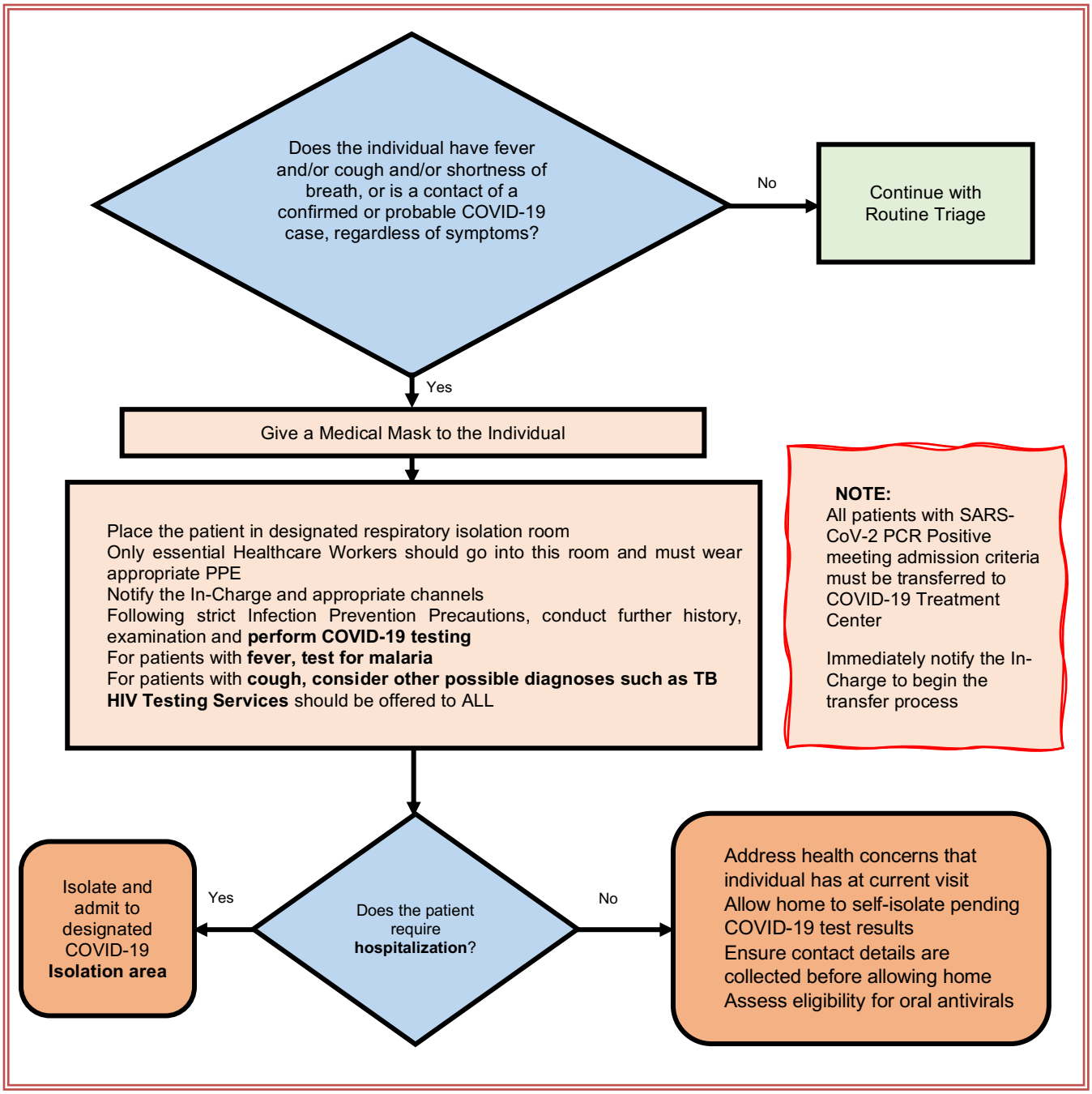


Figure 8: Triage of Individuals Entering a Health Facility

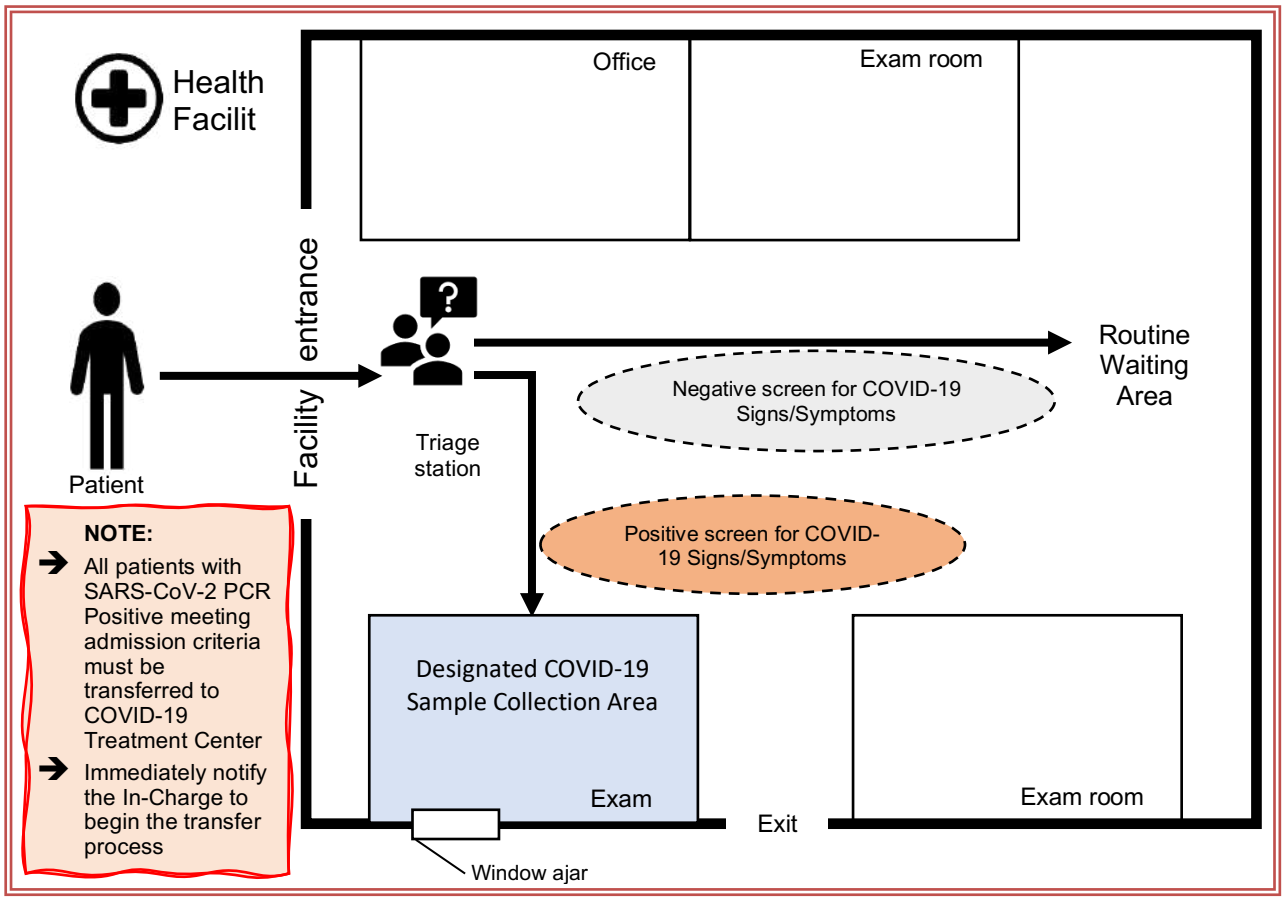


Figure 9: Example of Clinical Workflow in a Health Facility Testing for COVID-19

Nasopharyngeal (NP) swabs

1. Have patient blow nose prior to collection
2. Insert NP swab in level/flat position into the back of nasopharynx until resistance is felt
3. Rotate for 10-15 seconds

Oropharyngeal swab

4. Swab both tonsils and back of throat
5. Avoid touching tongue and teeth

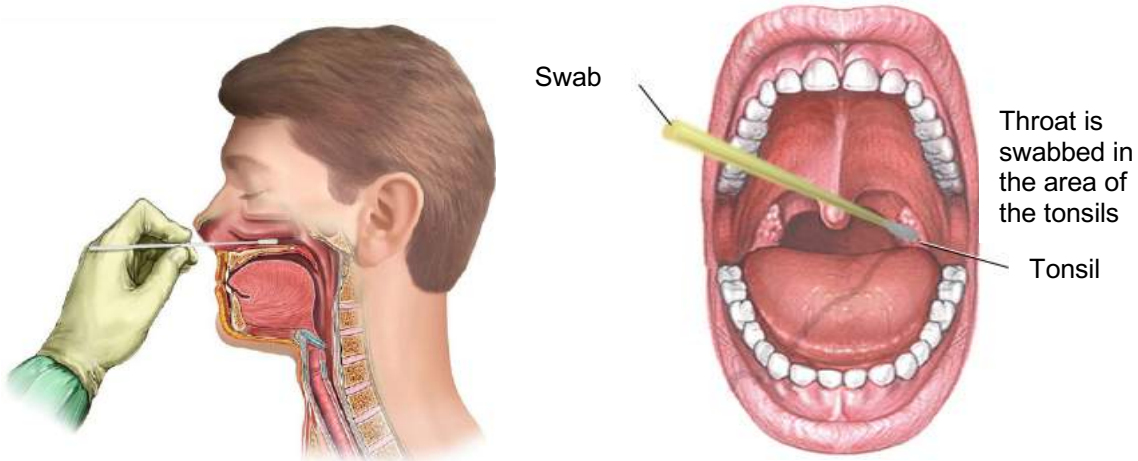


Figure 10: How to Collect Nasopharyngeal and Oropharyngeal Specimens

COVID-19 is diagnosed when SARS-CoV-2 is detected by PCR on respiratory tract specimens (or antigen test, if available). Upper (nasal and nasopharyngeal swab) and lower (expectorated sputum, tracheal aspirate, bronchoalveolar lavage) respiratory tract specimens are suitable for testing. Lower respiratory tract samples may have a higher sensitivity. Saliva appears to have comparable results to upper airway specimens. Although the virus has been isolated from other sites such as serum and stool, testing for these specimens is not available at this time.

For probable COVID-19 with symptom severity that warrants hospitalisation or medical therapy, do not wait for results to initiate therapy.

Operationalisation of Acute COVID-19 Clinics

Definitions

Although there are no widely accepted definitions of the stages of COVID-19 recovery, one classification framework includes:

Acute COVID-19: symptoms of COVID-19 for up to 4 weeks following the onset of illness

Post-Acute COVID-19 (PAC-19)

- **Ongoing symptomatic COVID-19 (long COVID-19)**: symptoms of COVID-19 from 4 to 12 weeks following the onset of illness
- Post COVID-19: symptoms that develop during or after COVID-19, continue for ≥12 weeks, not explained by an alternative diagnosis

A clinical case definition of post COVID-19 condition by a Delphi consensus (WHO)

- Post COVID-19 condition occurs in individuals with a history of **probable or confirmed SARS-CoV-2 infection**, usually **3 months** from the onset of COVID-19 with symptoms that **last for at least 2 months** and cannot be explained by an alternative diagnosis
- Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others
- Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. **A separate definition may be applicable for children**

Test and Treat Strategies for Patients with Confirmed COVID-19

Patients who are confirmed with SARS-CoV-2 infection, but not requiring hospitalisation can be seen from the Acute Covid Clinic, distinct from other patients seen in triage areas.

Early initiation of treatment at the onset of symptoms or before the onset of symptoms prevents the progression of disease or admission to the health care facility and/or death. Further early treatment leads to a break in transmission to close contacts and in the community. Various antiretroviral drugs and monoclonal antibodies (mABs) are available for treatment across the spectrum of diseases, as outlined in section 1.

A ‘test and treat’ approach will entail treating all patients who test positive for COVID19 using PCR or rapid test and meet eligibility based on risk factor assessment. The ‘test and treat’ approach can be offered both at the facility level or in the community based on availability. Patients should be assessed for eligibility for treatment based on the risk factors listed in **Box 1** (*page 3*).

Those who are above 50 years, with mildly symptomatic disease and have over risk factors for progression, can be offered outpatient antiviral therapy. For patients 50-64 years old who are vaccinated, the overall risk of progression to severe disease is low enough that the absolute benefit of treatment may not outweigh any potential risk of harm (eg, medication adverse effects, risk of "rebound COVID-19" requiring extension of the isolation period). For unvaccinated individuals 50-64 years old, the clinical benefit likely outweighs risks.

For the large subset of patients who will be asymptomatic at the time of diagnosis, it is important to return to the facility as soon as symptoms occur so that they can be assessed for eligibility for outpatient therapy or need for admission

Those patients who have severe disease, defined as: Shortness-of-breath/dyspnoea on exertion/difficulty breathing, Oxygen requirement (SpO_2 < 90% of room air), or tachypnoea (i.e., ≥ 30 breaths per minute), should be admitted for close monitoring and administration of intravenous therapy.

Expected Beneficiaries to be seen in the Acute COVID-19 Clinic

- At diagnosis and within first 30 days since diagnosis
- Mildly symptomatic with low risk for progression and needed review of results
- Mildly symptomatic with high risk for progression and eligible for oral antivirals
- Patients eligible for receiving outpatient intravenous antivirals
- Following home isolation with persistent or new onset symptoms
- Recrudescence of symptoms following antiviral therapy
- Presenting with uncontrolled comorbidities such as diabetes and hypertension
- Healthcare workers including assessment for return to work
- Clients in need of additional information on COVID-19 care

Checklist for Acute COVID-19 Clinic set up

- Healthcare Workers (HCWs)
- Initial acute COVID-19 clinical form
- Appropriate PPE
- Pulse oximeter, Blood Pressure machine, glucometer
- Patient registers
- Patient reviews at day 10 and day 30 may be physical or using telemedicine depending on availability
- Linkage to the post-acute COVID-19 clinic for continued follow-up if necessary

Approach to a patient with Post-Acute COVID-19 Symptoms

The Post-acute COVID-19 stage reflects symptomatic recovery and is not related to active viral infection and infectivity. Some aspects of Post COVID-19 may be unique, but many appear to be similar to recovery from other viral illnesses and/or critical illnesses.

Persistent physical symptoms are common, and typically include fatigue, dyspnoea, chest pain, and cough. Less common persistent physical symptoms include anosmia, joint pain, headache, sicca syndrome, rhinitis, dysgeusia, poor appetite, dizziness, myalgias, insomnia, alopecia, sweating, and diarrhoea. Patients may also experience psychological or cognitive complaints including post-traumatic stress disorder, anxiety, depression, and poor memory and concentration. Persistent symptoms are more common in persons who were hospitalised for COVID-19 but are also reported by those with less severe disease who were never admitted.

Fatigue is the most commonly reported symptom. Symptoms of dyspnoea, cough, or chest discomfort may resolve over months. Other symptoms may be shorter-lived, and most symptoms improve over time. However, high-quality data on prognosis among persons with persistent symptoms is lacking.

Infection Prevention and Control for Patients with Post-Acute COVID-19

Persons with Post-Acute COVID-19 are not actively infected and shedding the virus. Standard precautions should be followed. Respiratory precautions should adhere to standard recommendations. Masks should be used as per health facility policy.

Initial assessment will include a full history from the date of the first symptom, the current symptoms (nature and severity), and an assessment of co-morbidities. This should be accompanied by a full systematic physical examination and diagnostic investigations tailored to abnormalities found.

Expected Beneficiaries for PAC-19 Clinic

Post-Acute COVID-19 (clinical or laboratory confirmed) patients

- Typically, 14-days post discharge (maybe earlier for specific groups of patients)
- Previously admitted or had severe disease
- Following home isolation with persistent or new onset symptoms
- Presenting with uncontrolled co-morbidities

Checklist for PAC-19 Clinic set up

- Healthcare Workers (HCWs)
- PAC-19 clinical form
- Initial Mental health screening questionnaire
- Follow up Mental health assessment tools for
    - Depression
    - Post-traumatic stress disorder (PTSD)
    - Anxiety
    - Substance misuse
- Pulse oximeter, Blood Pressure machine, glucometer

Table 5: Roles for Healthcare Workers in the PAC-19 Clinic

HCW		Actions
Nurse	PAC-19 clinical form Mental health screening questionnaire	• Fill in vitals and other demographic parameters correctly • Fill in initial mental health screening questionnaire and the follow-up forms depending on the outcome of the initial screening questionnaire
Clinician	PAC-19 clinical form Mental health assessment form	• Complete PAC-19 clinical form and take appropriate action • Take appropriate action
Data	all	• Ensure all data is captured
Physiotherapist	PAC-19 clinical form	• As needed according to referral

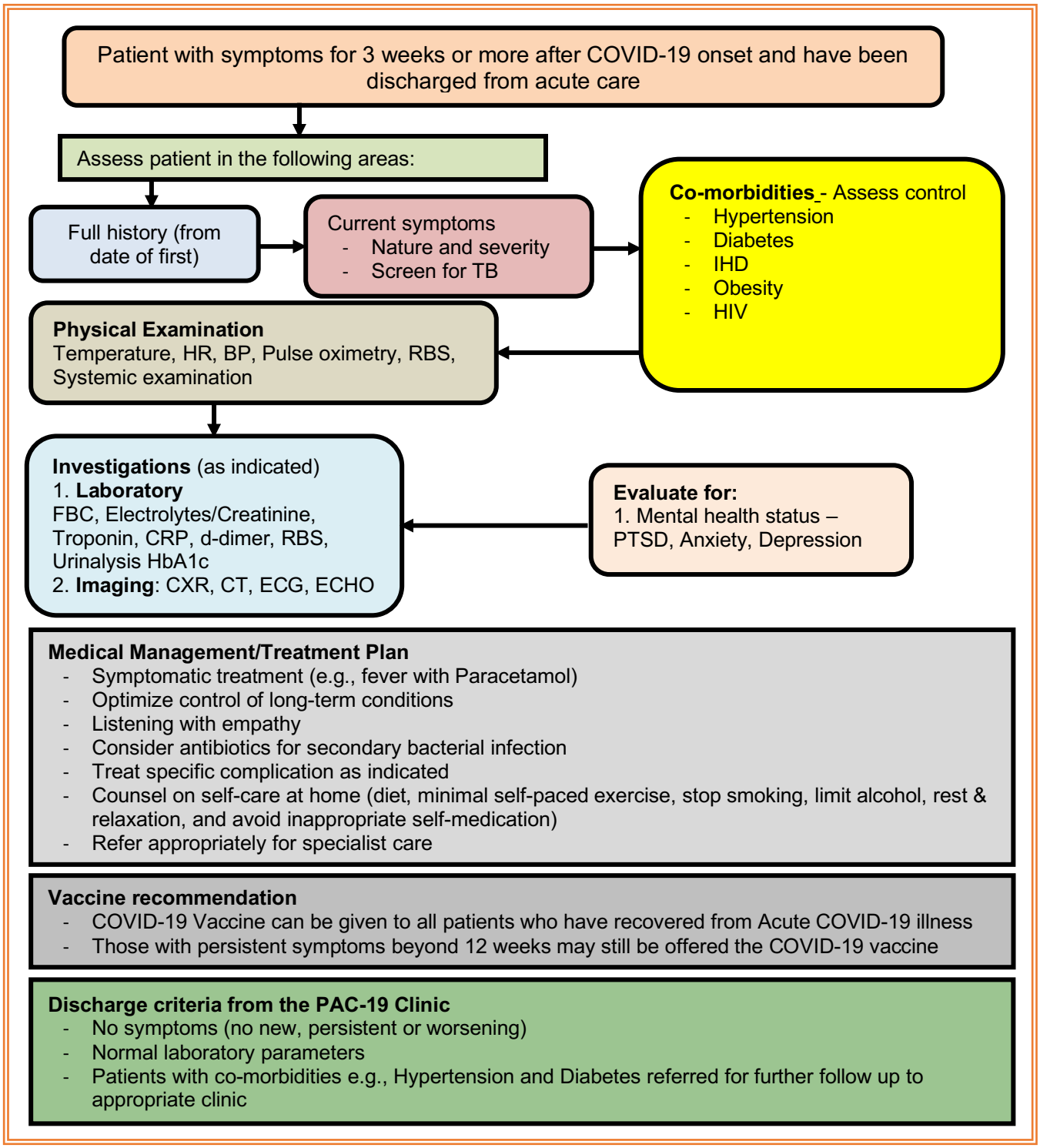


Figure 11: Approach to a Patient with PAC-19 Symptoms

Bidirectional Screening of TB and COVID-19

Because of the potential overlap in COVID-19 and TB disease, we recommend bidirectional screening of TB and COVID-19 in both TB and COVID-19 clinics. Patients presenting to a PAC-19 clinic with cough or other symptoms consistent with TB (i.e., fever, night sweats, weight loss, or chest pain) should be tested for tuberculosis with GeneXpert, sputum smear for AFB and culture, chest radiography (X-ray or CT), urine LAM, and/or bronchoscopy with bronchoalveolar lavage (see figure 12 below). Additionally, because of the ongoing COVID-19 pandemic in Zambia, patients attending TB clinics—specifically, newly diagnosed patients or patients on treatment with new or worsening respiratory symptoms—should be considered for COVID-19 testing by PCR, rapid antigen test, or (where available) GeneXpert SARS-CoV-2 test (Figure 13 overleaf).

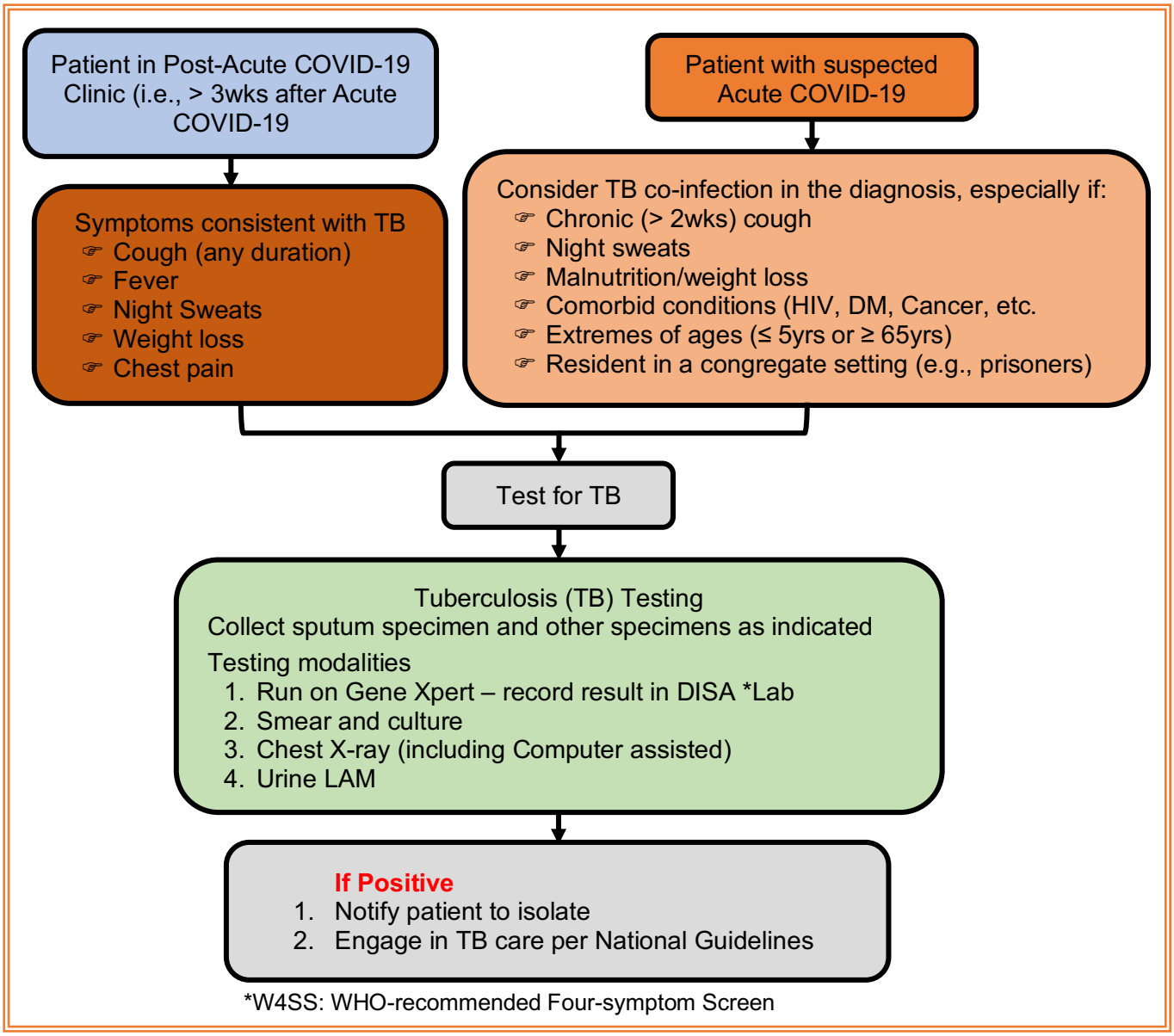


Figure 12: Screening for TB in the PAC-19 Clinic

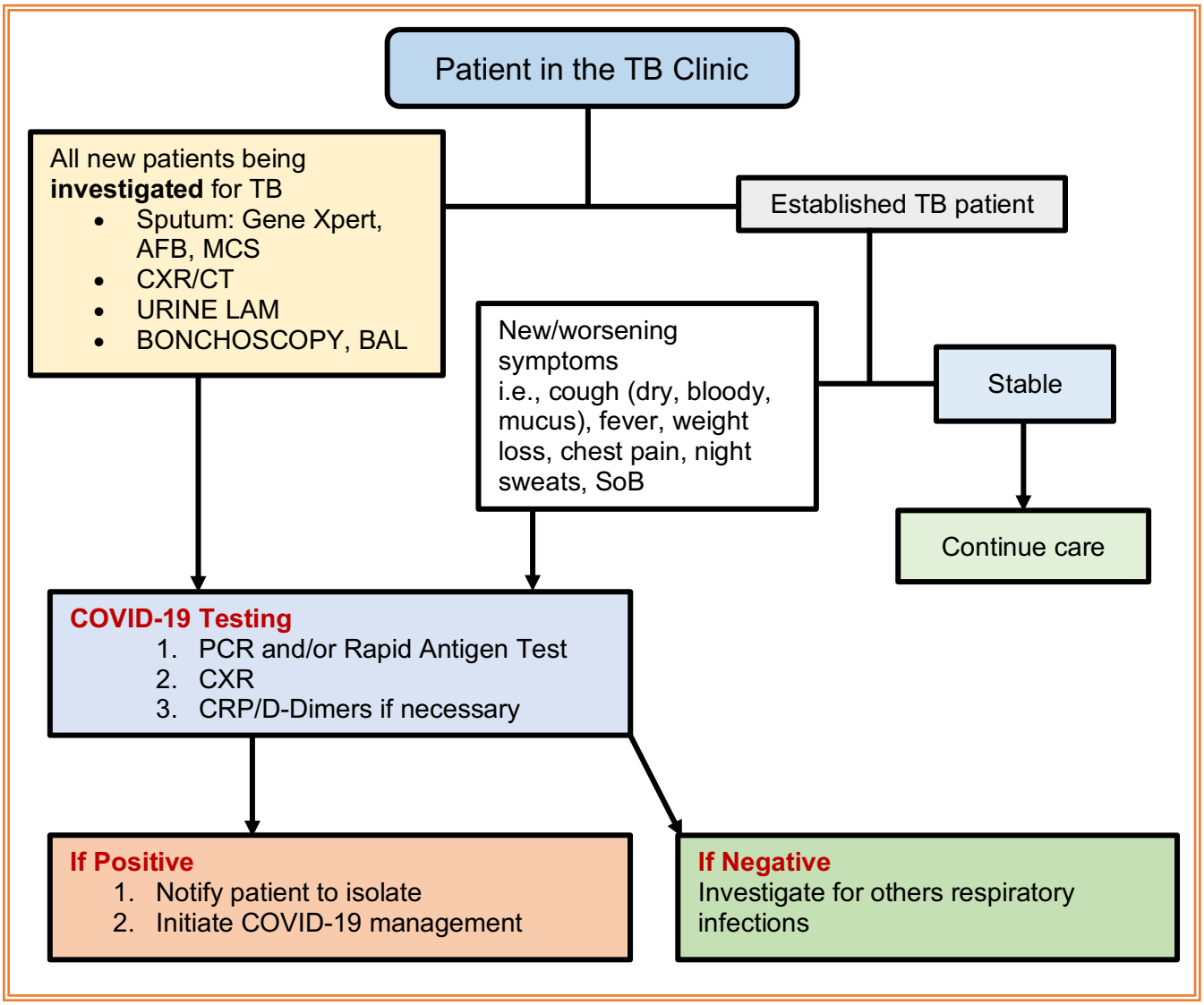


Figure 13: Screening for COVID-19 in the TB Clinic

Other activities in PAC-19

Details of activities in PAC-19 have been highlighted in the Zambia PAC-19 guidelines. However, the following activities should be considered:

1. Screening for Advanced HIV Disease
2. Domiciliary Oxygenation
3. Neurological management
4. Psychological support using appropriate psychological tools
5. Physical rehabilitation
6. Information and communication technology (ICT) and tele-health e.g., phone call appointments

Chapter 3: Principles of Care for Patients with COVID-19

Overview

Covid-19 can be managed in both outpatient and inpatient settings depending on the severity of the disease. The care of COVID-19 patients should begin with assessing the severity of the illness and identifying organ dysfunction or other comorbidities that could complicate potential therapy. Current therapy for COVID-19 includes both supportive and virus-specific therapies. An exhaustive review of these treatments is beyond the scope of this guidance. However, below are some general principles that Healthcare Providers should follow when caring for patients with COVID-19.

This chapter presents guidelines for three clinical scenarios: non-severe illness (managed at home), severe illness (managed in a hospital ward), and critical illness (managed in a hospital ward).

Recommendations for therapy, testing, and supportive care are summarised in *Table 6* below. Of note, these recommendations apply to all patients meeting clinical criteria for COVID-19, even if confirmatory testing is pending. In severe cases, patient outcomes will improve if attention is given to administer the treatments within one hour of admission.

Table 6: Summary of Recommended Therapy, Testing and Supportive Care for Non-severe, Severe and Critical Adult COVID-19 Cases

Disease severity	Recommended therapy/drugs	Lab tests	Supportive Care	Comment
Non-severe Defined as the absence of any criteria for severe or critical COVID-19	• Ibuprofen 400mg PO BD and/or • Paracetamol 1g TDS as needed for fever and aches • Antitussive, lozenges as needed • Antibiotics should **NOT** be prescribed unless there is clinical suspicion of a bacterial infection • Give **any one** of the following specific therapies based on availability **(indicated for those with highest risk of disease progression having ≥ 1 risk factors):** ❖ Nirmatrelvir-ritonavir (**Preferred)** 300m/100mg BD PO for 5 days ❖ Remdesivir 200mg IV day 1 followed by 100mg IV for 2 days ❖ Molnupiravir 800mg BD PO for 5 days • Dexamethasone should **NOT** be given in outpatient settings	• HIV test • Malaria RDT • Urine LAM • sputum gene Xpert • Chest X-ray • CRP • D-dimers • FBC+DC • LFT • Kidney Function Tests • Glucose	• blood pressure control • blood sugar control • Monitor closely and advise return for review at the first onset of or return of symptoms to be evaluated for possible Hospitalization	• Individuals with high risk of progression may require hospital management even when non-severe especially for the control of comorbidities and for the prevention of complications

Severe: Defined by any of: • SpO_2 < 90% on room air • Signs of severe respiratory disease • Signs of severe sepsis with low blood pressure <90/60mmhg resp rate>20bpm Pulse >100bpm	**WITHIN 1 HR OF ADMISSION** • **Oxygen** to bring O_2 saturation to ≥ 90%. *(refer to Respiratory Support Flow chart, below)* • **Empiric Antibiotics** if sever sepsis is suspected: Co-Amoxiclav plus Azithromycin and if **Hospital Acquired Pneumonia (HAP):** Cephalosporin (e.g., Ceftriaxone) plus an Aminoglycoside OR Imipenem plus a fluoroquinolone • **Dexamethasone** 6 mg IV OD for up to 10 days **(only for patients requiring O_2) or have markedly raised inflammatory markers or extensively abnormal chest imaging** • **Remdesivir** 200mg IV as a single dose on day 1, followed by 100 mg IV once daily for 5-10 days (see notes on therapeutics). • Tocilizumab single IV dose at 8 mg/kg infusion over 1 hour (upto max 800mg) or • Baricitinib 4mg PO daily for 14 days or until hospital discharge (give either of the two depending on availability as well as clinical factors; for details see therapeutics section) • DVT prophylaxis: Low molecular weight **Heparin** 1mg/kg/day subcutaneous • Patients with D-Dimers > 3000U or clinical suspicion of VTE should be put on treatment dose of heparin	**On Admission** • Malaria RDT • HIV: If HIV+, do CD4 count and viral load • Chest X-ray • Sputum for Xpert/microscopy • Liver & kidney tests • Electrolytes • Glucose • ABG • FBC w/diff, • Clotting Profile • CRP, other inflammatory markers • Blood cultures, • Pregnancy test **Daily labs** • CBC w/diff • Daily Fasting/ Random Blood Sugar • Monitor other abnormal labs as indicated		
Critical:	• Oxygen (escalate respiratory support as necessary) • Antibiotics, Dexamethasone (as in severe illness) • Tocilizumab or • Baricitinib (either of the two depending on availability as well as clinical factors; for details see therapeutics section)	See above for severe disease		

Management of Non-severe COVID-19

This category defines individuals with COVID-19 in the absence of any criteria for severe or critical COVID-19. This includes both inpatients and outpatients who meet the non-severe criteria. All patients with symptomatic COVID-19 and risk factors for severe disease should be closely monitored, whether their case is non-severe at initial presentation. In some patients, the clinical course may rapidly progress. Patients with non-severe symptoms but risk factors should be considered for hospitalisation for purposes of close monitoring.

Risk Factors for hospitalisation or severe illness include **any one** of the following:

- Older age (age ≥ 50 years of age with any of the additional risk factors listed below)
- Obesity or being overweight (adults with BMI > 25kg/m^2, or if age 12-17, have BMI ≥ 85th percentile for their age and gender)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment:
    - Immunosuppressive disease (e.g., cancer, not in remission; solid organ transplant; HIV with CD4 < 200 cells/m^3)
    - Immunosuppressive treatment (e.g., chemotherapy; Rituximab; steroid use at ≥ 20mg/day or ≥ 2mg/kg/day prednisone or equivalent for ≥ 14 days)
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease, thalassemias and other haematological conditions
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))
- Current smoking or substance misuse disorders
- Not being fully vaccinated against COVID-19 with any of the other risk factors listed above

a) Low risk of hospitalisation or severe disease

This category of patients includes those without highest risk for hospitalisation or severe disease as outlined above. Patients in this category can be managed in an ambulatory setting or at home through telemedicine or remote visits.

Patients with fever should be tested for malaria and HIV. Other possible causes of cough should be considered, such as TB, and appropriate testing arranged.

No specific laboratory evaluations are indicated in otherwise healthy patients with non-severe COVID-19. Patients should be given strict guidelines on when to seek care (e.g., development of difficulty breathing, altered mentation, or other alarming symptoms)

b) High risk of hospitalisation or severe disease

This category of patients is at high risk of hospitalisation or progression to severe disease.

Chest X-ray should be obtained. Other diagnostic tests (HIV, malaria, TB) as clinically indicated

Therapy for this group includes symptomatic treatment and COVID-19-specific therapeutics. Symptomatic therapy consists of Paracetamol 1g TDS as needed for fever and aches and antitussives and lozenges as needed.

Specific COVID-19 therapeutics include any one of the following.

- Nirmatrelvir-r (preferred option)
- Remdesivir (alternative)
- Molnupiravir
- Monoclonal antibodies **(to be given only when Nirmatrelvir-r or Remdesivir are not available, feasible or clinically appropriate. Additionally genotypic resistance must be done to ensure the patient has a variant which is susceptible to the available monoclonal antibodies)**
    - ❖ Sotrovimab
    - ❖ Bamlanivimab-Etesevimab

Given that pulmonary disease can rapidly progress in patients with COVID-19, close monitoring of patients with non-severe is recommended, ideally to include checking pulse oximetry.

Antibiotics should **NOT** be prescribed unless there is clinical suspicion of a bacterial infection. Bacterial supra-infection in COVID-19 is not common in patients on initial presentation. However, if bacterial pneumonia without severe signs is strongly suspected, administer empiric antibiotic treatment for community-acquired pneumonia, re-evaluate

daily, and de-escalate antibiotics as quickly as possible. An appropriate choice of oral antibiotics would be: In adults: Amoxicillin, in children: Co-trimoxazole or Amoxicillin.

Management of Severe Disease/Critical Disease

Patients with COVID-19 are considered to have severe illness per WHO criteria if they have: SpO_2 < 90% on room air; signs of pneumonia; or signs of severe respiratory distress. The diagnosis is clinical. Chest imaging can exclude complications, but a normal CXR does not exclude the diagnosis.

Be alert for the following signs and symptoms of severe illness.

Adolescent or adult: Fever or suspected respiratory infection, plus at least one of

- Respiratory rate > 30 breaths/min
- Severe respiratory distress, and/or
- SpO_2 < 90% on room air

Child: Cough or difficulty in breathing, plus at least one of the following:

- Central cyanosis or SpO_2 < 90%
- Severe respiratory distress (e.g., grunting, very severe chest indrawing)
- Inability to breastfeed or drink
- Lethargy or unconsciousness, or convulsions
- Other signs of pneumonia may be present in children:
    - Chest indrawing
    - Fast breathing (in breaths/min):
        - < 2 months, ≥ 60bpm
        - 2–11 months, ≥ 50bpm
        - 1–5 years, ≥ 40bpm

Urgent Provision of the Mainstays of Treatment

Patients with severe COVID-19 illness may experience rapid clinical deterioration. Within one hour of admission, these patients should be provided with the mainstays of management of severe COVID-19 cases in Zambia (Table 6). These are as follows:

- Oxygen therapy titrated to maintain O_2 saturations of ≥ 90%.
- Escalation of respiratory support if needed. Mechanical ventilation as last resort
- Dexamethasone or alternate corticosteroid
- Remdesivir
- Baricitinib (not to be given together with Tocilizumab)
- Tocilizumab
- Empiric antibiotics if bacterial pneumonia or sepsis suspected (elevated CRP or PCT if available)
- Fluid management as appropriate to the clinical syndrome: conservative in Acute Respiratory Distress Syndrome (ARDS) aggressive in sepsis or shock
- Optimal supportive and adjunct care, including management of hypertension and diabetes
- Regular monitoring of clinical status, including pulse oximetry, vital signs, and blood sugar

Symptomatic and Clinical Based Treatment of COVID-19

In situations where the COVID 19 test result is not available, the Ministry of Health recommends a clinical basis for initiating COVID-19 specific treatment to avoid delaying life-saving interventions. The following are features that can suggest COVID-19 infection even without SARS-CoV-2 test result and can be used to commence treatment for COVID-19:

The presence of either fever or respiratory symptoms for less than 14 days with any of the following:

1. Oxygen saturations < 90%
2. CT Chest findings CO-RAD > 3
3. Chest X-ray with features suggestive of bilateral pneumonia (see radiology findings in COVID-19)
4. CRP is five times above the upper limit of normal
5. D-Dimer above 3000ng/mL (3mg/L)
6. Adults > 50 years with either DM or Hypertension

Specific Available Therapeutics

Oxygen Therapy

Overview

Accumulated experience during the pandemic shows that oxygen therapy is one of the **best** treatment options to reduce morbidity, increase patient comfort, and prevent further deterioration (i.e., mortality). It is immediately beneficial to patients with severe COVID-19, and there is a paucity of other proven therapies.

In COVID-19, patients' true oxygenation status may be out of proportion to their sensation of air hunger. For example, patients may have oxygen saturations in the 70s and 80s although they appear quite comfortable. This phenomenon has been called **"happy hypoxia,"** and it underlies the need to use pulse oximetry during the initial evaluation and during monitoring of all suspected or confirmed COVID-19 patients.

Oxygen therapy should be made available in admission areas, wards, and wherever severe cases will be managed, not just in ICUs. All areas where hospitalised patients with COVID-19 are cared for should be equipped with pulse oximeters, functioning oxygen sources (wall oxygen, concentrators, or cylinders), and oxygen-delivering interfaces (nasal cannula, simple face masks, and masks with a reservoir bag). Use contact precautions when handling contaminated oxygen interfaces of patients with COVID-19 infection.

It is essential that hypoxemic patients with COVID-19 be monitored closely for signs of respiratory decompensation. To ensure the safety of both the patient and Healthcare Workers, intubation should be performed in a controlled setting by an experienced practitioner

When to administer oxygen:

- Give oxygen **immediately** to patients (adults and children) who have signs of severe illness:
    - Severe respiratory distress (increased patient work of breathing, use of accessory muscle for respiration, tracheal tagging, intercostal and subcostal recessions)
    - Sepsis with hypoperfusion or shock
    - Alteration of mental status or
    - Hypoxemia

- Give oxygen to patients whose measured oxygen levels are abnormal:
  - **SpO_2 < 90%** if the patient is hemodynamically normal
  - SpO_2 < 94% if the patient has any emergency signs of the airway, breathing or circulation
- SpO_2 < 92–95% if the patient is a pregnant woman Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma, or convulsions) should receive oxygen therapy during resuscitation to target SpO_2 ≥ 94%; otherwise, the target SpO_2 is ≥ 90%

Protocol for Escalation of Oxygen Therapy

Give supplemental oxygen therapy immediately to all patients with severe COVID-19. Initiate Oxygen therapy at 2 L/min and titrate flow rates upwards to reach a target of SpO_2 ≥90% in non-pregnant adults and SpO_2 ≥ 92-95 % in pregnant patients. The national protocol for escalation of respiratory therapy is presented in Figure 14 and Table 7.

Lower level COVID-19 isolation and treatment facilities should be capacitated to:

- Assess for hypoxia
- Deliver O_2 by nasal cannula
- Escalate to Venturi Mask
- Escalate to Poly Mask/non-rebreather and Refer to COVID-19 centre with ICU

COVID-19 Referral Centres should be capacitated to:

- All functions of the lower-level facilities as above
- ICU available
- Airway Adjuncts available (HFNC, BiPAP, CPAP)
- Mechanical Ventilation available (ventilator and skilled critical care team)

Protocol for de-escalation of Oxygen Therapy

Indications for de-escalation of care:

Improvement in patient condition

- SpO_2 above 94%
- Patients respiratory rate below 25/minute
- Reduced work of breathing
- Neurologically and hemodynamically stable

Assess the above and titrate oxygen delivery downwards in a step-down fashion, starting with poly mask to venturi mask and the nasal prongs at lower flow rates.

Oxygen Therapy Considerations for Pregnant Women

In pregnant women with severe pneumonia, there is an increased risk of maternal and perinatal mortality rate, therefore aggressive treatment is required. If in shock, hydration is necessary, and in an event that there is hypoxemia, oxygen therapy by nasal prongs or facemask should be administered.

If available, the patient should be placed in a negative pressure isolation room, preferably in a left lateral position. Care should be coordinated with the support of a multidisciplinary team (obstetricians, maternal-foetal medicine subspecialists, intensivists, obstetric anaesthetists, internal medicine or respiratory physicians, midwives, virologists, microbiologists, neonatologists, infectious disease specialists)

Oxygen therapy: supplemental oxygen should be used to maintain oxygen saturation equal to or greater than 95%. Oxygen should be given promptly to patients with hypoxemia. The maternal partial pressure of oxygen should be maintained at or above 70mmHg to maintain a favourable oxygen diffusion gradient from the maternal to the foetal side of the placenta. The method of ventilation should be according to the patient's condition and follow guidance from the intensivists and obstetric anaesthetists. Once the patient is stable, maintain oxygen saturation at 92-95% (WHO)

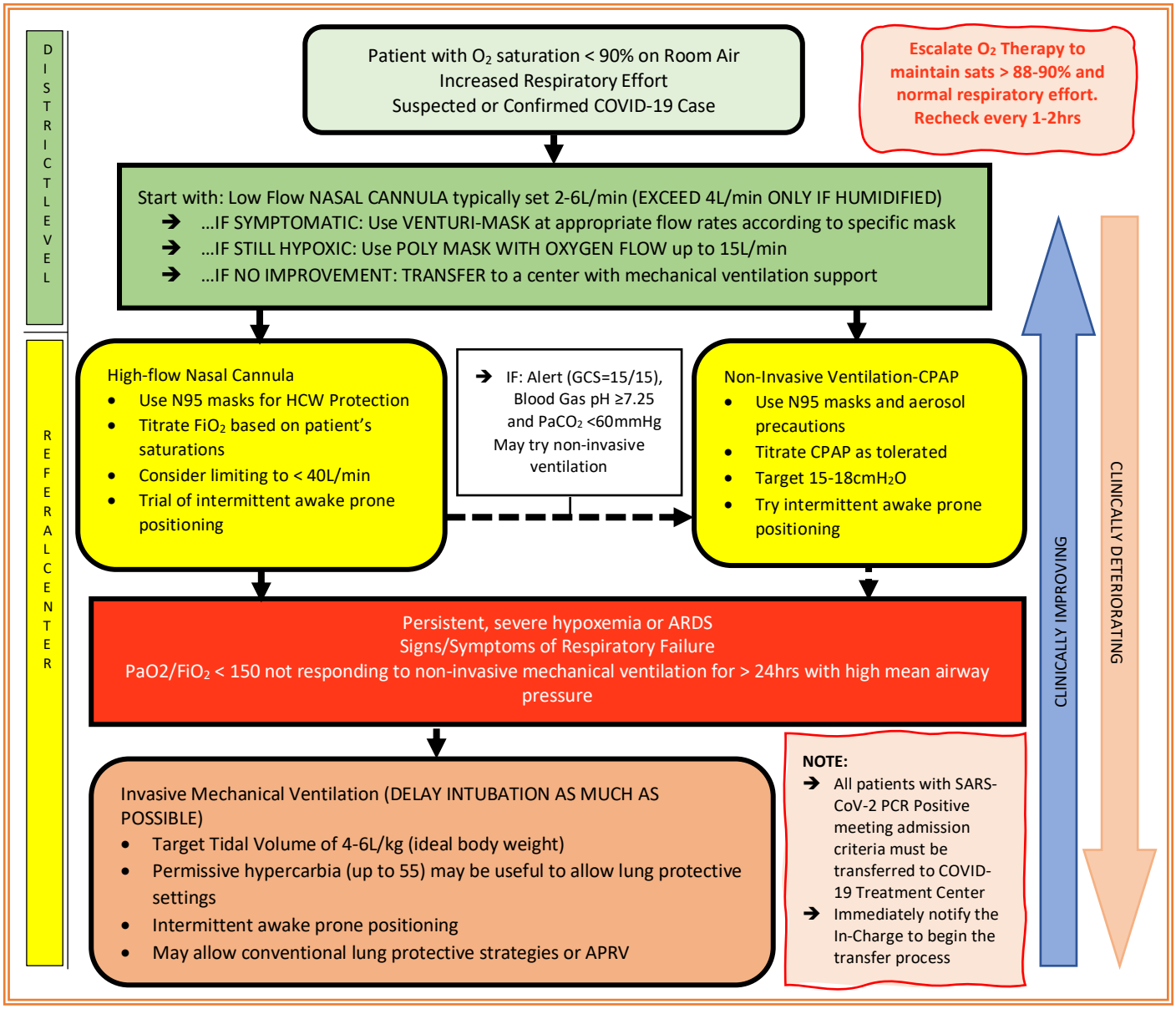


Figure 14: Protocol for Respiratory Support in Severe Cases of COVID-19

Table 7: Administration of Oxygen Therapy for Children

Age of child	Maximal Oxygen flow rates
Neonates (0–28 days)	0.5–1.0 L/min by nasal cannula
Infants (1 mo – 1 yr)	1–2 L/min by nasal cannula
Toddlers (1–2 yrs 11 mo & Pre-school aged (3–5 yrs)	1–4 L/min by nasal cannula
School-aged (> 5 yrs)	1–6 L/min by nasal cannula

If severe hypoxemia persists despite maximal flow rates:

- Oxygen therapy can be escalated upwards to increase flow and O_2 concentration depending on available delivery devices (Mask, Rebreather/Non-Rebreather Mask, Venturi, HFNC, etc)
- Start CPAP (if available) – visual aid in appendix 10
- Start secondary source of oxygen with face mask with reservoir bag

Awake, Intermittent Prone Positioning

Assisting patients to assume the prone position (lying with their chest downward) is a simple, inexpensive method that in many cases will improve oxygenation and patient outcomes in patients with moderate-to-severe disease. Proning is thought to improve oxygenation because it improves ventilation-perfusion matching and recruits collapsed alveoli in the dorsal (posterior) lungs.

Appropriate candidates for awake prone positioning are those who are able to adjust their position independently and tolerate lying prone. Awake-prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.

Contraindications to Proning:

- Contraindicated in patients who are in respiratory distress and who require immediate intubation
- Contraindicated in hemodynamically unstable patients
- Patients who recently had abdominal surgery
- Patients who have an unstable spine

For detailed guidance on proning, including nursing procedures, see Appendix 8

Antithrombotic Therapy

COVID-19 infection with the novel coronavirus SARS-CoV-2 and the resulting syndrome coronavirus disease (COVID-19) has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, and fibrinogen. These markers have been associated with worse clinical outcomes. There is an increase

in the incidence of venous and arterial thromboembolic disease during the hospital course and at autopsy. The thrombo-embolic phenomenon can present as; DVT, pulmonary embolism, Stroke, Renal failure with micro-infarctions, and myocardial infarction.

Low molecular weight heparin is preferred in hospitalised, severe, or critically ill patients compared to oral anticoagulants. This is due to its shorter half-life, ability to be administered subcutaneously, fewer drug-drug interactions, and has inherent anti-inflammatory properties. Low molecular weight heparin should be provided to all patients hospitalised with severe COVID-19 illness.

In hospitalised COVID-19 patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden localised loss of peripheral perfusion. Routine post-discharge anti-thrombotic is not recommended for patients with COVID-19 and without VTE [Ref: NIH] Patients with multiple risk factors for VTE including obesity, Diabetes, Hyperlipidaemia, or hypertension with elevated D-dimer (> 3000ng/mL) and CRP and post-treatment for severe disease could be considered for post-discharge anticoagulation

Dosing: Low molecular weight Heparin

See *Figure 15 below:*

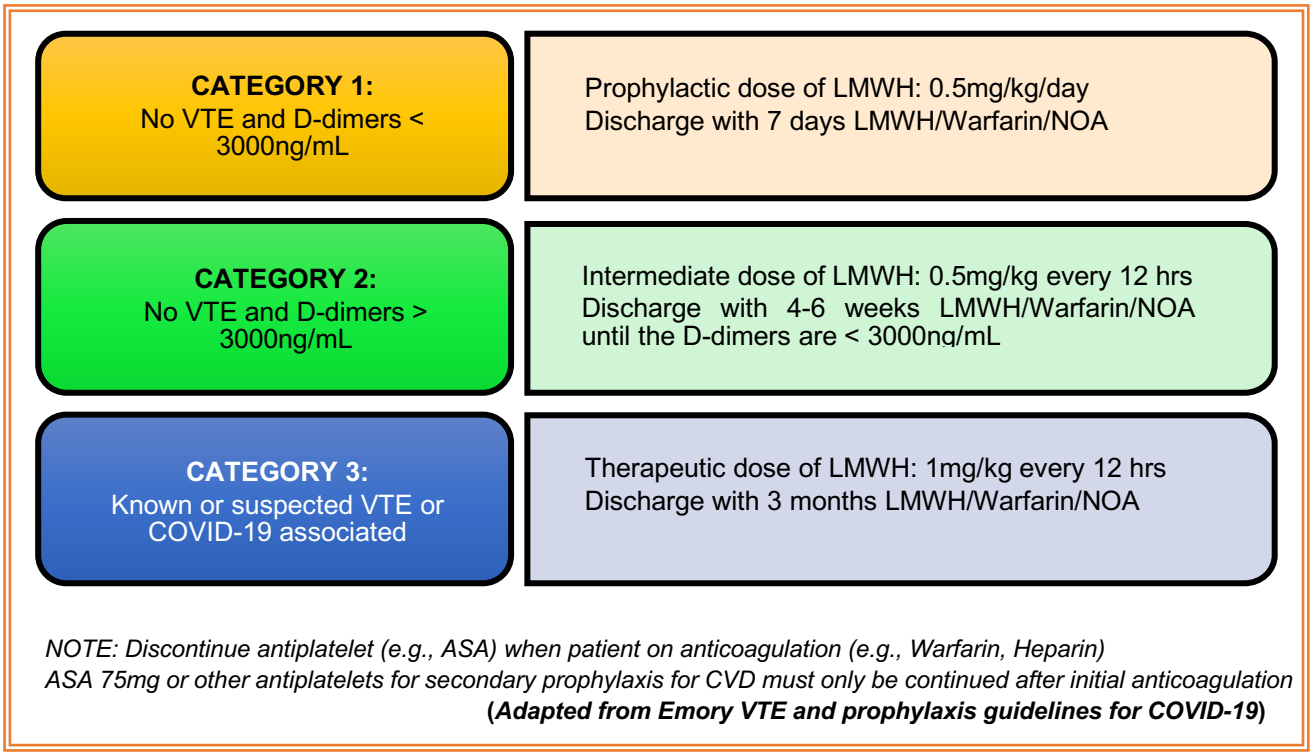


Figure 15: VTE Treatment and Prophylactic Doses for LMWH in Patients Admitted for COVID-19

Direct Acting Antiviral Agents

Table 8: Nirmatrelvir-Ritonavir (Paxlovid)

Mechanism of Action	Ritonavir-boosted Nirmatrelvir is an oral protease inhibitor with emergency use authorization for the treatment of mild-to-moderate COVID-19. It inhibits viral replication by inhibiting a cysteine residue in the 3C-like protease of the SARS-CoV-2 virion, without which non-structural proteins (including proteases) cannot be released to perform their functions
Indication	• Non-severe illness • At least one risk of hospitalisation/ progression • Positive COVID-19 result • Adults and paediatric patients (12 years of age and older or weighing at least 40kg) • Within 5 days of symptom onset • Reduces hospital admission by 92% and possibly time to symptom resolution
Administration (dose, route, duration)	Dosed twice daily for 5 consecutive days. Given as two 150mg tablets of Nirmatrelvir with a single 100mg tablet of Ritonavir • **Renal dysfunction:** eGFR ≥ 60mL/minute: No dosage adjustment • eGFR ≥ 30 to < 60mL/min: 150mg Nirmatrelvir (one 150mg tablet) with 100mg Ritonavir (one 100mg tablet), with both tablets taken together twice daily for 5 days • eGFR < 30mL/min: use alternative therapies
Storage	Solid tablets in blister packs according to dose Keep away from direct sunlight
Adverse events	• Generally, well tolerated • Rarely some patients get an altered sense of taste, mild diarrhoea, muscle aches or nausea and abdominal pains • Hypersensitivity reactions, including anaphylaxis**,** e.g., hives, throat tightness, swelling of the mouth, lips or face have been reported • Paxlovid "Rebound" • Renally excreted so be mindful of dose adjustments
Drug interactions[29]	(see appendix 7 for full list of drug interactions) *Drugs to avoid which may decrease the serum concentration of Nirmatrelvir due to induction of CYP3A4 enzymes*

[29] www.covid19-druginteractions.org for complete list of drug interactions with Nirmatrelvir/ritonavir

	Antiretrovirals: Atazanavir, Darunavir, Dolutegravir Antituberculous treatment: Rifampicin, Isoniazid, Cycloserine Antibiotics: Clarithromycin, Erythromycin, Azithromycin Antiepileptic medication: Carbamazepine, Phenobarbital Anti-arrhythmic agents: Amiodarone *Drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions (Avoid combination)* Colchicine, Ivabradine, Simvastatin, Atorvastatin, Sildenafil, Midazolam
Contraindications	● No interactions with food so can be taken with or without ● Not recommended in patients with severe renal impairment (eGFR < 30mL/min) ● Not recommended in patients with severe hepatic impairment (Child-Pugh Class C) ● History of clinically significant hypersensitivity reactions to the active ingredients (Nirmatrelvir or Ritonavir) or any other components ● History of clinically significant hypersensitivity reactions [e.g., Toxic Epidermal Necrolysis (TEN) or Stevens-Johnson Syndrome ● Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions ● Co-administration with potent CYP3A inducers where significantly reduced Nirmatrelvir or Ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance
Monitoring	Serum Creatinine, AST, ALT, Pregnancy when available

Table 9: Molnupiravir

Mechanism of Action	Molnupiravir is a prodrug of the synthetic nucleoside derivative N^4-hydroxycytidine (NHC) and exerts its antiviral action by introducing copying errors during viral RNA replication. It inhibits viral reproduction by promoting widespread mutations in the replication of viral RNA by RNA-directed RNA polymerase. It is metabolised into a ribonucleoside analogue that resembles cytidine, β-D-N^4-Hydroxycytidine 5′-triphosphate. During replication, the virus's enzyme incorporates NHC-TP into newly made RNA instead of using real cytidine.
Indication	• Adults with non-severe COVID-19 infection • Within 5 days of symptom onset • At least one risk factor for hospitalisation or progression of disease
Administration (dose, route, duration)	• 800mg (four 200mg capsules) taken orally every 12 hours for 5 days, with or without food • Taken as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset • Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximise viral clearance and minimise transmission of SARS-CoV-2 • Not authorised for use for longer than 5 consecutive days because the safety and efficacy have not been established • Advise individuals of childbearing potential to use a reliable method of contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last dose • No dosage adjustment in patients with any degree of renal or hepatic impairment is needed
Storage	Solid tablets in blister packs according to dose Keep away from direct sunlight
Adverse events	• Minimal side effects reported in adults • Some experience diarrhoea, nausea or dizziness • Possibly teratotoxic • Bone and Cartilage Toxicity • Hypersensitivity reactions, including anaphylaxis have been reported • Advice to patients if signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue, and report to the health facility for pharmacovigilance • Recrudescence of symptoms is possible
Drug interactions	No drug interactions have been identified based on the limited data currently available. However, the potential for Molnupiravir or NHC to interact with concomitant medications is considered unlikely since neither Molnupiravir nor NHC are inhibitors or inducers of major drug-metabolising

	enzymes or transporters
Contraindications	• Not authorised for persons under the age of 18 • Avoid in pregnant or breastfeeding women due to potential fetotoxicity • Not recommended in patients with severe renal impairment (eGFR < 30mL/min) • Not recommended in patients with severe hepatic impairment (Child-Pugh Class C) • History of clinically significant hypersensitivity reactions to the active ingredients (Nirmatrelvir or Ritonavir) or any other components • History of clinically significant hypersensitivity reactions [e.g., Toxic Epidermal Necrolysis (TEN) or Stevens-Johnson Syndrome • Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions • Co-administration with potent CYP3A inducers where significantly reduced Nirmatrelvir or Ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance
Monitoring	Serum Creatinine, AST, ALT, Pregnancy Bone mineral density if available

Table 10: Remdesivir

MOA	Remdesivir is a nucleoside drug. Its mechanism of action involves chain termination. The drug is incorporated preferentially into the endogenous adenosine nucleoside by the SARS-CoV-2 polymerase during replication of the RNA genome. Remdesivir elicits delayed chain termination because RNA synthesis is terminated after the addition of three more nucleotides, rather than at the point of Remdesivir incorporation
Indication	• Non-severe (at risk of hospitalisation/progression) • Severe and critical COVID-19
Administration (dose, route, duration)	• **Non-severe:** one dose daily for 3 consecutive days as an intravenous infusion. Given as 200mg intravenously on day 1, followed by 100mg intravenously on days 2 and 3. Infusion times of 30-60 minutes or longer (120 mins) are recommended • **Severe and critical**: 200mg intravenously on day 1 followed by 100mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation or ECMO) • If a patient is otherwise ready for discharge prior to completion of the course, Remdesivir can be discontinued • eGFR ≥ 30mL/minute: No dosage adjustment recommended • eGFR < 30mL/minute: No formal safety or pharmacokinetic data are available for patients **(avoid)**
Storage	Unopened vial: Refrigerate at 2-8ºC (36-46ºF); may store at room temperature up to 12 hr before dilution · Diluted solution: Stable for 24 hr at 20-25ºC
Adverse events	• Cardiac effects: bradycardia, hypotension • Hepatic effects: elevated transaminases (AST, ALT), ALT > 10 times the ULN and asymptomatic: Consider discontinuing Remdesivir • Kidney: acute kidney injury • Hypersensitivity reactions, including anaphylaxis and infusion-related reactions, have been reported during and following Remdesivir administration • Others: phlebitis, constipation, headache, and nausea
Drug interactions	• Chloroquine: May diminish the therapeutic effect of Remdesivir. *(Avoid combination)* • CYP3A4 Inducers (Strong): May decrease the serum concentration of Remdesivir. *(Risk C: Monitor therapy)* • Hydroxychloroquine: May diminish the therapeutic effect of Remdesivir. *(Risk X: Avoid combination)*
Contraindications	Hypersensitivity to Remdesivir or any component of the formulation.
Monitoring	AST, ALT, Creatinine

Monoclonal Antibodies

For non-severe COVID-19, monoclonal antibodies are used as alternative only when Paxlovid or Remdesivir are not available, not feasible or not clinically appropriate. As of 30th November 2022, the FDA revoked Emergency Use Authorization for the last monoclonal antibody Bebtelovimab because of lack of efficacy against newer viral variants. Hence these agents are no longer recommended for use in patients with COVID-19

Adjuvant Therapies

Table 11: Dexamethasone

MOA	Dexamethasone is a long-acting corticosteroid with minimal sodium-retaining potential. It decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response
Indication	Severe and critical COVID-19
Administration (dose, route, duration)	• 6mg per day PO or IV for up to 10 days for the treatment of COVID-19 in patients who are required supplemental oxygen or are mechanically ventilated • Higher doses (8mg) of Dexamethasone may be considered in some patient groups Alternatives: Although Dexamethasone has been the best studied, if unavailable it would be reasonable to use alternative corticosteroids such as: 1. Hydrocortisone 50mg IV Q8h x 10 days 2. Methylprednisolone 15mg IV BD x 10 days 3. Prednisone 40mg PO daily x 10 days
Storage	Store intact vials at 20-25° C. Protect from light, heat, and freezing
Adverse events	Hyperglycemia, insomnia, weight gain, acne, dry skin, bruising, psychosis (list not exhaustive)
Drug interactions	Aspirin, Apixaban, Furosemide
contraindications	Hypersensitivity to Dexamethasone or any component of the formulation
Monitoring	Blood glucose

Table 12: Tocilizumab

MOA	Tocilizumab is a monoclonal antibody approved for intravenous use in rheumatoid arthritis. It is works differently from the other Monoclonal antibodies against spike proteins because it antagonises the membrane-bound and soluble forms of the IL-6 receptor (IL-6R/sIL-6R). As such, it works also as an immunomodulator and is still useful in severe/critical COVID-19
Indication	Severe and Critical COVID-19
Administration (dose, route, duration)	Tocilizumab is administered as a single intravenous dose at 8mg/kg actual body weight, typically over 1 hour. A second dose may be administered 12 to 48 hours after the first dose depending on clinical response Renal dose adjustment is not currently warranted
Storage	Refrigerate at 2-8° C. Fully diluted solution for infusion may be stored at 2-8° C or room temperature for up to 24 hours
Adverse events	infusion-related reaction, infection site reaction, increased ALT, increased cholesterol, rash
Drug interactions	Atorvastatin, Apixaban
Contraindications	hypersensitivity reaction to Tocilizumab
Monitoring	• Routine blood work including neutrophil count, platelets, transaminases, and total bilirubin should be checked prior to initiation of therapy • All patients should be monitored for signs and symptoms of infection, given the increased risk with immunosuppression in addition to systemic corticosteroids • Patients on longer-term IL-6 receptor blocker therapy are at risk of active tuberculosis, invasive fungal infections, and opportunistic pathogens • Risks and benefits of therapy should be considered carefully in patients with any active, severe infection other than COVID-19; caution is advised when considering the use of Tocilizumab

Empiric antibiotics

If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate daily, and, if there is no evidence of bacterial infection, de-escalate or stop antibiotics.

Choice of Empiric Antibiotics

If sepsis or shock is suspected, empiric broad-spectrum antimicrobial therapy is the standard of care:

- **Community-Acquired Pneumonia (CAP)**: Co-amoxiclav plus Azithromycin
- **Hospital Acquired Pneumonia (HAP):** Cephalosporin (e.g., Ceftriaxone) plus an aminoglycoside OR Imipenem plus a Fluoroquinolone

Dosing: *See Chapter 4*.

Vitamin C

Vitamin and mineral supplements have been promoted for the treatment and prevention of respiratory viral infections; however, their roles in treating COVID-19 are yet unproven. Vitamin C (Ascorbic Acid) is a water-soluble vitamin that is thought to have beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines.

Pregnancy Considerations for Therapeutics

Dexamethasone: Dexamethasone 6mg daily for 10 days or until discharge is generally recommended for adult patients who are severely ill on oxygen or on ventilator support. Glucocorticoids may also have a role in the management of refractory shock in critically ill patients with COVID-19. For pregnant women at increased risk of preterm delivery at 28+0 and 33+6 gestation age, the initial doses should be to induce foetal lung maturity, given as 4 doses of Dexamethasone 6mg intramuscular 12 hours apart or 2 doses of Betamethasone 12mg given 24 hours apart.

This is then followed by oral daily Prednisolone of 40mg or intravenous 80mg of Hydrocortisone to complete the maternal steroid dose. The rationale is to avoid the adverse foetal effects of prolonged use of Dexamethasone and Betamethasone. **Nirmatrelvir-ritonavir:** Initiated as soon as possible after symptom onset is the preferred drug for pregnant women with non-severe illness

Remdesivir: Pregnant women with non-severe and severe COVID-19 can be given Remdesivir (alternative for Paxlovid in non-severe illness).

Molnupiravir: Should be avoided in women who are pregnant, breast feeding or with contraception potential due to concerns that mutagenesis can be associated with embryo-fetotoxicities. Currently only prescribed for those with absolute contraindications to Nirmatrelvir-r or Remdesivir.

Anticoagulants: Initiate anticoagulant prophylaxis in **all** pregnant/postpartum women with COVID-19 admitted to the hospital and give for at least 10 days post-admission even if the pregnant woman is discharged earlier. For antepartum prophylaxis in women likely to deliver in a few days, use unfractionated Heparin 5,000 units subcutaneously every 12 because it is more readily reversed than low molecular weight Heparin. Low molecular weight Heparin e.g., 40mg once daily is indicated in women remote from term.

Tests for Evaluation and Monitoring in Severe COVID-19

Recommended testing is summarised in *Table 2*.

Assessment of oxygen status through pulse oximetry is crucial in COVID-19 or suspected COVID-19, both at initial evaluation and at regular intervals during a hospitalisation. Where available, **Arterial Blood Gases** (ABG) will be useful, especially in critically ill patients and those requiring mechanical ventilation.

The initial evaluation should include pulmonary imagining (Chest X-ray, ultrasound, or, if indicated, CT). Obtain an ECG, if indicated.

Laboratory evaluation includes an FBC with differential and a metabolic panel, including liver and renal function tests.

Measurements of inflammatory markers such as CRP, D-dimer, and ferritin, while not part of standard care, may have prognostic value. [Ref: NIH guidelines]

Patients with a history of fever should be tested for malaria with RDT or microscopy. If TB is suspected, a sputum sample should be sent for testing by Xpert or microscopy, for some patients, a urine LAM may be informative.

Screen for HIV disease if the status is uncertain. Patients living with HIV should have viral loads and CD4 counts checked while patients who test positive should be linked to ART services.

Consider pregnancy tests in women of reproductive age. If sepsis or shock is suspected, blood cultures are indicated.

- Common lab findings:
    - Lymphopenia (low lymphocytes)
    - Elevated liver enzymes (AST/ALT)
    - Elevated Blood Sugar readings
    - Leukocytosis or leukopenia
    - Normal Procalcitonin
    - Raised CRP
    - Raised D-dimer
- Common Radiographic findings:
    - Bilateral lung involvement on chest imaging (Chest X-ray or CT scan)

General Principles of Hospital Care in COVID-19

Infection Prevention and Control Measures for COVID-19

Hospital Infection Prevention and Control (IPC) measures include use of personal protective equipment for droplet and contact precautions along with eye protection (e.g., masks, face shields/goggles, gloves, gowns) and single patient dedicated medical equipment (e.g., stethoscopes, blood pressure cuffs, thermometers).[5,6]

The number of individuals and providers entering the room of a patient with COVID-19 should be limited. If necessary, patients with confirmed COVID-19 may be cohorted in the same room.

If available, airborne infection isolation rooms (AIIRs) should be used for patients who will be undergoing any aerosol-generating procedures. During these procedures, all staff should wear fit-tested respirators (N95 respirators) or powered, air-purifying respirators (PAPRs) rather than a surgical mask.[7]

The following IPC guidelines apply:

1) Apply contact droplet precautions (in addition to standard precautions) (*see Appendix 2*)
   a) PPE should be donned before entering the patient care area
   b) Hand hygiene should be performed before donning and after doffing PPE
   c) A video of how to wear appropriate PPE for COVID-19 is available at: https://www.dropbox.com/s/ym9g5c0hhr16gul/DonningDoffing_COVID19_PPE_480p_04Mar2020.mov?dl=0
   d) Add airborne precautions if there is an emergent need for intubation or cardiopulmonary resuscitation at triage
2) Provide the suspect patient a medical mask for source control
3) Instruct the patient to practice respiratory hygiene and hand hygiene and to avoid movements within the facility
4) Locate suspect COVID-19 patients into a separate waiting area (i.e., cohort patients), and separate patients by ≥ 1-meter
5) Use dedicated patient equipment, when possible, (such as stethoscopes) or wash and disinfect between patients
6) Frequent clean areas where suspect patients are waiting, with particular focus on frequently touched surfaces

☐ **Safe Transfer of Patients in Health Facilities**

This applies for transfer of patients from one point to another

1) Ensure IPC measures are always applied
2) Ensure appropriate diagnostics and emergency treatments have been given and patient is stable and ready for transport
3) Ensure all monitors and ongoing treatments, including oxygen therapy, are secured, and can be maintained during transport
4) Ensure appropriate documentation and handover of care to next responsible clinicians
5) Ensure the responsible Healthcare Worker is prepared

☐ **Handling Demised COVID-19 Patients**

1) Always apply IPC interventions while coming into contact with the deceased or surfaces or materials that may be contaminated by secretions from the deceased
2) Because respiratory droplets produced when an infected person coughs or sneezes, this route of transmission is not a concern when handling human remains or performing post-mortem procedures
3) Post-mortem activities should be conducted with a focus on avoiding aerosol generating procedures

Hospital Discharge Criteria

Prior to hospital discharge, patients should be afebrile for a minimum of three days and have improvement in respiratory symptoms and other medical issues such as hyperglycaemia. Patients **do not** require a repeat SARS-CoV-2 test for discharge.

1) *Symptom-based strategy:* -

At least 2 days have passed since clinical recovery defined as:

i) Resolution of fever without the use of fever-reducing medications
ii) No persistent cough without the use of cough-suppressing medications
iii) No shortness of breath and an oxygen saturation > 90% on room air
iv) Oxygen saturations DO NOT drop by more than 3% on exercise

2) *Time-based strategy* - asymptomatic persons who are confirmed cases: -
7 days have passed since the date of the first positive PCR test

Note: *Clinical judgement should be used to determine the timing of discharge in patients who do not strictly meet the clinical criteria. The criteria above should not be used as the sole basis for guiding discharge.*[30]

Discharge Instructions to Patients

Because the duration of viral shedding is still not well defined, patients should be instructed to **practise physical distancing** (avoiding public gatherings, remaining home from work, staying ≥1 metre away from others in public) for at least 7 days after the onset of symptoms.

At every stage of care, **emphasise preventive measures** to patients, their family, and indeed all people can and should take to protect themselves from COVID-19. These include:

a) Wash hands often with soap and water for at least 20 seconds. Use an alcohol-based hand sanitizer if soap and water are not readily available
b) Wear a mask
c) Avoid touching eyes, nose, and mouth with unwashed hands
d) Cover cough or sneeze with a tissue, then throw it away
e) Clean and disinfect frequently touched objects and surfaces
f) Practice physical distancing (≥ 1-metre distance) when you must interact with other people
g) Avoid close contact with people who are sick (≥ 1-metre distance)
h) Seek medical attention again, e.g., at Post-Acute COVID-19 Clinic, if symptoms recur

[30] *See Chapter 6 on Home Care for additional guidance*

Chapter 4: Principles of Care for Critical Patients

Critical cases of COVID-19 may be associated with acute respiratory distress syndrome (ARDS), septic shock that may represent virus-induced distributive shock, cardiac dysfunction, elevations in multiple inflammatory cytokines that provoke a cytokine storm, and/or exacerbation of underlying comorbidities.

In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease. Because patients with critical illness are likely to undergo aerosol-generating procedures, they should be placed in the Airborne Infection Isolation Room (AIIRs) when available.

Recommendations for therapy, testing and supportive care in critical cases of COVID-19 are summarised in *Table 13*. Of note, these recommendations apply to all patients meeting clinical criteria for COVID-19, even if confirmatory testing is pending. In severe or critical cases, patient outcomes will improve if attention is given to administering the treatments within one hour of admission.

Table 13: Recommended Therapy, Testing and Supportive Care in Critical Cases of COVID-19

Disease severity	Recommended therapy/drugs	Lab tests	Supportive Care
Critical (ARDS) • SpO_2 < 90% • SpO_2/FiO_2 < 300 while on at least 10 L/min oxygen therapy • Need for mechanical ventilation or other ICU needs	**WITHIN 1 HR OF ADMISSION** • **Oxygen** to bring O_2 saturation to > 90% • **Empiric Broad-Spectrum Antibiotics** within one hour if sepsis or bacterial pneumonia is suspected: **Community Acquired Pneumonia (CAP)**: Co-Amoxiclav plus Azithromycin and if **Hospital Acquired Pneumonia (HAP):** Cephalosporin (e.g., Ceftriaxone) plus an aminoglycoside OR Imipenem plus a fluoroquinolone • **Dexamethasone IV/IM** 6mg OD for up to 10 days • **Remdesivir** 200mg as a single dose on day 1, followed by 100mg once daily **DURING COURSE OF ADMISSION** • DVT prophylaxis: Low molecular weight Heparin 1mg/kg/day subcutaneous • Vitamin C 1000mg tab OD – parenteral • Paracetamol 1g TDS for fevers • Nebulization ONLY if indicated (aerosol generating)	**On Admission** • COVID-19 PCR • Malaria RDT • Hb/FBC • HIV: If HIV+, do CD4 count and viral load • Chest X-ray • Sputum for Xpert/microscopy • Liver & kidney tests • Electrolytes • Glucose • Chest CT scan • Chest Ultrasound • Blood culture • Arterial Blood Gases • Clotting Profile • CRP **Daily laboratory testing** • Daily Fasting/ Random Blood Sugar • Monitor other abnormal labs as indicated	• Sedation and analgesia as needed for mechanically ventilated patients • Prone position intermittently • IVFs (sparingly if ARDS) • Blood Pressure management • Blood sugar management • Fluid Balance (ins/outs) – urine output • Bowel movement • Feeding • No visitors • Skin care for pressure areas

The clinical syndromes associated with critical illness in COVID-19 include the following:

1. Severe Acute Respiratory Infection (SARI) or pneumonia
2. Acute Respiratory Distress Syndrome (ARDS)
3. Sepsis and septic shock
4. Multi-system illness (renal, cardiac, thrombo-embolic, neuropsychiatric)

Special focus is given here to the differences in fluid management between the syndromes of SARI and ARDS as compared to sepsis/shock. The chapter also covers principles for ventilatory management and cardiovascular support where indicated.

Most of the recommendations for the management of critically ill patients with COVID-19 are extrapolated from experience with other life-threatening infections.[8] The critical care management of patients with COVID-19 does not differ substantially from the management of other critically ill patients, although special precautions to prevent environmental contamination by SARS-CoV-2 is warranted.

Best Practices for Care of COVID-19 Care in the ICU Setting

Closely monitor patients with severe or critical COVID-19 illness for signs of further clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and apply supportive care interventions immediately. Application of timely, effective, and safe supportive therapies is the cornerstone of therapy for patients that develop severe or critical manifestations of COVID-19.

Signs of clinical deterioration. Triage to ICU:

- Signs of severe respiratory distress, i.e., increased work of breathing
- Hypoxemia (SpO_2 < 90%) despite escalating oxygen therapy
- SpO_2/FiO_2 < 300 while on at least 10L/min oxygen therapy
- SBP ≤ 90mmHg, mean arterial pressure < 65, or heart rate > 120. Hemodynamic instability after initial conservative fluid resuscitation
- ABG with pH < 7.3 or PCO_2 > 50 or above patient's baseline
- Urine output < 0.5mL/kg/hr
- Altered mentation with inability to protect one's airway

Key points to remember in treatment

1) **Administer oxygen** to all patients with severe or critical illness. This applies to all clinical syndromes, whether SARI, shock, sepsis, or multi-system illness
2) **Consider advanced ventilatory support** in patients not responding to increasing oxygen therapy. Signs of acute hypoxemic respiratory failure: include patient in severe respiratory distress, hypoxemia (SpO_2 < 90%) despite escalating oxygen therapy, and SpO_2/FiO_2 < 300 while on at least 10L/min oxygen therapy
3) If indicated, **endotracheal intubation should be performed by a trained and experienced provider** using airborne precautions
4) **In sepsis, administer appropriate empiric antimicrobials within one hour**, even though the patient may have COVID-19. Empiric antibiotic treatment should be based on the suspected infected source (e.g., lung, urine, blood), local epidemiology and susceptibility data, and treatment guidelines
5) **Unless there is evidence of shock, use conservative fluid management in COVID-19**. Patients should be treated cautiously with intravenous fluids because aggressive fluid resuscitation may worsen oxygenation in ARDS, especially in settings where there is limited availability of mechanical ventilation. The FEAST trial revealed that fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in resource-limited settings in Africa, due to worsening respiratory and neurological function, anaemia and metabolic acidosis[26]
6) **Understand the patient's co-morbid condition(s)** to tailor the management of critical illness and appreciate the prognosis. Manage conditions which include the risk of severe complications and death in COVID-19, including hypertension, cardiovascular disease, diabetes, renal disease, asthma. In Zambian experience, critical COVID-19 illness is often associated with exacerbation of these comorbidities, and patient recovery depends in part on adequate adjunct treatment of these conditions, following usual protocols
7) **Practise rigorous Infection Control and Prevention (IPC):** Healthcare Workers who are performing aerosol-generating procedures on patients with COVID-19 should use fit-tested respirators (N95 respirators) or PAPRs, if available, rather than surgical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection such as a face shield or safety goggles)

Management of Acute Respiratory Distress Syndrome (ARDS)

COVID-19-positive patients not responding to increasing oxygen therapy are developing acute hypoxemic respiratory failure and require ICU admission. It may be assumed that most patients with COVID-19 who require ICU level of care will develop ARDS. However, the clinician needs to first consider the following diagnoses, which would alter management:

- Rule out cardiogenic pulmonary oedema as the primary cause of poor oxygenation. (COVID-19 can cause myocarditis and cardiac ischemia)
- Rule out bacterial pneumonia with sepsis
- Consider pulmonary embolism (with or without ARDS) as a cause for deterioration

Principles of ARDS Management

1. Recognize ARDS early
2. Initiate respiratory support without delay, but avoid intubation and mechanical ventilation if possible

Recognize ARDS early

ARDS is an acute, diffuse, inflammatory form of lung injury that is associated with a variety of aetiologies, including COVID-19. It is essential to recognize ARDS when a patient with respiratory distress is failing standard oxygen therapy.

Patients may continue to have increased work of breathing or hypoxemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10-15L/min, which is typically the minimum flow required to maintain bag inflation; FiO_2 0.60-0.95). Hypoxemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation (*see Table 14*).

Table 14: Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome (Berlin Criteria)	
Timing	New or worsening respiratory symptoms within one week of known clinical insult
Imaging	Bilateral opacities- not fully explained by effusions, lobar or lung collapse, or nodules
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiograph) to exclude hydrostatic oedema if no risk factor present
Oxygenation	
Mild	200 mmHg < PaO_2/FiO_2 ≤ 300mmHg (with PEEP or CPAP ≥ 5 cmH_2O
Moderate	100 mmHg < PaO_2/FiO_2 ≤ 200mmHg with PEEP ≥ 5 cmH_2O
Severe	PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥ 5 cmH_2O

In diagnosis ARDS, the Berlin Criteria shown above is often used. However, when arterial blood gases are not available, the Kigali criteria which bases calculations on the SpO_2 may be used instead. Below we show comparison with the Kigali modification which is easier to use in low resource settings such as ours.

Table 15: Berlin and Kigali Criteria for Acute Respiratory Distress Syndrome

	Berlin Criteria	Kigali Modifications
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Oxygenation	PaO_2/FiO_2 ≤ 300	PaO_2/FiO_2 ≤ 315
PEEP Requirement	Minimum 5cm H_2O PEEP required by invasive mechanical ventilation (noninvasive acceptable for mild ARDS)	No PEEP requirement
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or CT	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or ultrasound
Origin of Oedema	Respiratory failure not fully explained by cardiac failure or fluid overload [need objective assessment (e.g., echocardiography) to exclude hydrostatic oedema if no risk factor present]	Respiratory failure not fully explained by cardiac failure or fluid overload [need objective assessment (e.g., echocardiography) to exclude hydrostatic oedema if no risk factor present]

ARDS – Acute Respiratory Distress Syndrome; PEEP – Positive End Expiratory Pressure

Recommendations for Ventilatory Support in COVID-19

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options include high-flow nasal cannula (HFNC), Non-invasive Positive Pressure Ventilation (NIPPV), or intubation and invasive mechanical ventilation. HFNC is preferred over NIPPV in patients with acute hypoxemic respiratory failure. Both HFNC and NIPPV are aerosol generating and airborne precautions (including use of N95) should be instituted.

The following recommendations represent current international best practice[31].

General Recommendations

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, recommend high-flow nasal cannula (HFNC) oxygen over Non-Invasive Positive Pressure Ventilation (NIPPV)
- In the absence of an indication for endotracheal intubation, recommend closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available. Additionally, NIPPV is preferred for patients with concomitant hypercapnic respiratory failure (i.e., if patient also has acute exacerbation of emphysema/COPD)
- For adults with COVID-19 who are receiving supplemental oxygen, recommend close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, recommend considering a trial of awake prone positioning to improve oxygenation
- Recommend against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation

Recommendation for Mechanically Ventilated Patients

1) Endotracheal intubation for patients with COVID-19 should be performed by Healthcare Providers with extensive airway management experience, if possible
2) Intubation should be achieved by video laryngoscopy, if possible
3) For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS), use low tidal volume (VT) ventilation (VT 4–8mL/kg of predicted body weight) over higher tidal volumes (VT > 8mL/kg)

[31] NIH Clinical Guidelines https://www.covid19treatmentguidelines.nih.gov/ accessed 18 August 2020

- The initial tidal volume is 6 mL/kg PBW; tidal volume up to 8mL/kg PBW is allowed if undesirable side effects occur (e.g., dyssynchrony, pH < 7.15). Hypercapnia is permitted if meeting the pH goal of 7.30. Ventilator protocols are available. The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets. Although high driving pressure (plateau pressure−PEEP) may more accurately predict increased mortality in ARDS compared to high tidal volume or plateau pressure, RCTs of ventilation strategies that target driving pressure are not currently available

4) For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimised ventilation, prone ventilation for 12 to 16 hours per day is recommended
   - Application of prone ventilation is strongly recommended for adult and paediatric patients with severe ARDS but requires sufficient human resources and expertise to be performed safely
5) Patients with ARDS, especially young children or those who are obese or pregnant, may desaturate quickly during intubation. Pre-oxygenate with 100% FiO_2 for 5 minutes, via a face mask with reservoir bag, bag-valve mask, HFNO, or NIV. Rapid sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation
6) For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimised ventilation and other rescue strategies, recommend using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off
7) In patients with moderate or severe ARDS, higher PEEP instead of lower PEEP is suggested
8) In patients with moderate-severe ARDS (PaO_2/FiO_2 < 150), neuromuscular blockade by continuous infusion should not be routinely used

TIPS ON VENTILATOR SETTINGS IN ARDS
Low tidal volume of 6mL/kg ideal body weight
Titrate tidal volume with $Sp0_2$
Target low plateau airway pressure of < 30cm H_2O
Moderate high PEEP levels to recruit airways
Consider neuromuscular blockade
Nurse in prone position

NOTE: Consult Critical Care Specialists on Ventilator Settings if in doubt

Management of Sepsis and Shock

DEFINITION:

SEPSIS: Acute severe life-threatening organ dysfunction caused by dysregulated host response to infection

SEPTIC SHOCK: Sepsis with hypotension unresponsive to fluids and requiring vasopressors to maintain Mean Arterial Pressure (MAP) ≤ 65mmHg and Lactate ≥ 2mmol/L in the absence of hypovolaemia

Recognize patients with Sepsis and Septic Shock:

- Patients with sepsis have suspected or documented infection and acute, life-threatening organ dysfunction
- A subset of these patients may have septic shock and show clinical signs of circulatory failure and hypoperfusion
- Patients with sepsis and septic shock need treatment and resuscitation immediately!
  - ☞ Step 1: Get Intravenous access
  - ☞ Step 2: Get bloods for investigations
  - ☞ Step 3: Give empiric antibiotics without delay preferably within the first 1 hour
  - ☞ Step 4: Start IV fluids

Fluid Resuscitation

In resuscitation from septic shock in adults, give at least 30mL/kg of isotonic crystalloid in adults in the first 3 hours

- Give initial fluid challenge of 20–30mL/kg over 30–60 minutes (or faster)
- Perform sequential evaluations to assess clinical response
- If shock persists, continue to give additional fluid challenges (i.e., 250–500mL) over 30 minutes as long as there is a clinical response

Cautions:

- *Do not use hypotonic crystalloids, starches, or gelatins for resuscitation*
- Fluid resuscitation may lead to volume overload, resulting in respiratory failure. If there is no response to fluid loading and signs of volume overload appear (for example, jugular venous distension, crackles on lung auscultation, pulmonary oedema on imaging, or hepatomegaly in children), then reduce or discontinue fluid administration. This step is particularly important where mechanical ventilation is not available. Alternate fluid regimens are suggested when caring for children in resource-limited settings

Empiric Antimicrobials in Suspected Sepsis or Shock

Administer appropriate empiric antimicrobials within ONE hour of identification of sepsis. Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia [if infection was acquired in healthcare setting], or sepsis), local epidemiology and susceptibility data, and treatment guidelines

Broad Spectrum Antibiotics

- Community Acquired Pneumonia (CAP):
  - β-lactam (Amoxicillin, Co-amoxiclav) PLUS Macrolide (Clarithromycin or Azithromycin)
  - Penicillin allergy: Doxycycline OR Respiratory quinolone (Levofloxacin OR Moxifloxacin) OR third generation cephalosporin
- Hospital Acquired Pneumonia (HAP): consider MDR organisms including Pseudomonas

***Antibiotics for Pseudomonal Coverage*:**

Pseudomonas infection can be treated with a combination of an antipseudomonal β-lactam (e.g., Piperacillin, Ticarcillin in the PCNs

- Cefepime in the cephalosporins **and** an aminoglycoside OR
- Carbapenems (e.g., Meropenem or Imipenem **not** Ertapenem) **with** antipseudomonal activity
- Fluoroquinolone (e.g., Levofloxacin [high dose] or Ciprofloxacin) may be used **in conjunction with** an aminoglycoside (e.g., Tobramycin, Amikacin, Gentamicin)

***Antibiotics in People Living with HIV (PLHIV) and Immunosuppressed*:**

- Consider PCP treatment with high-dose Sulfamethoxazole/Trimethoprim

Antibiotics in Pregnant Women:

- Use of macrolides, cephalosporins and penicillins are safe
- Do not use fluoroquinolones or Doxycycline

Antibiotics in Children

Combination therapy:

- Ampicillin or Penicillin G for fully immunised child if local epidemiology documents **lack** of substantial high-level penicillin-resistance for invasive *S. pneumoniae. or*
- Third generation cephalosporin (e.g., Cefotaxime or Ceftriaxone) for incompletely immunised child, known high-level of penicillin-resistance for invasive *S. pneumoniae* or life-threatening infection
    - And antibiotic against atypical pneumonia (i.e., macrolide)
    - If community-acquired *S. aur*eus suspected: add Vancomycin or Clindamycin based on local susceptibility data

* Fluoroquinolones and Doxycycline are not used to treat CAP in children

When to stop Antimicrobial Treatment:

Considerations include:

- Signs of clinical improvement (i.e., once shock resolved)
- Signs of infection resolution (i.e., Procalcitonin)
- 5–10 days of duration of treatment is adequate for most serious infections associated with sepsis
- Absence of documented bacterial infections such as positive blood cultures

Longer treatment courses may be appropriate in patients with slow clinical response, undrainable foci and certain infections (i.e., *S. aureus* bacteraemia).

Management of Septic Shock in Children

Recognize septic shock in children with any hypotension (systolic blood pressure [SBP] < 5th centile or > 2 SD below normal for age) or 2-3 of the following:

- Altered mental state
- Tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children)
- Prolonged capillary refill (> 2 seconds) or
- Warm vasodilation with bounding pulses OR cold shock with cold extremities and weak pulse
- Tachypnea
- Mottled skin or petechial or purpuric rash
- Increased lactate
- Oliguria
- Hyperthermia or hypothermia

In the absence of a lactate measurement, use MAP and clinical signs of perfusion to define shock. Standard care includes early recognition and the following treatments within 1 hour of recognition:

Immediate goals [ABCDE]

A. Stabilise the airway, ensure patent using airway adjunct (e.g., airway positioning, chin tilt head lift, jaw thrust, guedel airway)

A. If severe angioedema, consider severe anaphylaxis as cause

B. Provide oxygen by mask or nasal catheter if mask unavailable

C. Establishment of vascular access

- Two age-appropriate large bore peripheral intravenous catheters should be established, or a central line placed

C. Assess for **malnutrition** (wasting, peripheral oedema, skin changes, z-score) and **severe anaemia** (pallor)

D. Disability (AVPU – Alert/responsive to Voice/responsive to Pain/Unresponsive) and Do Not Forget Glucose (do RBS and treat appropriately)

E. Exposure and everything else (body temperature, rash)

Weigh the child or estimate the child's weight using formulas below

- If < 1 year old (kg): (Age in months + 9) /2
- > 1year old (kg): (Age +4) x 2
- This does not substitute a child's true weight – the child must be weighed immediately once stable

SEE MANAGEMENT ALGORITHM ON NEXT PAGE

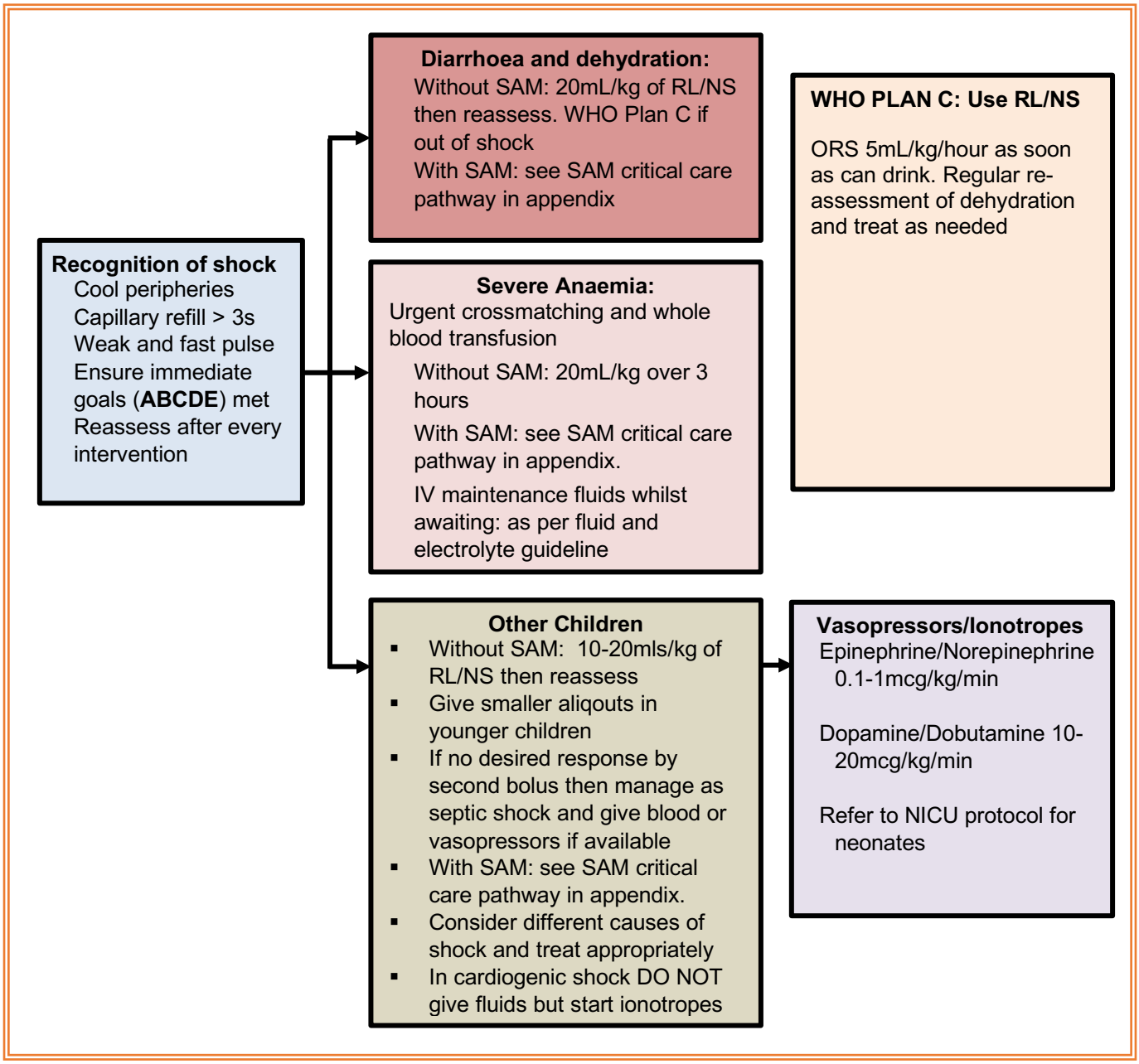


Figure 16: Shock Management in Children

Considerations for differential diagnosis in children:

- Severe acute malnutrition
- Severe malaria with profound anaemia (i.e., Hb < 5g/dL)
- Diarrhoea and severe dehydration
- Severe dengue shock syndrome

Vasopressors

If MAP < 65 after initial fluid bolus, start vasopressors:

- But can be given early, during ongoing resuscitation when shock is severe and diastolic pressure is low
- Do not delay administration

Administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥ 65mmHg in adults and age-appropriate targets in children.

If central venous catheters are not available, vasopressors can be given through a peripheral IV, but use a large vein and closely monitor for signs of extravasation and local tissue necrosis. If extravasation occurs, stop infusion. Vasopressors can also be administered through intraosseous needles.

If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors, consider an inotrope such as Dobutamine.

Vasopressors (i.e., Norepinephrine, Epinephrine, Vasopressin and Dopamine) are most safely given through a central venous catheter at a strictly controlled rate, but it is also possible to safely administer them via peripheral vein and intraosseous needle. Monitor blood pressure frequently and titrate the vasopressor to the minimum dose necessary to maintain perfusion and prevent side effects.

Norepinephrine is considered first-line in adult patients; Epinephrine or Vasopressin can be added to achieve the MAP target. Because of the risk of tachyarrhythmia, reserve Dopamine for selected patients with low risk of tachyarrhythmia or those with bradycardia. In children with cold shock (more common), Epinephrine is considered first-line, while Norepinephrine is used in patients with warm shock (less common).

WHEN TO STOP VASOPRESSORS
Titrate vasopressors to desired effect
Target MAP range ≥ 65–70mmHg
consider higher MAP (i.e., ≥ 80mmHg) in patients with chronic hypertension
Check markers of perfusion:
Mental status, urine output, **normalization of lactate* and skin examination.**
Titrate down vasopressors if blood pressure in above target range

Blood Transfusion in Septic shock

Give packed red blood cells (PRBCs) transfusion when there is severe anaemia:

- Hb ≤ 70g/L (7.0g/dL) in absence of extenuating circumstances such as myocardial infarction, severe hypoxemia, or acute haemorrhage
- Targeting higher thresholds (≥ 90–100g/L) does not lead to better outcomes in patients with sepsis

Management of Shock in Pregnant Women

Ensure adequate hydration, use IV fluids as necessary:

- Close attention to fluid balance to prevent fluid overload and pulmonary oedema.
- Use fluid cautiously, limit to 75mL/hour to avoid untoward outcomes of pulmonary oedema
- Oncotic pressure decreases throughout pregnancy and in the postpartum period.

Vasopressors – use cautiously with appropriate available monitoring:

- May decrease uterine perfusion
- Administer with IV fluids – uteroplacental flow will not be adequate with vasopressors alone
- Continuous electronic foetal monitoring is recommended

Additional Topics in Critical Care for COVID-19

Nebulization or Metered-Dose Inhalers

In patients with asthma or others with suspected reactive airway disease (e.g., prominent wheezing and prolonged expiratory phase), consider treatment with inhaled beta-agonists:

1. Nebulization is considered an aerosol generating procedure and may contribute to disease transmission. Nebulization requires appropriate PPE (e.g., N95) and room (e.g., negative airflow)
2. If possible, use metered dose inhalers (MDIs) + spacer rather than nebulizers.

Acute Kidney Injury and Renal Replacement Therapy

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe disease.[3] Continuous renal replacement therapy was needed in more than 15% of cases of critical disease in one case series.[5]

- For critically ill patients with COVID-19 who have acute kidney injury and who develop indications for renal replacement therapy, recommend Continuous Renal Replacement Therapy (CRRT), if available
- If CRRT is not available or not possible due to limited resources, recommend prolonged intermittent renal replacement therapy rather than intermittent haemodialysis (BIII)

Cardiac Complications

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis There is a growing body of literature relating COVID-19 to myocarditis and pericardial dysfunction in approximately 20% of patients.[3,5,8-11] Acute cardiac injury and arrhythmias have also been described in patients with COVID-19.

Other Intensive Care Unit-Related Complications

Patients who are critically ill with COVID-19 are at risk for nosocomial infections and other complications of critical illness care, such as VAP, HAP, catheter-related bloodstream infections, and venous thromboembolism. When treating patients with COVID-19, clinicians also need to minimise the risk of conventional ICU complications in order to optimise the likelihood of a successful ICU outcome.

Special considerations for Pregnant Patients

Supportive therapies should take into account the physiologic adaptations of pregnancy.

The use of investigational therapeutic agents outside of a research study should be guided by individual risk-benefit analysis based on potential benefit for mother and safety to foetus, with consultation from an obstetric specialist and ethics committee.

Emergency delivery and pregnancy termination decisions are challenging and based on many factors: gestational age, maternal condition, and foetal stability.

Pregnant women with comorbidities should continue to receive the usual care while minimising frequent face to face visits unless the benefits outweigh the risks, this is in order to protect them from getting infected during multiple hospital visits.

Communicate early with Patient and Family

During intensive care management of sepsis, determine which chronic therapies should be continued and which therapies should be stopped temporarily. Communicate proactively with patients and families and provide support and prognostic information. Understand the patient's values and preferences regarding life-sustaining interventions.

Table 16: Prevention of Complications Related to Hospitalisation

Anticipated Outcome	Interventions
Reduce days of invasive mechanical ventilation	• Use weaning protocols that include daily assessment for readiness to breathe spontaneously • Minimise continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions
Reduce incidence of ventilator-associated pneumonia	• Keep patient in semi-recumbent position (head of bed elevation 30-45º) • Use a closed suctioning system; periodically drain and discard condensate in tubing • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged but not routinely • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days
Reduce incidence of venous thromboembolism	• Use pharmacological prophylaxis (low molecular-weight heparin [preferred if available] or Heparin 5000 units subcutaneously twice daily) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices)
Reduce incidence of catheter-related bloodstream infection	• Use a checklist with completion verified by a real-time observer as reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed
Reduce incidence of pressure ulcers	• Turn patient every two hours
Reduce incidence of stress ulcers and gastrointestinal bleeding	• Give early enteral nutrition (within 24–48 hours of admission) • Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for gastrointestinal bleeding include mechanical ventilation for ≥ 48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score
Reduce incidence of ICU-related weakness	• Actively mobilise the patient early in the course of illness when safe to do so

Chapter 5: COVID-19 Considerations for Paediatrics

Acute care of Children and Adolescents with Confirmed COVID-19

Clinical Presentation

The clinical spectrum of COVID-19 in children ranges from asymptomatic to critical illness. No specific data is available establishing risk factors for severe COVID-19 in children. A rare but serious inflammatory syndrome in children has been linked to COVID-19. This condition is referred to as Multisystem Inflammatory Syndrome in Children (MIS-C). (*see **Box 3**: COVID-19 Severity Classification, page 24*)

Table 17: Summary of Recommended Therapy, Testing and Supportive Care for Non-Severe, Severe Paediatric COVID-19 Cases

Disease severity	Recommended therapy/drugs	Lab tests	Supportive Care	Comment
Non-severe	• Paracetamol as needed for fever and aches-doses as above • Nasal congestion and sore throat to be managed symptomatically as above • Antibiotics should NOT be prescribed unless there is clinical suspicion of a bacterial infection and only appropriate antibiotics to be used • **Paxlovid** only for children ≥ 12 years and/or 40kg (300m/100mg BD PO for 5 days)	• HIV, TB as clinically indicated • Chest X-ray (+/- CT chest) • CRP • D-dimers • FBC+DC • LFT • KFT • Glucose	• Hospitalise for monitoring if has risk factors for severe illness • Blood pressure management • Blood sugar management • Consider IVF • Oxygen therapy where indicated in some high-risk patients	• Evaluate patients for Severe Acute Malnutrition (SAM) • Individuals with high risk of progression may require hospital management **High risk patients include** • SCD, Renal Disease, Obesity, Diabetic, Heart Disease, HIV and those on immunosuppressive therapy, Cancer patients • Decision for further testing and admission will be on a case-by-case basis
Severe/Critical:	**WITHIN 1 HR OF ADMISSION** • **Oxygen** to bring O_2 saturation to ≥ 90%. *(refer to Respiratory Support Flow chart,)* • **Empiric Antibiotics** if sepsis is suspected: **Community Acquired Pneumonia (CAP)**: Co-Amoxiclav or Benzylpenicillin and if **Hospital Acquired Pneumonia (HAP):** Cephalosporin (e.g., Ceftriaxone) plus an Aminoglycoside OR Imipenem plus a fluoroquinolone • Corticosteroids: for patients with markedly abnormal radiographs or on vent • **Dexamethasone** 0.15mg/kg orally, intravenously (IV), or nasogastrically (NG) once daily (maximum dose 6mg); OR	**On Admission** • Malaria RDT • HIV: If HIV+, do CD4 count and viral load • Chest X-ray • Sputum for Xpert/microscopy • Liver & kidney tests • Electrolytes • Glucose • ABG • FBC w/diff, • Clotting Profile • CRP, other inflammatory markers • Ferritin • LDH • D-dimers • Blood cultures, • Pregnancy test (case by case)	• Prone position intermittent • IVFs • Blood Pressure management • Blood sugar management • Fluid Balance (ins/outs) – urine output • Bowel movement • Feeding • No visitors • Skin care for pressure areas	• Evaluation patients for SAM • Early referral with frequent oxygen monitoring is necessary • Dexamethasone dose can be increased for ICU and overweight patients • High risk patients with comorbidities should have treatment considerations for their conditions

	• **Prednisolone** 1mg/kg orally or NG once daily (maximum dose 40mg); OR • **Methylprednisolone** 0.8mg/kg IV OD (maximum dose 32mg) • **Remdesivir** Has now been approved for use in children from 3kg or 28days: 5mg/kg intravenous (IV) loading dose on day 1, followed by 2.5mg/kg IV every 24 hours for 5 to 10 days (5 days for those with a rapid clinical response) • ≥ 40kg: 200mg IV loading dose on day 1, followed by 100mg IV every 24 hours for 5 to 10 days (5 days for those with a rapid clinical response) • (If supplies limited, reserve for patients on supplemental oxygen but NOT on mechanical ventilation) • DVT prophylaxis: Low molecular weight **Heparin** 1mg/kg/day subcutaneous • Patients with increased D-dimers > 3000 or those with clinical suspicion of VTE should be on treatment dose of Heparin	**Daily labs** • CBC w/diff • Daily Fasting/ Random Blood Sugar • Monitor other abnormal labs as indicated		

Initial Tests to order at Admission

Full blood count, biochemistry (LFTs & KFTs), CRP/ESR, D-Dimers, ferritin, lactate dehydrogenase (LDH), and chest imaging.

Laboratory Findings

- The white blood cell count can be normal or reduced. Leukopenia and Lymphocytopenia have been reported
- C-reactive protein levels can be normal or elevated
- Severe or critical cases may be accompanied by an elevation in hepatic and muscular enzyme levels and high D-dimer levels[2,4]

Imaging Findings

Chest radiographic findings include:

- Small irregular lung opacities and interstitial alterations, usually affecting peripheral areas in initial phases
- Ground glass opacities (GGO) and consolidation may be observed in severe cases
- Pleural effusion is uncommon

Chest computed tomography also exhibits:

- Ground glass opacities and segmental consolidation in both lungs.
- Children presenting with severe infection may show lobar consolidation bilaterally.[2]

Lung ultrasonography (US) exhibits:

- Single or grouped, usually bilateral, pneumogenic-type vertical artefacts and/or small areas of white lung.
- Advanced COVID-19 pneumonia is characterised by evident consolidation, particularly in the posterobasal regions, and widespread patched artifactual changes, similar to those in Acute Respiratory Distress Syndrome (ARDS).[7]

Thoracic electrical impedance tomography can be used to monitor the distribution of regional ventilation in patients with ARDS and to identify refractory hypoxemia that requires alveolar recruitment manoeuvres.

Therapeutic Management of a Child with Confirmed COVID-19

Four main principles for adequate therapeutic management:

1. Early identification
2. Early isolation
3. Early diagnosis
4. Early treatment

At triage stage, suspected COVID-19 patients should be kept in a single room (where this is possible) adhering to all IPC precautions.

Mild and Moderate cases

- Children with non-severe COVID-19 may require hospital admission if they are at risk for severe disease due to underlying conditions (e.g., immune compromise) or are febrile infants younger than 30 days or < 1 year
- Treated with symptomatic relief medication, preferably Paracetamol to control fever

Management of Hospitalised Children with COVID-19

Quickly identify all those paediatric patients who need hospital care and admit them for immediate appropriate care.

Supportive care

Supportive care should be provided for all paediatric patients with COVID-19 as it is the mainstay of therapy for patients with severe or critical COVID-19. Most children with COVID-19 improve with supportive care, even those with severe disease.

Routine Supportive Care Measures include:

1. Provision of respiratory support
   a. Supplemental oxygen
   b. Ventilatory support (non-invasive or invasive)

NB: Respiratory status may change suddenly after approximately one week of symptoms.

2. Provision of fluid and electrolyte support (where required)
3. Provision of empiric antibiotics as indicated for community-acquired or health care-associated pneumonia; continuation of empiric antibiotics should be determined by cultures and other microbial tests and clinical condition
4. Monitoring for cytokine release syndrome by monitoring blood pressure for hypotension, oxygen saturation for worsening hypoxemia, and biomarkers
   a. Obtain baseline C-Reactive Protein (CRP), D-dimer, Ferritin, Lactate Dehydrogenase (LDH)
   b. Where possible, monitor CRP, D-dimer, Ferritin and LDH two or three times per week or if there is concern for worsening disease
5. **Antiviral Therapy for Selected Patients**
   a. Given the lack of data from controlled trials supporting the efficacy of antiviral agents for the treatment of COVID-19 in children (according to several recommendations from multi-center initial guidance and expert views) antiviral agents should be considered on a case-by-case basis and preferably occur in the context of a clinical trial, if a clinical trial is available.[6,23]
   b. Antiviral therapy for COVID-19 should be reserved for children with documented Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection if testing is available
   c. Potential indications – Decisions to use antiviral therapy should be individualised according to; disease severity, clinical trajectory, existing evidence of effectiveness and underlying conditions that may increase the risk for progression
   d. Children with COVID-19 in whom the risks of unproven antiviral therapy may be warranted include those with severe or critical disease and those with mild or moderate disease and an underlying condition that increases or may increase the risk of severe disease (e.g., medical complexity, congenital heart disease)

Nirmatrelvir-ritonavir – Mounting evidence has allowed for the approval of Nirmatrelvir-ritonavir (Paxlovid) for children above the age of 12 years or weight greater than 40kgs with non-severe disease but at risk of disease progression due to underlying comorbidities listed in **Box 1** (*page 3*). Paxlovid dosing is 300mg twice daily where there is no renal impairment, else dosage is reduced to 150mg twice daily when CrCl < 30mL/min. Risk Factors for severe COVID-19 include:

- Age ≤ 1 year with higher risk among neonates
- Congenital and acquired heart disease
- Diabetes
- Immunosuppression such as uncontrolled HIV disease, cancer, chronic steroid use
- Neurological illnesses including cerebral palsy, and developmental delay
- Haematological illness (sickle cell)
- Renal disease
- Patients dependent on medically related devices such as tracheostomy tubes, urinary catheters, intracardiac devices, nasogastric feeding tubes, extra-ventricular drains, etc

Molnupiravir is contraindicated for children

Remdesivir – More evidence is emerging supporting the use of Remdesivir in children with Severe COVID-19 with low incidence of adverse events. It has now been approved for hospitalized patients as young as 28 days or 3kg for severe disease. Additionally, benefit has been shown for early outpatient infusions of Remdesivir to prevent disease progression leading to hospitalization.

Remdesivir is dosed according to weight as follows:

1. ≥ 3.5 to < 40kg: 5mg/kg intravenous (IV) loading dose on day 1, followed by 2.5mg/kg IV every 24 hours for 5 to 10 days (5 days for those with a rapid clinical response)
2. ≥ 40kg: 200mg IV loading dose on day 1, followed by 100mg IV every 24 hours for 5 to 10 days (5 days for those with a rapid clinical response)
3. Remdesivir should not be administered with Hydroxychloroquine or Chloroquine because coadministration may decrease Remdesivir's antiviral activity.[28]

Glucocorticoids

1. For select children with severe COVID-19 (i.e., those who require mechanical ventilation or those who require supplemental oxygen and have risk factors for disease progression), low-dose glucocorticoids may be warranted
2. The duration of therapy is up to 10 days or until discharge, whichever is shorter
3. Low-dose glucocorticoid regimens include:
   a. Dexamethasone 0.15mg/kg orally, intravenously (IV), or nasogastrically (NG) once daily (maximum dose 6mg); Prednisolone 1mg/kg orally or NG once daily (maximum dose 40mg) or
   b. Methylprednisolone 0.8mg/kg IV once daily (maximum dose 32mg)[41]

Other Adjunctive Therapies

a. **Monoclonal antibodies such as Bamlanivimab (BAM) and Etesevimab (ETE)** no longer recommended, unless genetic sequencing is available to show that the patient has a susceptible strain of the virus.

b. **Convalescent plasma** from recovered COVID-19 patients can be used in the treatment of children with COVID-19 on a case-by-case basis although the benefits and risks remain uncertain.[43-45]

c. **IVIG - Inconclusive data to support use**

d. **Anticoagulation:** Pharmacologic prophylaxis or therapeutic anticoagulation should be considered unless contraindicated. Currently there are no specific recommendations for paediatric patients with COVID-19

Paediatric COVID-19 hospitalised patients should be assessed based on risk factors as outlined below:

- Individual VTE risk factors should be evaluated on admission and reassessed every 48-72 hours for the duration of the hospitalisation
- Enoxaparin prophylaxis should be strongly considered in paediatric patients with confirmed COVID-19 unless contraindicated
- An assessment of bleeding risks versus benefit should be completed on each patient
- Alternative methods of prophylaxis, such as early ambulation or mechanical prophylaxis should be considered in contraindicated patients and all COVID-19 paediatric patients, if applicable

Management Principles of Severe & Critical Cases in Children

Severe cases

All cases with respiratory distress and/or hypoxia (SaO_2 < 94%) (Severe Acute Respiratory Syndrome – SARS) should be admitted to the hospital.

Critical cases

Characterised by the occurrence of ARDS with hypoxemic acute respiratory distress and bilateral pulmonary infiltrates that are not explained by cardiac dysfunction or fluid overload.

Indications for ICU admission

- Respiratory failure requiring mechanical ventilation
- Shock or other organ dysfunction requiring treatment

Treatment Principles of ARDS

- Tracheal intubation - rapid sequence intubation is the best practice in this situation. Preoxygenation should be performed using a flexible nasal cannula (up to flows of 4 L/min) or a reservoir mask with a lower flux to maintain an SaO_2 > 93%
- Positive pressure ventilation with a bag-valve-mask or other similar apparatus should be used with caution because it generates aerosols. Sedation can be performed using fentanyl (1-2µg/kg) or ketamine (1-2mg/kg, if there is no contraindication such as pulmonary hypertension) and neuromuscular blocking with Rocuronium (0.6-1.2mg/kg), preferably. Video laryngoscopy should be utilised if available
- Non-invasive Ventilation (NIV) has a high risk for aerosol dispersion and contamination among health practitioners and whenever it is employed as an intervention, all IPC measures must be followed using the appropriate PPE
- Prone positioning, especially if PaO_2/FiO_2 < 150mmHg. The patient should be maintained in this position at least 18 hours per day with oximetry and capnography monitoring (were available)
- Treatment with Nitric Oxide and/or Sildenafil (0.5-2mg/kg/dose each 4-6 hours with a maximum of 20mg/dose each 8 hours) for patients with persistent hypoxemia
- Patients with wheezing and lower airway obstruction should be treated using a dosimetric inhalers
- Patients with cardiocirculatory dysfunction and shock should be treated with fluid therapy or vasoactive/inotropic drugs. Milrinone (0.1-1.0µg/kg/min) or Dobutamine (5-15µg/kg/min) can be useful in patients with a low cardiac index as a consequence of

pulmonary hypertension and normal arterial pressure. Epinephrine at an inotropic dose (≤ 0.3µg/kg/min) can be used in patients with hypotension

Multisystem Inflammatory Syndrome in Children

Management of Multisystem Inflammatory Syndrome – COVID-19 (MIS-C)

Recent reports describe a rare but serious COVID-19 associated syndrome in children referred to as MIS-C.

MIS-C consists of:

- Persistent fever
- Elevated inflammatory markers (including cytokine storm)
- Neutrophilia
- Lymphopenia
- Coagulopathy
- A variety of clinical manifestations;
  - Vasodilatory shock with normal or mildly depressed systolic function
  - Cardiogenic shock with ≥ moderate systolic dysfunction
  - Kawasaki disease (KD) features (can be complete or incomplete KD)
  - Clinical and laboratory features of cytokine storm
  - Coronary artery dilation and aneurysms (up to 25% of children and teens with MIS-C)
  - Hemophagocytic lymphohistiocytosis
  - Any combination of the above

NB: Some patients with MIS-C will not have respiratory symptoms and may have negative SARS-CoV-2 PCR and serology tests

MIS-C Case Definition in Children – Patients who present with ALL Age < 21 years with:

- Fever: ≥ 38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours
- Laboratory evidence of inflammation – 1 or more of the following:
  - Increased – CRP, ESR, Ferritin, Procalcitonin, LDH, IL-6, Neutrophils, VBG w/Lactate, LDH, D-Dimer and BNP
  - Decreased – Lymphocytes, Albumin
- Evidence of clinically severe illness requiring hospitalisation with multisystem (> 2) organ involvement (cardiac, renal, respiratory, haematologic, gastrointestinal, dermatologic or neurologic)

No alternative plausible diagnoses

Positive for current or recent COVID-19 infection or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Treatment of MIS-C

Aside supportive care a few drugs are under investigation for treatment of MIS-C including; corticosteroids, IVIG and Anakinra. For details on agents under investigation for treatment of COVID-19 and MIS-C, *see Appendix 7.*

Child Health Services

Infant and Young Child Feeding

Breastfeeding remains the cheapest source of nutrition for neonates, infants, and toddlers in Zambia. The benefits of breastmilk to a neonate, infant and toddler are well elucidated. There is currently no evidence of vertical mother to child transmission of COVID-19.

1. Breastfeeding to continue among all non-COVID-19 mothers
2. Suspected, probable and confirmed mothers to continue breastfeeding or to provide breastmilk in the form of expressed breast milk (EBM) for their neonates, infants and toddlers while practising infection prevention measures
3. A mother choosing to breastfeed should wear a surgical mask and practice hand hygiene and observe other health prevention measures during this period
4. EBM can be given to the neonate, infant or toddler by a non-COVID-19 caregiver or nurse
5. Babies with mothers unable to express milk due to severe illness to be provided with donor breast milk or appropriate formula milk

Immunisation

There is risk of disruption to routine immunisation activities due to both COVID-19 related burden on the health system and decreased demand for vaccination because of physical distancing requirements or community reluctance. Disruption of immunisation services, even for brief periods, will result in increased numbers of susceptible individuals and raise the likelihood of outbreak-prone Vaccine Preventable Diseases (VPDs) such as measles[32].

Such VPD outbreaks may result in increased morbidity and mortality predominantly in young infants and other vulnerable groups, which can cause greater burden on health systems already strained by the COVID-19 response. The high potential for VPD outbreaks makes it imperative to maintain continuity of immunisation services as follows:

[32] Suk et al. Post-Ebola Measles Outbreak in Lola, Guinea, January–June 2015. Emerging Infectious Diseases. 2016; 22(6):1106-1108.

1. All new-born babies should receive all age-appropriate vaccinations as per existing MoH guidelines from the maternity ward before discharge
2. Vaccinations SHOULD CONTINUE in all health facilities with strict adherence to infection prevention measures such as physical distancing, wearing of surgical masks and hand hygiene and be equipped with the necessary supplies for those precautions.
3. High volume sites are being encouraged to consider the following:
    - Where possible multiple service points be set up within the facility
    - Or the service be spread out to smaller health posts and more outreach vaccination sites (such as nearby schools or empty churches) to decongest high volume facilities
    - All vaccination points to conduct screening of all clients for COVID-19 while adhering to infection preventive measures before providing vaccinations
4. VPD surveillance should be maintained and reinforced to enable early detection and management of VPD cases, and where feasible, contribute to surveillance of COVID-19
5. Under circumstances of a VPD outbreak, the decision to conduct outbreak response mass vaccination campaigns, appropriate measures will be taken after a risk-benefit assessment on a case-by-case basis, in conjunction with the Central level Ministry of Health

Malnutrition

Zambia's burden of stunting stands at 35%, wasting at 4% and severe wasting at 2% among children under 5 years of age as of 2018[33].The following provisions are proposed:

1. Provision of nutrition services from health facilities should continue while adhering to infection preventive measures such as physical distancing, hand hygiene, etc
2. More outpatient therapeutic programs (OTPs) should be offered and supported
3. High density facilities providing inpatient care of severe acute malnutrition (SAM) patients should be decongested by referring stable SAM patients to OTPs
4. Civil society organisations (CSOs) and Non-governmental Organisations (NGOs) currently or willing to get involved in supplementing MoH efforts in provision of food supplements to continue providing the service and can be engaged to help with OTPs
5. Door to door screening of children for malnutrition in disaster settings for the purpose of identifying those that need urgent food supplements must be done in conjunction with the DMMU while adhering to infection preventive measures

[33] Central Statistical Office [Zambia], Ministry of Health [Zambia], 2019

New-born Care

Recent data show that infants < 1 year of age have more severe disease than older children. Therefore, protecting these infants to the greatest extent possible is cardinal due to the high risk of severe disease[4].

Breast milk confers immunity and important nutrients throughout infancy and childhood. This protection is through both direct transfer of antibodies, anti-infective factors and long-lasting transfer of immunological competence and memory[5,6]. Therefore, it is highly recommended to give breast milk to infants with appropriate infection prevention and control (IPC) precautions[5,7]. The following provisions are proposed:

Mothers with suspected/patient under investigation (PUI), probable, or confirmed COVID-19:

1. Neonates to COVID-19+/PUI Mothers should be breastfed according to standard infant feeding guidelines, while applying necessary precautions for IPC[3,8,9]
2. Breastfeeding should be initiated within 1 hour of birth. Exclusive breastfeeding should continue for 6 months with introduction of correct, adequate and safe complementary foods at age 6 months. Breastfeeding should be continued up to 2 years or beyond[9]
3. Mothers not able to initiate breastfeeding during the first hours after delivery should still be supported to breastfeed as soon as they are able to e.g., those sedated from anaesthesia after delivery by caesarean section[10]
4. Skin-to-skin contact or kangaroo mother care (KMC) can be practised while observing standard, contact and airborne precautions i.e., hand and respiratory hygiene, routine cleaning and disinfecting of surfaces around[8]
5. Breastfeeding counselling, practical feeding support, basic psychosocial support should be provided by healthcare workers with the help of community-based volunteers[5,6]
6. Expressed breast milk with emphasis on appropriate IPC measures can be used when a mother with COVID-19 is severely ill or has other complications preventing breastfeeding[8]
7. If Mother with COVID-19 is very ill to breastfeed or express, appropriate breast milk substitutes should be used while following IPC[5,8,9]
8. Breast milk substitutes, feeding bottles and teats, pacifiers or dummies should be not promoted in any facilities[9]

9. Mothers and/or neonates who are COVID-19+/PUI should remain together and be allowed to practice skin- to-skin contact; kangaroo mother care and rooming-in throughout the day and night especially starting immediately after birth as it helps establish breastfeeding[5,8]
10. Disruption of breastfeeding during the stay in the health facilities/ at home should be highly discouraged. Mother should breastfeed for as much, as frequently, and as long as she wishes[5,8]
11. Parents and caregivers who may need to be separated from their infants should have access to appropriately trained health or non-health workers for mental health and psychosocial support[11]
12. All neonates of COVID 19+/PUI mothers needing admission to either the neonatal intensive care unit or neonatal wards should be isolated from other neonates[12]
13. No routine swabs are recommended immediately after birth unless or when neonate becomes symptomatic due to no demonstrable intrauterine transmission[1,2]. Incubation is 2-14 days
14. BCG, OPV_0 and Vitamin K can be administered according to normal schedule soon after birth[12]

A neonate can be separated from the mother in the following circumstances:

1. **COVID-19 positive mother who is critically ill and unable to breastfeed or express breast milk. The neonate will be placed in a separate room in NICU or nursery where they will receive alternative feeding options such as formula milk**
2. **When IPC standards will not be followed by COVID-19 positive mother when handling and breasting the neonate due to her mental state**

Care of Chronic Paediatric Conditions

Tuberculosis

There is paucity of evidence regarding COVID-19 and Tuberculosis in Children. Theoretically, there would be increased morbidity and mortality from comorbidity. The recommendation from the Paediatric Childhood TB group is for heightened IPC measures in presumptive TB as well as confirmed child TB cases. The following have been recommended for patients with TB:

1. It is critical to ensure that there are no TB or TB preventive therapy interruptions during the response to the COVID-19
2. children less than 5 years of age, the child should be reviewed monthly in the intensive phase and every two months in the continuation in the usual designated spaces
3. For children older than 5 years of age, during the intensive phase of TB treatment, caregivers should be dispensed with a two months' supply of ATT with scheduled return to the health facility for clinical assessment 8 weeks after TB treatment start
4. Where possible HCW's/Treatment Supporters should endeavour to call the client after 2 weeks of initiation to assess for side effects, treatment response and side effects
5. If bacteriologically confirmed and able to expectorate, then the patient should be given a container for sputum sample collection at month 2 to coincide with their clinical visit
6. The next clinical visit should be at month 4 at which point a sputum container is given to the client to be presented at month 6 at the last visit to declare an outcome
7. For a client, whose sputum sample comes out positive, the facility needs to make every effort to re-evaluate the patient in accordance with national paediatric TB guidelines
8. Results should be communicated by phone where possible to prevent unnecessary contact with the facility

Asthma

There is currently no evidence that people with Asthma have a higher chance of developing COVID-19. However, there is evidence that should patients with asthma develop COVID-19 the disease is more severe[1].

1. Asthma patients should continue taking all their prescribed medication including inhaled corticosteroids. For patients with acute severe exacerbation give the lowest possible dosages
2. Avoid the use of shared nebulizers to reduce the risk spread of COVID-19[34]
3. Metered dose inhaler via spacers is preferred during severe acute attacks
4. Should you need to nebulize a suspected/probable or confirmed case of COVID-19 optimise IPC measures including N95 masks as it is aerosol generating. This should be done in a well-ventilated room

Renal

Renal patients currently offer a unique problem in that they may require prolonged in-hospital management, and some may be vulnerable to infection as they may be on immunosuppressant drugs. The following are the recommendations in the care of renal patients:

1. All staff and caregivers on renal wards should be in masks and scale up on handwashing as routine
2. Patients on Continuous Abdominal Peritoneal Dialysis (CAPD) will continue home based dialysis with intermittent reviews
3. Patients on immunosuppressant drugs should have fewer scheduled hospital visits and practice social distancing
4. Referrals to specialised renal units should consult respective renal units (especially for non-emergency cases)

Diabetes Mellitus

People with pre-existing medical conditions such as poorly controlled diabetes appear to be more vulnerable to becoming severely ill with this viral infection. There is no reliable data suggesting that children with well-managed endocrine conditions (including type 1 diabetes mellitus) are at increased risk of getting infected or becoming severely ill with coronavirus. Also, it is encouraging to know that the coronavirus illness generally has a milder course in children *(European Society for Paediatric Endocrinology (ESPE)).* The guidance for patients living with diabetes mellitus is:

[34] *Global Initiative for Asthma - GINA*, March, 2020

1. Three monthly reviews. Frequent reviews should be discouraged
2. For patients with poor glycaemic control/other concerns more regular follow up can be done by phone
3. Sugar Dairies are encouraged
4. Three months stock of insulin and hypoglycemic drugs and proper storage should be emphasised. Those without proper storage caregivers should collect on monthly

Cardiac

Most of the children with structural cardiac disease in Zambia have unrepaired lesions and are on medical Treatment. Acknowledging the paucity of data, there is concern that this population has a high risk for severe disease with COVID-19 infection. Given the potential risk for severe disease. The following are the country context specific recommendations:

1. Improve access to anti-failure drugs and benzathine prophylaxis at local clinics
2. Tele reviews 3 to 6 monthly at the discretion of the attending clinician
3. Post-op patients stable on no medication may be reviewed every 1-2 years
4. Patients acutely unwell must be encouraged to seek medical help at the hospital because of anticipated rapid deterioration that may require cardiorespiratory support
5. Encourage parents of these children to observe strict physical distancing and to wear masks when movements must be made

Sickle Cell Disease and Thalassaemia

Patients with sickle cell disease are in more frequent contact with the hospital than other individuals because of the need for emergency care and preventive visits. The guidance for patients suffering from sickle cell disease is as follows:

1. Continue treatment and prevention care at the health facility in the emergency department
2. Stable patients requiring drug refills can obtain prescriptions and make short consultation at the designated out-patient clinic
3. In patients with symptoms of cough, fever, fatigue or other symptoms suggestive of an acute respiratory illness, test for COVID-19 along with other respiratory viral pathogen
4. A CXR for all sickle cell disease and thalassaemia patients who have respiratory symptoms should be obtained. In addition, a CXR should be obtained for sickle cell disease patients who are admitted for a vaso-occlusive crisis
5. If COVID-19 is present or infiltrates present on CXR suggestive of ACS in SCD, patients should be admitted to intensive care and managed according to national and international guidelines for addressing ACS

6. Likewise, for infected with COVID-19 thalassaemia patients, arrangements for admission to the intensive care should be made and close monitoring both by the intensive unit medical staff and the patients' treating physician should be established
7. Management of ASC in SCD Patients Infected with COVID-19 includes:
    - Early exchange transfusion and
    - Broad spectrum antibiotics – include MRSA coverage, atypical pneumococcus

Aplastic anaemia

All patients with Aplastic anaemia have impairment in the bone marrow's ability to produce blood cells. This renders them vulnerable to viral, fungal and bacterial infections which can trigger serious and life-threatening sepsis. If infected by the virus patients may also develop secondary bacterial infections. Patients may require:

1. Frequent red and platelet transfusion which are currently in short supply.
2. Therapy may include steroids or immunosuppressive cytotoxic drugs which may further suppress the immunity

Haemophilia

Haemophilia is a condition characterised by a deficiency of coagulation factors 8 and 9, resulting in a tendency to bleed in body cavities. This does not increase susceptibility to contracting the virus. Like sickle cell disease patients, they are in more frequent contact with the hospital than other individuals because of the need for emergency care and preventive visits for their bleeding tendencies requiring urgent or weekly coagulation factor infusion. Patients may require:

1. Plasma transfusion in some emergency situations
2. We are facing a critical shortage in transfusion blood supply as donation rates are down in these times
3. Continued emergency and prevention treatment care at the health facilities

Immune Thrombocytopenic Purpura

Immune disorder characterised by thrombocytopenia resulting in bleeding of varying degrees. Patients with this condition require blood transfusion as supportive therapy. Treatment includes long-term steroid therapy which may predispose to immunosuppression and increased susceptibility to infection.

Chapter 6: Home Care of Patients with COVID-19

According to WHO guidelines, home care should be considered for an adult or child with confirmed or suspected COVID-19 with mild or moderate symptoms when inpatient care is unavailable or unsafe (e.g., when capacity is insufficient to meet the demand for health-care services).

Hospitalisation may not be required for those with **mild disease**, unless there is concern for rapid deterioration. If hospitalisation is not medically necessary, and there is limited capacity in healthcare systems, home care is preferable if the individual's home situation allows. Patients who have been discharged from hospital may also be cared for at home.

The decision as to whether to isolate and care for an infected person at home depends on the following three factors:

1. Clinical evaluation of the COVID-19 patient
2. Evaluation of the home setting and
3. The ability of the home carer to monitor the clinical evolution of a person with COVID-19

Clinical Evaluation

To qualify for home isolation and care the client should meet **ALL** the following criteria:

1. Clinical presentation – should be asymptomatic or mild disease
2. Should **not** require hospital care, such as close monitoring or nursing care
3. Should **not** have any risk factors for severe disease (i.e., age (> 50 years), smoking, obesity and non-communicable diseases such as cardiovascular disease, diabetes mellitus, chronic lung disease, chronic kidney disease, immunosuppression and cancer)

Once the client meets the above criteria, the following two requirements should be fulfilled in the home setting:

A. Conditions for implementing appropriate IPC as outlined in the appendix are met;
B. Close monitoring for any signs or symptoms of deterioration in their health status by a trained health worker is feasible

These two requirements also apply for special populations such as pregnant and postpartum women and children. It is also necessary to ensure adequate provisions for appropriate PPE for both patients and caregivers.

Evaluation of the Home Setting

1. The patient should have at least one adult caregiver available to support them. A "caregiver" refers to parents, spouses and other family members or friends providing informal care as opposed to the care provided by formal health-care providers
2. The house should have at least one separate well-ventilated room that can be spared or made available to isolate the client especially from other vulnerable household members (e.g., those over 50)
3. The home should be easily within reach of a designated health facility in case the patient's condition deteriorates
4. The family should have means to call a designated/named health professional in case the client deteriorates
5. The family should have the means to reach a health facility quickly, preferably in less than 30 minutes, should the condition of the client deteriorate
6. The family/household should have access to the appropriate type and amount of PPE in order to ensure IPC. The patient and family members should be instructed to wear masks in the house to reduce new transmission
7. The family should have access to water and sanitation, as well as resources for cleaning, disinfecting and general hygiene

Ability to Monitor the Clinical Evolution of a Patient with COVID-19 at Home

1. Daily home-based care can be provided by trained Healthcare Workers, trained community or outreach workers, where resources are available. This can be done by phone/telemedicine with the consent of the patient
2. The monitoring team should establish functional communication link with the patient until symptoms resolve and at least 10 days after receipt of a positive COVID-19 test result
3. The monitoring team should provide the caregiver and patient with adequate information to care for the client including IPC and information on when to seek professional care
4. The monitoring team should provide the caregiver and patient with a daily symptom check sheet which tracks fever, respiratory rate etc. This sheet should include symptoms that should trigger the client to seek professional health care
5. The monitoring team should provide the required supportive medications such as Paracetamol, Vitamin C, lozenges and any dietary and hygiene advice

IPC Considerations for Home Care

1. Patient should be placed in a well-ventilated single room (i.e., open window and door)
2. Limit the movement of the patient to shared spaces e.g., kitchen, bathroom, etc.
3. Family members should maintain a physical distance of at least 1m apart from the patient
4. Limit the number of caregivers to the patient (identify 1 person to care for the patient)
5. Perform hand hygiene at all times; use soap and water and avoid the use of same towels
6. The patient should wear a medical mask at all times which should be properly discarded. If medical masks are unavailable, a cloth mask may be used
7. The caregiver should wear a well fitted medical mask covering both nostrils and mouth while caring for the patient. Disposable masks should not be reused. Masks should be discarded if they become wet or soiled
8. Avoid direct contact with body fluids particularly oral and respiratory secretions and stool
9. Use disposable gloves when caring for infected persons. Do not reuse gloves
10. Use dedicated linen and utensils for the patient, and reusable utensils may be re-used after proper disinfection and washing
11. Clean and disinfect frequently touched surfaces throughout the patients care space. Use regular household soap and then disinfect with household sodium hypochlorite 0.5%
12. Clean and disinfect commonly used areas e.g., bedroom, bathroom with emphasis on commonly touched things like door handles at least twice daily
13. Use gloves, and protective clothing e.g., aprons when attending to the infected patient at all times
14. Waste generated when caring for the patient should be placed in a separate bin and covered with a lid
15. HCW home assessment should select appropriate PPEs

Discontinuation of Isolation and Infection Prevention Measures

Persons with COVID-19 who have symptoms under home care can discontinue isolation if they have:

- At least 7 days from symptom onset **and**
- At least 24 hours since resolution of fever without the use of fever-reducing medications and other symptoms have improved

Persons infected with SARS-CoV-2 who never develop COVID-19 symptoms (i.e., asymptomatic) may discontinue isolation and other precautions 7 days after the date of their first positive PCR test.

Management of a Household Member who falls ill

1. The person should inform the designated Healthcare Provider when they fall ill
2. Notify the receiving health facility that a symptomatic contact of a confirmed case will be coming to their facility
3. During transportation, the person should wear the medical mask at all times. If medical mask is unavailable, a cloth mask may be used
4. Should avoid public transport. Use personal vehicle, taxi, or designated district transportation. If this is unavailable, use an ambulance
5. Disinfect any surfaces soiled with respiratory secretions and other body fluids during transportation with diluted bleach at 0.5%

All household members should be advised to monitor their health including temperature for 14 days from the last day of possible contact with the person with a confirmed COVID-19

Over-the-Counter Medicines (in Mild Cases)

- Antipyretics – Paracetamol 1g q6-8h
- Avoid Aspirin in children less than 12yrs
- Sore throat – Lozenges
- Cough – Cough suppressants, mucolytics, and expectorants alone or in combination
- Nasal congestion – Antihistamines and/or decongestants
- Should be assessed at the nearest facility for eligibility for oral antivirals

Table 18: Checklist to Evaluate Preparedness for Home-based Care for COVID-19 Patients

A	Clinical evaluation	Yes	No
	Does the patient have moderate, severe, or critical disease?		
	Does the patient require hospital care, such as close monitoring or nursing care?		
	Does the patient have any of the following risk factors for severe disease: ● Age above 50 years ● individuals not fully vaccinated against COVID-19 ● HIV positive individuals ● Other immunosuppression such as Chronic Steroid Use ● Cancer ● Diabetes ● Hypertension ● Heart Conditions ● Obesity or overweight (BMI >25 kg/m^2) ● Pregnancy ● Chronic Lung, Kidney or Liver Disease ● Tuberculosis ● Neurological and psychiatric conditions ● Current smoking and substance use disorders ● Patients dependent on medically related devices such as tracheostomy tubes, urinary catheters, intracardiac devices, nasogastric feeding tubes, extraventricular drainage devices, etc		
	If you answer 'yes' to any other questions in this section, then the patient is recommended for assessment at the facility for eligibility of oral antivirals		
B	**Follow-up and clinical monitoring**	**Yes**	**No**
	Is there a functional communication link between the health facility and the patient until symptoms resolve and at least 10 days after receipt of a positive COVID-19 test result?		
	Have the healthcare workers provided the caregiver and patient with adequate information on care for the client including IPC and information on when to seek professional care?		

	Have the healthcare workers informed the caregiver and patient of the daily symptoms to check e.g., fever, saturations, blood pressure, respiratory rate etc.? The patient should know when to be triggered to seek further professional health care		
	If you answer 'no' to any of the questions in this section, ensure you put corrective measures then re-evaluate. Ensure a functional communication link is established and adequate information on IPC and symptom check is given to patients and caregivers		
C	**Evaluation of the Home Setting**	**Yes**	**No**
	Does the patient have at least one adult caregiver available to support them?		
	Does the house have at least one separate well-ventilated room that can be spared or made available to isolate the client especially from other vulnerable household members (e.g., those over 50)?		
	Is the home within reach of a designated health facility in case the patient's condition deteriorates?		
	Does the family have the means to reach a health facility quickly, preferably in less than 30 minutes, should the condition of the client deteriorate?		
	Does the family/household have access to the appropriate type and amount of PPE to ensure IPC?		
	Does the household have access to water and sanitation, as well as resources for cleaning, disinfecting and general hygiene?		
	If you answer 'no' to any of the questions in this section, provide the necessary support to the patient and the household		

Chapter 7: Special Clinical Considerations for Caring for PLHIV during the COVID-19 Outbreak

Evidence has shown that the clinical course of COVID-19 among PLHIV is similar to those without, when the patient is well stable on ART with a good immune status. However, COVID-19 Outcomes for those with advanced HIV disease are usually more severe. To optimise outcomes for both illnesses, it is essential for HIV service providers to adhere to national and WHO guidelines for COVID-19.

The measures below can help ensure high quality care for Recipients of Care (RsOC) as more information becomes available:

1. Ensure RsOC are provided with 6 months' Multi-month Dispensing (6MMD) (if eligible by MoH Zambia Consolidated Guidelines) – where 6MMD is not feasible (e.g., due to low stock levels) provide a minimum of 3MMD. Ensure children and adolescent RsOC are also provided the appropriate MMD according to national guidelines
2. Ensure VL is collected prior to providing 6MMD if the result is more than 6 months old
3. Ensure cervical cancer screening is provided to the RsOC prior to dispensing 6MMD whenever eligible
4. Verify that all eligible RsOC have received their COVID-19 vaccine and update SmartCare accordingly
5. Stagger ART Clinic appointments (time/hour blocks) to reduce congestion
6. Where feasible, RsOC can have their ART delivered to them at home or they can send a well buddy to collect on their behalf
7. Ensure all RsOC are given the Health Facility's (HF) phone number (ART Clinic phone number should be clearly displayed) so that RsOC can easily contact the HF e.g., to plan for collection/delivery of medication
8. All RsOC and HCWs who develop respiratory symptoms or flu-like symptoms (fever ≥38ºC + cough) should follow the MoH guidance for seeking care
9. Triage any ROC or HCWs who are unwell (flu-like/ respiratory symptoms) to be seen first and provide them with a face mask immediately upon arrival
10. All RsOC and HCWs in the ART clinic should wear a face mask for the duration of the clinic visit
11. If a ROC or Healthcare Provider with suspected, probable or confirmed COVID-19 infection has to come to the HF, he/she should call ahead to notify the ART In-charge,

so that they are aware and able to immediately separate the patient from other patients and immediately place a face mask on them

1. Adhere to MoH guidelines for prevention of COVID-19, including:
    a. All HCWs who are unwell/ill with respiratory symptoms or flu-like symptoms should be assessed for COVID-19 and depending on the risk be referred for either home or facility isolation awaiting confirmation
    b. All HCW with suspected or confirmed COVID-19 (with mild to moderate disease) may return to work if the following criteria is met:
        i. At least 7 days have passed since symptoms first appeared AND
        ii. At least 24 hours have passed since recovery defined as resolution of fever (without the use of antipyretics) and improvement in symptoms (e.g., cough, shortness of breath)
        iii. If HCW has COVID-19 ruled out and has an alternate diagnosis (e.g., tested positive for influenza), criteria for return to work should be based on that diagnosis
    c. HCWs and RsOC should practice frequent hand hygiene, including
        i. Before and after patient care
        ii. When coming into contact with secretions
        iii. Before eating and after using the toilet

To facilitate this, Health facilities must ensure access to clean water and soap for hand washing (at least 20 seconds) or provide adequate supply of ≥60% alcohol-based sanitizer (NOTE: sanitizer can be made by HF staff once provided with necessary ingredients)

2. Healthcare Providers should use the necessary PPE for all staff e.g., gloves and face masks. If a ROC is suspected of having COVID-19, a gown and goggles should be used in addition to gloves and medical face mask (where feasible). Face mask and gloves are most important PPEs
3. Maintain infection prevention standards in the HIV clinics by sanitising all surfaces e.g., with Hypochlorite per MoH guidelines

Inform MoH, relevant authorities and the district health office in case of any suspected COVID-19 case in ART patients. Documenting the clinical course of COVID-19 in PLHIV is important to inform optimal care

Chapter 8: Short and Long-term Rehabilitation Considerations for COVID-19 Afflicted Individuals

Cases of COVID-19 have been associated with rehabilitation needs related to the consequences of ventilatory support, and prolonged immobilisation and bed rest

Clinical follow up may be necessary even after a relatively mild COVID-19 illness and may present with non-specific symptoms such as fatigue and muscle aches

Post-acute COVID-19 extends beyond the first 3 weeks of the initial symptoms while chronic COVID-19 is the period beyond 12 weeks from onset of the initial symptoms. Long COVID-19 is a term commonly used to describe symptoms that persist after the initial COVID-19 illness

For severe COVID-19 long term sequelae include impaired lung function; physical deconditioning and muscle weakness; delirium and other cognitive impairments; impaired swallow and communication; and mental health disorders and psychosocial support needs.

MoH recommends that all facilities set up clinics and appropriate referrals for the care of patients in the post-acute COVID-19 period. Due to the possibility of false negatives, patients meeting criteria must still be included in this category despite lack of a positive SARS-CoV-2 result

While a few may be required in-person, consideration must be made to set up telephonic and telemedicine reviews for this population as self-management is an option for these patients, a multi-disciplinary and holistic approach is cardinal in the management of patients in the post-acute COVID-19 period. *See Table 11*. Counselling of patients on a possibly prolonged and gradual return to usual health may alleviate the anxiety that comes with this experience.

Comprehensive Mental Health Care for Patients with COVID-19

Although mental health symptoms are common in COVID-19, a diagnosis of mental health disorder should be considered upon thorough assessment and ruling out all physical causes. Furthermore, a mental health diagnosis should be made in consultation with a mental health specialist as COVID-19 has been and continues to be a stress-inducing epidemic that predisposes to normal distress responses in people. Common psychological and behavioural responses include distress reactions (insomnia, anxiety, decreased perception of safety, anger and increased presentation to healthcare due to fears of illness), health risk behaviours (increased use of alcohol and tobacco, altered work/life balance, social isolation, increased family conflict, and violence). Children and adolescents may also become

distressed, which can manifest in “misbehaviours”, social isolation, or diminished academic performance.

A minority of individuals will develop disorders, such as depression, anxiety, or posttraumatic stress, that require formal treatment. During the COVID-19 outbreak, most patients with pre-existing mental health conditions will manage adequately with tailored support and some may improve their functioning in the face of the challenges and needs of others. However, healthcare workers are likely to encounter some patients who have increased emotional distress resulting from the outbreak’s impact on them, their families, and their communities.

Good communication skills and addressing uncertainty is of paramount importance for patient care not just for patients but for caregivers of patients as well. Healthcare workers should:

1. Acknowledge concerns and uncertainty about emerging diseases,
2. Share medical knowledge that is accurate and timely, and
3. Identify steps the patient can take to reduce distress and sustain normal health behaviours, particularly sleep

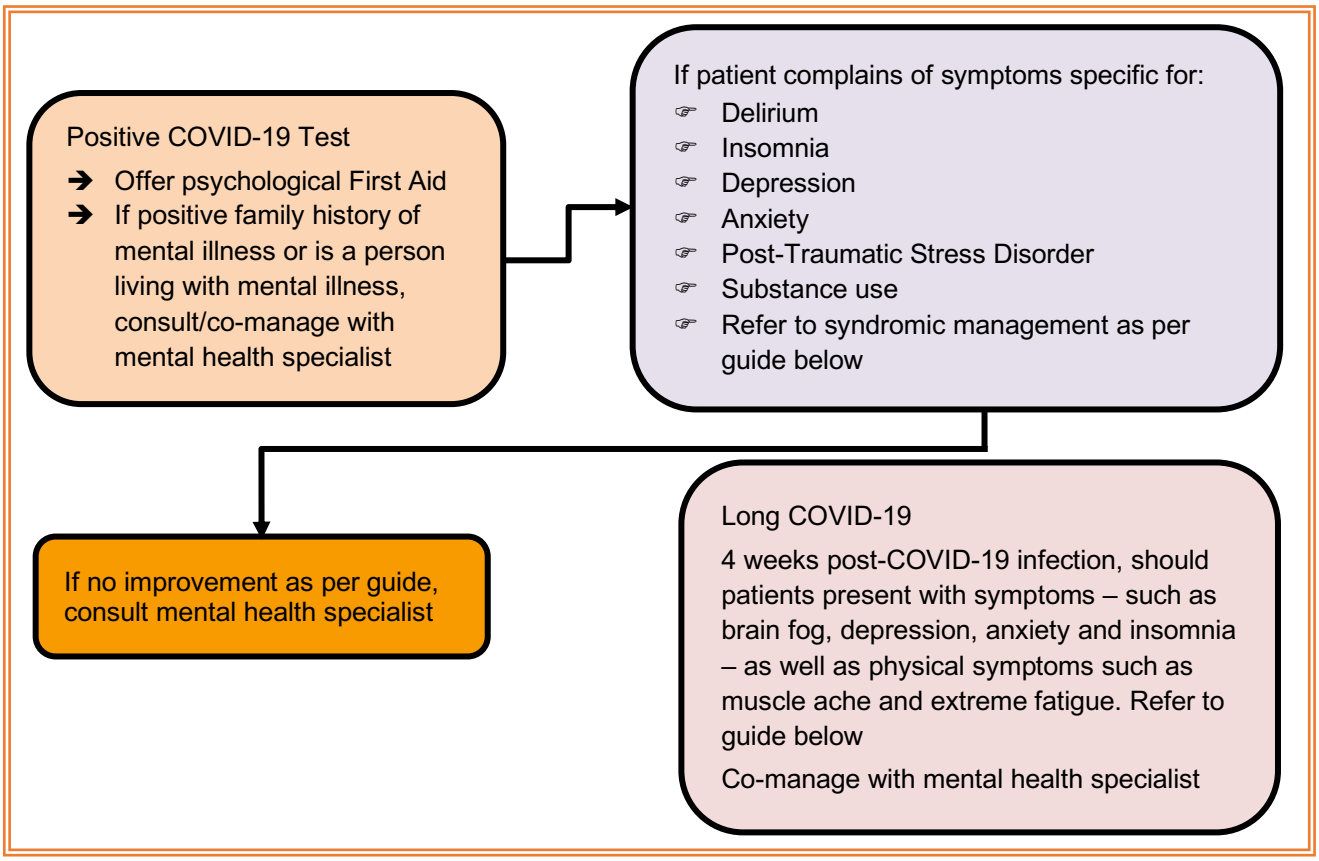


Figure 17: Flow Chart for Mental Health Assessment for COVID-19 Positive Cases

Common syndromic support and management for mental health symptoms specific for adults. The guide is not exhaustive and consultation with mental health specialists is recommended for a thorough management plan. For further reference on disorder-specific management, refer to the 2022 Zambia Mental Health Treatment Guidelines.

Delirium

Presenting complaints

- Families may request help because the patient is confused or agitated
- Delirium may occur in patients hospitalized for physical conditions such as urea and electrolyte imbalance, hypoxia, and hypoglycaemia
- Patients may appear uncooperative or fearful

Diagnostic Features

Acute onset of:

- Confusion (patient appears confused and struggles to understand surroundings)
- Clouded thinking or awareness
- Often accompanied by:
    - Poor memory
    - Agitation
    - Disturbed sleep (Reversal of sleep pattern)
    - Emotional Upset
    - Loss of Orientation
    - Hearing voices
    - Wandering attention
    - Suspiciousness
    - Visions of illusions
    - Withdrawal from others
- Symptoms often develop rapidly and may change from hour to hour
- May occur in patients with previously normal mental function or in those with dementia. Milder stresses (medication, mild infections) may cause delirium in older patients or those with dementia.

Differential Diagnosis

Identify and correct possible physical causes of confusion, such as:

- Alcohol intoxication or withdrawal
- Drug intoxication or withdrawal
- Severe infection
- Metabolic changes (e.g., liver disease, dehydration, hypoglycaemia)
- Head trauma
- Hypoxia

If symptoms persist, delusions and disordered thinking predominate, and no physical cause is identified, consult mental health specialist.

Essential Information for patient and family

- Strange behaviour or speech are symptoms of an illness
- Take measures to prevent the patient from harming him/herself or others (e.g., remove unsafe objects)
- Supportive contract with familiar people can reduce confusion
- Provide frequent reminders of time and place to reduce confusion
- In-patient care may be required because of agitation or because of physical illness which is causing delirium

Medication

- Avoid use of sedative or hypnotic medications (e.g., benzodiazepines) except for the treatment of alcohol or sedative withdrawal
- Antipsychotic medication in low doses (e.g., haloperidol low dose at 1mg to 2.5mg max 5mg once or twice a day, Risperidone 1mg once a day or Olanzapine 2.5mg once a day) may sometimes be needed to control agitation, psychiatric symptoms or aggression
- Beware of drug side-effects (parkinsonian symptoms, anticholinergic effects) and drug interactions

Consider specialist consultation for:

- Physical illness requiring specialist treatment.
- Uncontrolled agitation in 24 to 48 hours with a psychiatrist.

Sleep Problems, Insomnia

Presenting complaints

Patients are distressed and sometimes disabled by the daytime effects of poor sleep.

Diagnostic Features

- Difficulty falling asleep
- Restless or unrefreshing sleep
- Frequent or prolonged periods of wakefulness

Differential Diagnosis

- Short-term sleep problems may result from stressful life events, acute physical illness or change in sleep schedule. Persistent sleep problems may indicate another cause:
    - If low, sad or irritable mood, and loss of interest in activities are prominent, see Depression
    - If daytime anxiety is prominent, see anxiety
- Sleep problems can be a presenting complaint of alcohol or substance abuse. Enquire about current substance use
- Consider medical conditions which may cause insomnia. (e.g., heart failure and chronic physical conditions)
- If the patient snores loudly while asleep, consider sleep apnoea. It will be helpful to take a history from a family member. Patients with sleep apnoea often complain of daytime sleepiness but are unaware of night-time awakenings

Essential Information for patient and family

- Temporary sleep problems are common at times of stress or physical illness
- The normal amount of sleep varies widely and usually decreases with age. Average hours of sleep are between 6.5 – 8 hours in a night
- Improvement of sleeping habits (not sedative medication) is the best treatment ie sleep hygiene
- Keeping to regular hours for going to bed and getting up in the morning, trying not to vary the schedule or “sleep in” on the weekend
- Getting up at the regular time even if the previous night’s sleep was poor
- Daytime naps to not exceed beyond 45 minutes to 1 hour. Avoid daytime naps as they can disturb the next night’s sleep
- Recommend relaxation exercises (Appendix 1) to help the patient to fall asleep
- Worry about not being able to sleep

- Alcohol may help a person to fall asleep but can lead to restless sleep and early awakening
- Stimulants (including coffee and tea) can cause or worsen insomnia
- Daytime exercise can help the patient to sleep regularly, but evening exercise may contribute to insomnia

Medication

- Hypnotic medication should not be prescribed without consultation with mental health specialist. Risk of dependence increases significantly after 14 days of use. Avoid hypnotic medication in cases of chronic insomnia
- Treat underlying psychiatric or physical condition
- Make changes to medication, as appropriate

Consider consultation:

- If more complex sleep disorders (e.g., narcolepsy, sleep apnoea) are suspected
- If significant insomnia continues despite measures above

Depression

Presenting complaints

- The patient may present initially with one or more physical symptoms (fatigue, headache, pain). Further enquiry will reveal depression or loss of interest
- Irritability is sometimes the presenting symptom
- Some groups are at a higher risk (e.g., those who have recently given birth or had a stroke or those with neurocognitive decline)

Diagnostic Features

- Low or sad mood
- Loss of interest in usual activities (withdrawal or inactivity)
- The following associated symptoms are frequently present:

• Disturbed sleep	• Poor concentration	• Guilt or low self-worth
• Disturbed appetite	• Agitation or slowing of activity	• Loss of energy
• Decreased libido	• Self-harm thoughts or acts	• Fatigue

Symptoms of anxiety or nervousness are also frequently present

Symptoms should be present for more than 14 days or severe in intensity that renders the patient inactive (unable to perform routine day-to-day activities)

Differential Diagnosis

- Some medications may produce symptoms of depression (e.g., beta-blockers, other antihypertensive, H2 blockers, oral contraceptives, corticosteroids)
- If the patient has a history of manic episodes (excitement, elevated mood, rapid speech), they may have bipolar mood disorder
- If hallucinations (hearing voices, seeing visions) or delusions (false fixed, unusual beliefs contrary to evidence) are present, consult mental health specialist
- If heavy alcohol use is present, see substance use, alcohol use disorder

Essential Counselling for patient and family

- Clinical Depression is common and effective support and treatments are available.
- Depression in not a weakness or laziness; patients are trying hard to cope
- Plan short term non-strenuous activities which are tailored to the patient's enjoyment or build confidence
- Encourage the patient through engagement to resist pessimism and self-criticism, not to act on pessimistic ideas (e.g., giving up on personal goals), and not to concentrate on unhelpful or guilty thoughts
- If physical symptoms are present, discuss link between physical symptoms, stress, and mood

Medication

- Consider antidepressant drugs if sad or loss of interest are prominent for at least two weeks and four or more of these symptoms are present:

• Loss of energy	• Poor concentration	• Guilt or low self-worth
• Disturbed appetite	• Loss of energy	• Self-harm thoughts or acts
• Decreased libido	• Agitation or slowing of activity	• Disturbed sleep

- In severe cases (Appendix 2 PHQ 9 Scoring tool), consider medication at the first review. In moderate cases, consider medication if counselling is not sufficiently helpful
- Build up to the effective dose. (e.g., Fluoxetine 10mg titrated to 20mg in the morning once a day over a period of 3 weeks, to be maintained for 3 months). Lower doses should be given if the patient is older or physically ill
- Explain to the patient that the medication must be taken every day, that improvement will build up over 2 to 3 weeks, and that mild side-effect (nausea, insomnia, and nervousness) may occur but usually fade in 7-10 days
- Advise patient always to check with health care worker before stopping the medication

- Continue antidepressant medication for at least 3 months after the condition improves

Specialist Consultation

- Consider consultation if the patient shows significant risk of harm to self or other, or if psychotic symptoms are present
- Ask about risk of self-harm (suicide intent) and risk of harm to others. Has the patient often thought of death or dying? Does the patient have a specific suicide plan? Has he/she made suicide attempts in the past? Can the patient be sure not to act on the suicidal plans? Close supervision by family or friends, or in-patient cate may be needed. Co-manage with mental health specialist
- If significant depression persists, consider consultation about other therapies. More intensive psychotherapies (e.g., cognitive behavioural therapy, interpersonal therapy, mindfulness activities, acceptance, and commitment therapy) may be useful for treatment of acute cases and prevention of relapse

Anxiety

Presenting complaints

The patient may present initially with tension-related physical symptoms (e.g., headache, pounding heart). Enquiry (Appendix 12) will reveal prominent anxiety.

Diagnostic Features

- Fear, uncertainty, and overwhelming feeling or worry (exaggerated worry, inability to relax), often accompanied by multiple symptoms of anxiety or tension
- Mental tension (Worry, feeling tense or nervousness, Poor concentration)
- Physical tension (Restlessness, Headaches, Tremors, Inability to relax)
- Physical arousal (Dizziness, Sweating, Fast or pounding heart, dry mouth, stomach pains)
- Symptoms may last for months and recur often, there are often triggered by stressful events in those with chronic worry
- Episodes may occur as sudden attacks of anxiety or fear
- Some patients may have extreme fear of specific situations. Common feared situations include: Leaving home, crowds, social events, buses or high foot traffic areas such markets, religious gatherings, school etc. Patients may be unable to be alone in these situations or may avoid them altogether

Differential Diagnosis

- If low, sad or irritable mood is predominant, see depression
- If heavy alcohol use or drug use present is present, see substance use, alcohol use disorder
- If sudden attacks of unprovoked anxiety are present, consider panic attack
- Certain physical conditions (thyrotoxicosis) or medications (beta agonists) may cause anxiety symptoms

Essential Counselling for patient and family

- Stress and worry have both physical and mental effects
- Learning skills to reduce the effects of stress (not sedative medication) is the most effective relief
- Anxiety often produces frightening physical symptoms. Chest pain, dizziness, or shortness of breath are not necessarily signs of a physical illness
- Avoiding feared situations allows the fear to grow stronger: gradually exposing and confronting to these situations will reduce the fear
- Encourage patient to practice relaxation methods such as deep muscle relaxation (Appendix12) to reduce physical symptoms of anxiety
- Identify exaggerated fears which occur with anxiety (e.g., patient feels a pounding heart and fears that they are having a heart attack)
- Discuss ways to challenge these fears when they occur (e.g., patients remind themselves “I am not having a heart attack. This is a panic attack, and it will pass in a few minutes”)
- For specific phobias, co-manage with mental health specialist though gradual exposure therapy
- Do not use alcohol or drugs to help cope with feared situation

Medication

- Medication is not frequently prescribed for anxiety unless the symptom intensity is severe (Appendix 12 GAD 7 Tool). With tailored psychotherapy, many patients will be able to deal with anxiety without medication
- If panic attacks are frequent (more than 2-3 attacks in a week) or if the patient is also depressed, antidepressants may be helpful. Consult mental health specialists
- For patients with more severe anxiety, short term use of antianxiety medication may be helpful. Regular use may lead to dependence with symptoms returning when the medication is discontinued

Specialist Consultation

- Consultation may be helpful if sever anxiety lasts longer than 3 months
- If significant anxiety persists, consider consultation about other therapies. More intensive psychotherapies (e.g., cognitive behavioural therapy, exposure therapy, interpersonal therapy, acceptance, and commitment therapy) may be useful for treatment of cases and prevention of relapse

Substance Use

For the purpose of the guide, we will focus on Alcohol Use Disorder. Look out for signs and symptoms of delirium tremens which is a medical emergency and treat immediately.

Presenting complaints:

- Depressed mood
- Nervousness
- Insomnia
- Physical complications of alcohol use (ulcer, gastritis, liver disease)
- Accidents or injuries due to alcohol use
- Poor memory or concentration
- There may also be:
    - Legal and social problems due to alcohol use (marital problems, missed work)
    - Signs of alcohol withdrawal (sweating, tremors, morning sickness, hallucinations)
- Patients may sometimes deny or be unaware of alcohol problems. Family may request help before patient does (e.g., because patient is irritable at home, missing work)

Diagnostic Features

- Heavy Alcohol use, quantity defined by using over 21 drinks per week for men, over 14 drinks per week in women for lagers and beers
- Overuse of alcohol has caused physical harm (e.g., liver disease, gastrointestinal bleeding), psychological harm (e.g., depression or anxiety due to alcohol) or has led to harmful social consequences (e.g., loss of job)
- Alcohol Dependence (Continued alcohol use despite harm, Difficulty controlling alcohol use, Strong desire to use alcohol)
- Tolerance (drinks large amounts of alcohol without appearing intoxicated)
- Withdrawal (anxiety, tremors, sweating after stopping drinking)

Differential Diagnosis

- Symptoms of anxiety or depression may occur with heavy alcohol use. If these continue after a period of abstinence, see depression

Essential Counselling for patient and family

- Alcohol dependence is an illness with serious consequences
- Stopping or reducing alcohol use will bring mental and physical benefits
- Drinking during pregnancy can harm the baby
- In some cases of harmful alcohol use without dependence, controlled or reduced drinking is a reasonable goal
- For patients with alcohol dependence, abstinence from alcohol is the goal, however this may not be an immediate target that may be achieved. Because abrupt abstinence can cause withdrawal symptoms, medical supervision is necessary
- Relapses are common. Controlling, responsible drinking habits or stopping drinking often requires several attempts
- For patients willing to stop:
    - Set a definite date to quit by enrolling in motivational interviewing through a mental health specialist (e.g., Psychologist or psychiatric nurse)
- If reducing drinking is a reasonable goal (or if patient is not ready/does not wish to quit)
    - Negotiate a clear goal for decreased use (e.g., no more than one drink per day with two alcohol-free days per week)
    - Discuss strategies to avoid or cope with high-risk situations (e.g., social situations, stressful events)
    - Introduce self-monitoring procedures and safer drinking behaviour also known as responsible drinking habits (e.g., time restrictions, slowing down drinking, eating a meal before drinking, drinking water between alcohol use)

For patients not willing to stop or reduce use now

- Do not reject or blame
- Clearly point out medical, psychological and social problems caused by alcohol
- Make a future review to reassess health or link with mental health specialist for motivational interviewing on alcohol use

For patients who do not succeed or relapse

- Identify and give credit for any success
- Discuss situations which led to relapse
- Return to earlier steps above
- Link to Mental Health Specialist

Medication and Treatment guide

- Titrate benzodiazepines from high dose to low dose as per body mass index and nutrition status of patient. Refer to Zambia Mental Health Treatment 2022, guidelines
- Do not prescribe antipsychotics or antiepileptic medications

Table 19: Guide on Urgent Management for Alcohol Withdrawal

Treat 1st Measure, Stabilise and Monitor Vitals
- Treat Hypoglycemia
- Hypothermia

Treat 2nd Adminitser Fluids
- Rule: Dextrose Normal Saline =/- Ringers Lactate
- Calculate based on patient profile

Treat 3rd Correct U & E imbalance
- Micronutrients
- Thiamine (wait till glucose levels are corrected before administering thimaine)

Specialist Consultation: Septic screen investigation

Table 20: Multidisciplinary Approach to Management of COVID-19 Sequelae

Issues	Home/self-management	Medical management	Consult service/or Referrals
Extreme fatigue	Rest and relaxation	Listening and empathy	Physiotherapy, rheumatology
Easy fatigability on exertion	Self-pacing and gradual increase in exercise	Listening and empathy	Physiotherapy, rheumatology
Low grade Fever		Paracetamol only consider antibiotics if secondary bacterial infection suspected	Infectious Diseases
Muscle fatigue	Self-pacing and gradual increase in exercise		Physiotherapy, rheumatology
Inability to concentrate		Listening and empathy	Psychiatry/mental health unit
Memory lapses		Listening and empathy	Psychiatry/mental health unit
Changes in mood		Listening and empathy	Psychiatry /mental health unit
Difficulties in sleep	Attention to general health		Psychiatry/mental health unit
Headaches		Listening and empathy	Neurology, psychiatry
Needle pains in arms and legs		Listening and empathy	Neurology
Diarrhoea and vomiting	ORS	IVFs	Physician Gastroenterology
Erectile dysfunction		Listening and empathy, optimise control of underlying conditions	Endocrinology, urology
Focal weakness suggestive of stroke			Neurology
Polyurea			Neurology, endocrinology
Persistent Loss of taste and smell			Neurology, ENT
Sore throat and throat discomfort			ENT
Chest pains			Pulmonology, cardiology, infectious diseases
Shortness of breath	Daily pulse oximetry		Pulmonology and respiratory rehabilitation service, infectious diseases
Palpitations			Cardiology, pulmonology
DM and hyperglycaemia	Diet, attention to general health	Optimise control while avoiding hypoglycaemia	Endocrinology, Physician
Chronic Hypertension and new onset hypertension	Diet, attention to general health	Optimise control while avoiding hypotension	Physician, cardiology
New rash			Dermatology

Table 21: Rehabilitation Needs of Patients with Severe COVID-19

Needs	Possible Complications	Interventions	Effects of Mechanical Ventilation coupled with sedation and/or paralysis
• Hospitalisation • Oxygen support	• Acute respiratory distress syndrome (ARDS) • Sepsis and septic shock • Multi-organ failure (including kidney, liver and cardiac injury)	• Invasive mechanical ventilation in the ICU	There are many detrimental musculoskeletal effects including reduced muscle strength and physical function. Other effects: • Impairments in respiratory function, cognitive status, swallow, and communication, as well as the potential for delirium

In the long-term, the multifaceted aspects of post intensive care syndrome, which can persist for many months or years after discharge, may also manifest in reduced exercise capacity, independence with activities of daily living, and health-related quality of life.

The rehabilitation needs associated with COVID-19 may be amplified by underlying health conditions and older age.

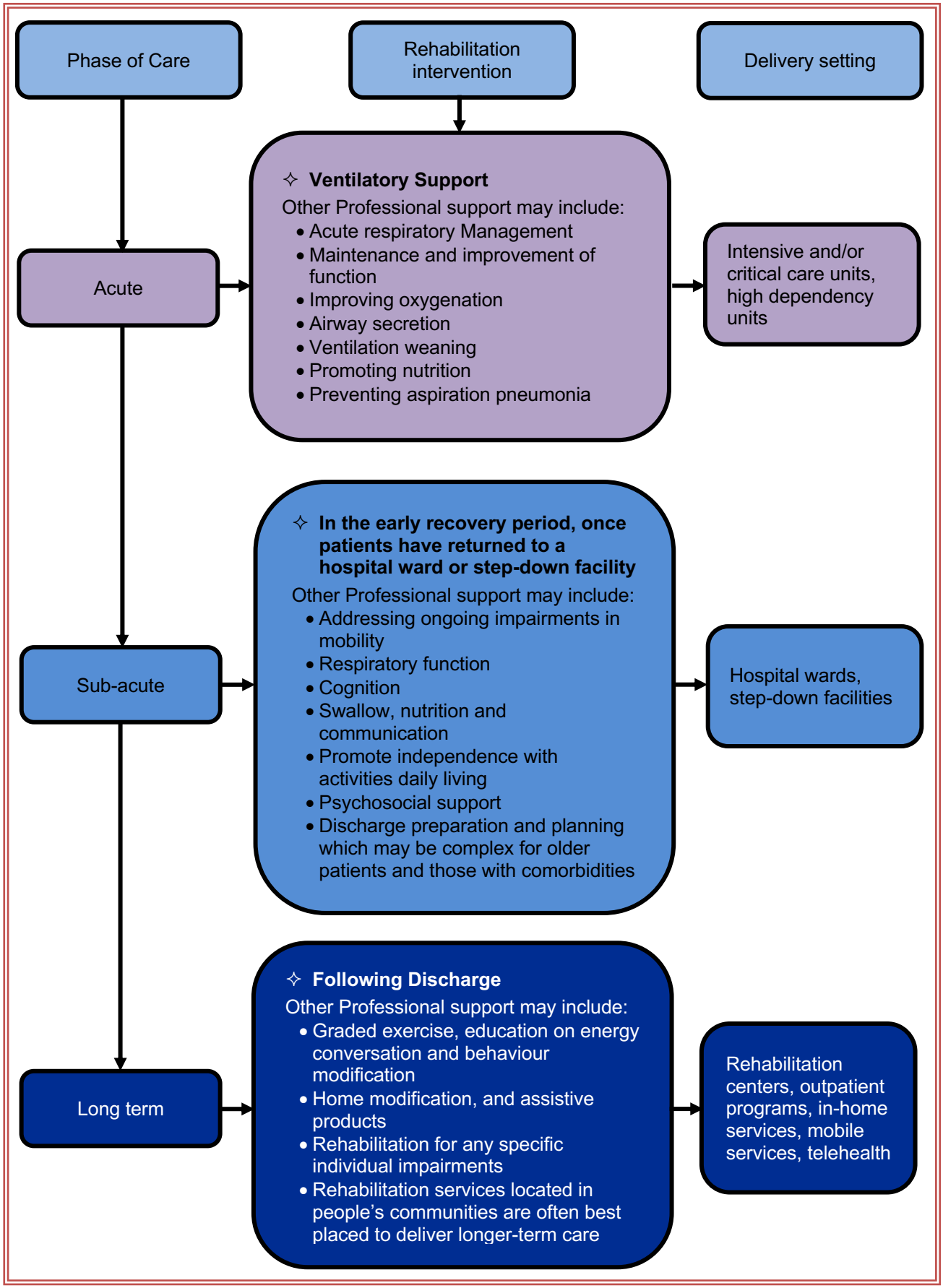


Figure 18: Rehabilitation Interventions for Patients with Severe COVID-19

Appendices

Appendix 1: Step by Step Guide for Sample Collection

1. **Assemble materials** for respiratory specimen collection


2. **Label sample containers** with suspected case/deceased person's name, **EPID ID number**, hospital number, date of sample collection and time. (Contact State Epidemiologist for Epid ID no)

3. **Fill the Case Investigation form**.

4. **Don PPE**. Allow buddy (trained observer) to mirror you for proper donning

5. **Perform hand hygiene**

Wet hands with water and enough soap to cover all hand surfaces


Rub hands, palm-to-palm


Right palm over left dorsum with interlaced fingers and vice versa


Palm to palm with fingers interlaced


Back of fingers to opposing palms with fingers interlocked

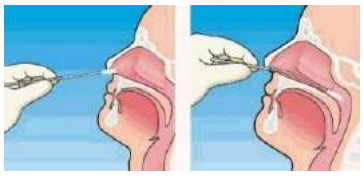

Rotational rubbing of left thumb clasped in right palm and vice versa


Rinse hands with water


Dry hands thoroughly with single use towel

6. **Nasopharynx/nasopharyngeal sample collection:**

Two swabs should be collected. Swab each nostril for 10 – 15 secs. Place both swabs into a single Viral Transport Medium (VTM). Wrap VTM with parafilm



7. **Oropharyngeal sample collection:**

Use tongue depressor to hold down the tongue. Swab each tonsil for 10 – 15 secs. Place swab into a single VTM. Wrap the lid of VTM tube with parafilm

8. **Sputum collection:**

For suspect/ill persons coughing, ask the person to take a deep breath and cough to produce sputum sample into the leak-proof screw cap sputum collection cup or sterile-dry collection bottle.

9. **For severely ill persons**, bronchoalveolar lavage or tracheal aspirate may be considered (to be collected by respiratory physicians or trained personnel only).

1. Packaging of sample

Place the VTM tubes into a Falcon tube. Place the Falcon tube into a Ziploc bag

2. Packaging of container:

Place Ziploc bag into Geostyle container

13. **Discard sample collection materials in a properly labelled biohazard bin.** Decontaminate work surfaces with freshly prepared 0.5% hypochlorite solution

14. Doff PPE

a.

b.

c.

15. Perform hand hygiene

Wet hands with water and enough soap to cover all hand surfaces

Rub hands, palm to palm

Right palm over left dorsum with interlaced fingers and vice versa

Palm to palm with fingers interlaced

Back of fingers to opposing palms with fingers interlocked

Rotational rubbing of left thumb clasped in right palm and vice versa

Rinse hands with water

Dry hands thoroughly with single use towel

Appendix 2: Infection Prevention and Control (IPC) Measures in the Healthcare Setting

How to implement infection prevention and control measures for patients with suspected or confirmed COVID-19 infection	
At triage	Give suspect patient a medical mask and direct patient to separate area, an isolation room if available. Keep at least 1meter distance between suspected patients and other patients Instruct all patients to cover nose and mouth during coughing or sneezing with tissue or flexed elbow for others. Perform hand hygiene after contact with respiratory secretions
Apply droplet precautions	Droplet precautions prevent large droplet transmission of respiratory viruses. Use a medical mask if working within 1-2 meters of the patient. Place patients in single rooms, or group together those with the same etiological diagnosis. If an etiological diagnosis is not possible, group patients with similar clinical diagnosis and based on epidemiological risk factors, with a spatial separation. When providing care in close contact with a patient with respiratory symptoms (e.g., coughing or sneezing), use eye protection (face-mask or goggles), because sprays of secretions may occur. Limit patient movement within the institution and ensure that patients wear medical masks when outside their rooms
Apply contact precautions	Droplet and contact precautions prevent direct or indirect transmission from contact with contaminated surfaces or equipment (i.e., contact with contaminated oxygen tubing/interfaces). Use PPE (medical mask, eye protection, gloves and gown) when entering room and remove PPE when leaving. If possible, use either disposable or dedicated equipment (e.g., stethoscopes, blood pressure cuffs and thermometers) If equipment needs to be shared among patients, clean and disinfect between each patient use Ensure that Healthcare Workers refrain from touching their eyes, nose, and mouth with potentially contaminated gloved or ungloved hands. Avoid contaminating environmental surfaces that are not directly related to patient care (e.g., door handles and light switches). Ensure adequate room ventilation Avoid movement of patients or transport. Perform hand hygiene
Apply airborne precautions when performing an aerosol generating procedure	Ensure that Healthcare Workers performing aerosol-generating procedures (i.e., open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) use PPE, including gloves, long-sleeved gowns, eye protection, and fit-tested particulate respirators (N95 or equivalent, or higher level of protection). (The scheduled fit test should not be confused with user seal check before each use) Whenever possible, use adequately ventilated single rooms when performing aerosol-generating procedures, meaning negative pressure rooms with minimum of 12 air changes per hour or at least 160 litres/second/patient in facilities with natural ventilation Avoid the presence of unnecessary individuals in the room Care for the patient in the same type of room after mechanical ventilation commences

Appendix 3: Personal Protective Equipment (PPE) and Use

PPE	Characteristics and how to use
Eye protection (goggles or face shield) 	○ Face shield or goggles can be used ○ Should adequately protect the Healthcare Workers conjunctival mucous membranes from splashes ○ Goggles should be preferably used for high risk situations ○ Normal reading glasses are not acceptable as PPE for eye protection so a face shield with anti-fog should be worn over the glasses or goggles big enough to cover the glasses ○ Goggles must fit comfortably and securely; each person should have his/her own goggles/face shield with personal names on them ○ Condensation of the goggles can be a major problem: it impairs the user's vision and is dangerous but can be minimised by anti-fog spray
Mouth and nose protection (surgical face mask) 	○ Healthcare Workers must cover the mouth and nose to avoid body fluid splashes and droplet spread ○ Medical-surgical mask should be fluid-resistant with structured design that does not collapse against the mouth
Respiratory protection (N95, FFP3) 	○ The respirator protects from the inhalation of droplets and particles ○ Given that the fitting of different types of respirators will vary for each user, the respirator will require a fitting test in order to find the best match of PPE to user ○ A respirator should always be used when performing aerosol-generating procedures in a COVID-19 patient
Gloves 	○ Correctly sized latex or nitrile examination gloves should be used to protect hands against both direct and indirect contact ○ A new pair of gloves should be used for each patient. Remember that for invasive procedures you need sterile gloves ○ DO NOT touch eyes, nose or mouth areas with gloved hands
Body protection (gowns) 	○ Long-sleeved water-resistant gowns should be used. This PPE does not need to be sterile, unless used in a sterile environment (e.g., operating room) ○ If water-resistant gowns are not available, single-use plastic aprons can be used on top of the non-water- resistant gowns to prevent body contamination

PPE	Characteristics and how to use
Apron 	○ When the risk of splashes from patient's vomiting, diarrhoea or bleeding is high, aprons should be worn over the gown or coverall because fluid-proof aprons provide extra protection of the front part of the body and is easier to replace than a soiled gown or coverall ○ Disposable aprons should be used
Protective body wear (Coverall) 	○ Disposable gown or coverall made of fabric that is tested for resistance to penetration by blood or body fluids or blood borne pathogens should be worn over scrubs. This should only be used when there is a risk that the environment is highly contaminated and there will be very close contact with the patient
Footwear 	○ Rubber or gum boots are preferred over closed shoes because they are fluid-proof, easier to clean and disinfect ○ They provide optimal protection from splashes/wetness and protect from sharp injuries ○ If not available, then wear closed shoes with disposable impermeable shoe covers ○ Boots should also be cleaned to remove gross contamination and then disinfected prior to reuse
Head cover 	○ The purpose of head covers is to protect the skin and hair from virus contamination with subsequent unrecognised transmission to the mucosa of the eyes, nose or mouth
Heavy-duty rubber gloves 	○ Cleaners, laundry workers and Healthcare Workers when handling infectious waste (i.e., solid waste or any secretion or excretion of with visible blood) should wear heavy duty rubber gloves over nitrile gloves ○ Movement of human remains or performing environmental cleaning activities also requires the use of heavy-duty rubber gloves
• Before exiting isolation area, carefully remove PPE and dispose in waste containers in a designated doffing area • Do not recycle any single-use PPE • Remove PPE under supervision of a trained buddy • Avoid any contact with soiled items and areas of the face or skin • Place reusable equipment in bin for decontamination	

Appendix 4: PPE Recommendations in the Care and Management of Suspected or Confirmed Cases of COVID-19: Inpatient Setting

Inpatient settings			
Area	**Target personnel**	**Activity**	**Type of PPE or IPC precaution**
Patient room	Healthcare Workers	Providing direct care to COVID-19 patients	• Medical mask Gown • Gloves • Eye protection (goggles or face shield)
		Aerosol-generating procedures performed on COVID-19 patients	• Respirator N95 or FFP2 standard, or equivalent • Gown
		COVID-19 patients	• Gloves • Eye protection Apron
	Cleaners	Entering the room of COVID-19 patients	• Medical mask Gown • Heavy duty gloves • Eye protection (if risk of splash from organic material or chemicals) • Boots or closed work shoes
	Visitors	Entering the room of a COVID-19 patient	• Medical mask Gown • Gloves
	All staff, including Healthcare Workers	Any activity that does not involve contact with COVID-19 patients	• No PPE required
Other areas of patient transit (e.g., wards, corridors)	All staff, including Healthcare Workers	Any activity that does not involve contact with COVID-19 patients	• No PPE required
Triage	Healthcare Workers	Preliminary screening not involving direct contact	• Maintain spatial distance of at least 1m • No PPE required
	Patients with respiratory symptoms	Any	• Maintain spatial distance of at least 1m • Provide medical mask if tolerated by patient
	Patients without respiratory symptoms	Any	• No PPE required
Laboratory	Lab technician	Manipulation of respiratory samples	• Medical mask Gown • Gloves • Eye protection (if risk of splash)
Administrative areas	All staff, including Healthcare Workers	Administrative tasks that do not involve contact with COVID-19 patients	• No PPE required

Appendix 5: PPE Recommendations in the Care and Management of Suspected or Confirmed Cases of COVID-19: Outpatient Setting

Outpatient setting			
Area	**Target personnel**	**Activity**	**Type of PPE or IPC precaution**
Consultation room	Healthcare Workers	Physical examination of patient with respiratory symptoms	• Medical mask • Gown • Gloves • Eye protection
	Healthcare Workers	Physical examination of patients without respiratory symptoms	• PPE according to standard precautions and risk assessment
	Patients with respiratory symptoms	Any	• Provide medical mask if tolerated
	Patients without respiratory symptoms	Any	• Face mask
	Cleaners	After and between consultations with patients with respiratory symptoms	• Medical mask • Gown • Heavy duty gloves • Eye protection (if risk of splash from organic material or chemicals) • Boots or closed work shoes
Waiting room	Patients with respiratory symptoms	Any	• Provide medical mask if tolerated • Immediately move the patient to an isolation room or separate area away from others; if this is not feasible, ensure spatial distance of at least 1m from other patients
	Patients without respiratory symptoms	Any	• Face mask
Administrative areas	All staff, including Healthcare Workers	Administrative tasks	• Face mask
Triage	Healthcare Workers	Preliminary screening not involving direct contact	• Maintain spatial distance of at least 1 meter • Face mask
	Patients with respiratory symptoms.	Any	• Maintain spatial distance of at least 1 meter • Provide medical mask if tolerated
	Patients without respiratory symptoms	Any	• Face mask

Appendix 6: Established and Other Potentially Significant Drug Interactions of Nirmatrelvir-Ritonavir

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
Anticoagulants	Warfarin	↑↓ Warfarin	• Closely monitor INR if co-administration with Warfarin is necessary • Increased bleeding risk with Rivaroxaban. Avoid concomitant use • Increased bleeding risk with Dabigatran. Depending on Dabigatran indication and renal function, reduce dose of Dabigatran or avoid concomitant use • Combined P-gp and strong CYP3A4 inhibitors increase blood levels of Apixaban and increase the risk of bleeding. Dosing recommendations for co-administration of Apixaban with Paxlovid depend on the Apixaban dose. Refer to the Apixaban product
	Rivaroxaban	↑ Rivaroxaban	
	Dabigatran	↑ Dabigatran	
	Apixaban	↑ Apixaban	
Anticonvulsants	Carbamazepine Phenobarbital, Primidone, Phenytoin	↓ Nirmatrelvir-r	Co-administration contraindicated due to potential loss of virologic response and possible resistance
Anticonvulsants	Clonazepam	↑ Anticonvulsant	A dose decrease may be needed for Clonazepam when co-administered with Paxlovid and clinical monitoring is recommended
Antidepressants	Bupropion	Bupropion and active metabolite hydroxy-bupropion	Monitor for an adequate clinical response to Bupropion
Antifungals	Voriconazole, Ketoconazole, Itraconazole	↓ Voriconazole ↑ Ketoconazole ↑ Itraconazole ↑ Nirmatrelvir-r	Avoid concomitant use of Voriconazole. Refer to product labels for further information
Anti-gout	Colchicine	↑ Colchicine	Co-administration contraindicated due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment
Antibiotics	Clarithromycin, Erythromycin	↑ Clarithromycin ↑ Erythromycin	Refer to the respective prescribing information for anti-infective dose adjustment
Anti-HIV protease inhibitors	Atazanavir, Darunavir, Tipranavir	↑ Protease Inhibitor	For further information, refer to the respective protease inhibitors'

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			prescribing information Patients on Ritonavir-or Cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased Paxlovid or protease inhibitor adverse events
Anti-HIV	Efavirenz, Maraviroc, Nevirapine, Zidovudine, Bictegravir/Emtricitabine /Tenofovir	↑ Efavirenz ↑ Maraviroc ↑ Nevirapine ↓ Zidovudine ↑ Bictegravir ↔ Emtricitabine ↑ Tenofovir	For further information, refer to the respective anti-HIV drugs prescribing information
Anti- mycobacterial	Rifampin	↓ Nirmatrelvi-r	Co-administration contraindicated due to potential loss of virologic response and possible resistance. Alternate antimycobacterial drugs such as Rifabutin should be considered
Anti- mycobacterial	Bedaquiline Rifabutin Rifapentine	↑ Bedaquiline ↑ Rifabutin ↓ Nirmatrelvir-r	Refer to the Bedaquiline product label for further information Refer to rifabutin product label for further information on Rifabutin dose reduction Avoid concomitant use with Paxlovid
Antipsychotics	Inasidone, Pimozide	↑ Lurasidone ↑ Pimozide	Co-administration contraindicated due to serious and/or life-threatening reactions such as cardiac arrhythmias
Antipsychotics	Quetiapine clozapine	↑ Quetiapine ↑ Clozapine	If co-administration is necessary, reduce dose of antipsychotic and monitor for quetiapine-associated adverse reactions
Benign prostatic hyperplasia agents	Tamsulosin	↑ Tamsulosin	Co-administration contraindicated due to potential for postural hypotension
Calcium Channel Blockers	Amlodipine, Diltiazem, Felodipine, Nicardipine, Nifedipine	↑ Calcium Channel Blocker	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with Paxlovid
Cardiovascular agents	Ivabradine	↑ Ivabradine	Co-administration with Ivabradine is contraindicated due to potential for bradycardia or conduction disturbances
Corticosteroids	Betamethasone,	↑ Corticosteroid	Co-administration with corticosteroids

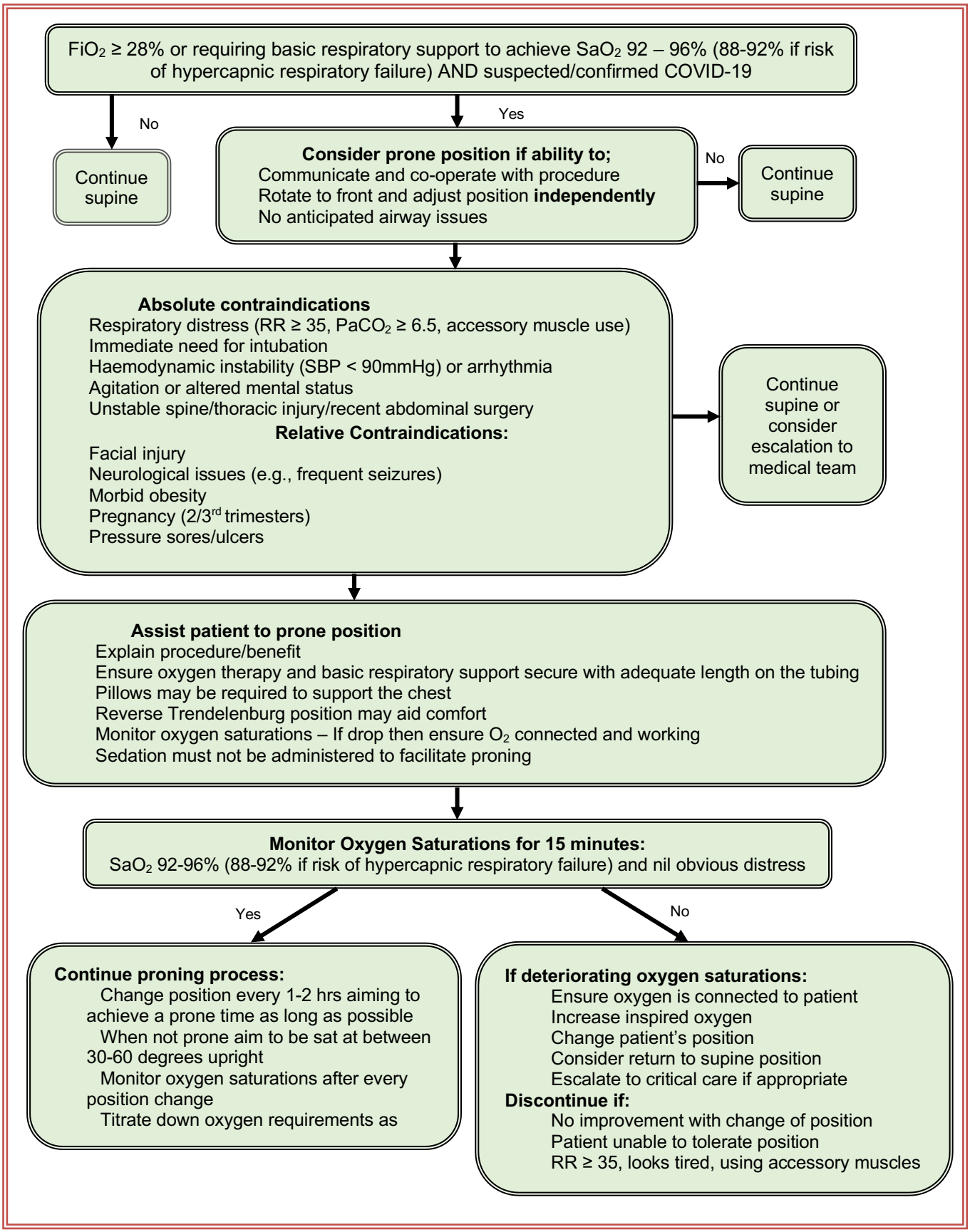
Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
primarily metabolized by CYP3A	Budesonide, Ciclesonide, Dexamethasone, Fluticasone, Methylprednisolone, Mometasone, Triamcinolone		of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression but risk is low. Alternative corticosteroids including Beclomethasone, Prednisone, and Prednisolone should be considered
Dipeptidyl peptidase 4 (DPP4) inhibitors	Saxagliptin	↑ Saxagliptin	Dosage adjustment of Saxagliptin is recommended. Refer to the Saxagliptin product label for more information
Hepatitis C direct acting antivirals	Elbasvir/Grazoprevir, Glecaprevir/Pibrentasvir Ombitasvir/Paritaprevir /Ritonavir and Dasabuvir Sofosbuvir/Velpatasvir	↑ Antiviral	Increased Grazoprevir concentrations can result in ALT elevations. Patients on Ritonavir-containing HCV regimens should continue their treatment as indicated. Monitor for increased Paxlovid or HCV drug adverse events with concomitant use
HMG-CoA reductase inhibitors	Lovastatin, Simvastatin, Atorvastatin, Rosuvastatin	↑ Lovastatin ↑ Simvastatin	Co-administration contraindicated due to potential for myopathy including rhabdomyolysis. Discontinue use of Lovastatin and Simvastatin at least 12 hours prior to initiation of Nirmatrelvir, during the 5 days of Nirmatrelvir-r treatment and for 5 days after completing Nirmatrelvir-r. Consider temporary discontinuation of Atorvastatin and Rosuvastatin during treatment with Nirmatrelvir-r
Hormonal contraceptive	Ethinyl Estradiol	↓ Ethinyl Estradiol	An additional, non-hormonal method of contraception should be considered during the 5 days of treatment and until one menstrual cycle after stopping
Immunosuppressants	Cyclosporine, Tacrolimus	↑ Cyclosporine ↑ Tacrolimus	Avoid use of Paxlovid when close monitoring of immunosuppressant concentrations is not feasible. If co-administered, dose adjustment of the immunosuppressant and monitoring for immunosuppressant concentrations and immunosuppressant-associated adverse reactions is recommended.
Long-acting beta-adrenoceptor agonist	Salmeterol	↑ Salmeterol	Avoid concomitant use with Paxlovid. The combination may result in increased risk of cardiovascular adverse events associated with Salmeterol, including QT prolongation,

Drug Class	Drugs within Class	Effect on Concentration	Clinical Comments
			palpitations, and sinus tachycardia
Narcotic analgesics	Fentanyl, Hydrocodone, Oxycodone, Meperidine Methadone	↑ Fentanyl ↑ Hydrocodone ↑ Oxycodone ↑ Meperidine ↓ Methadone	Careful monitoring of therapeutic and adverse effects (including potentially fatal respiratory depression) is recommended when Fentanyl, Hydrocodone, Oxycodone, or Meperidine is concomitantly administered with Paxlovid. If concomitant use with Paxlovid is necessary, consider a dosage reduction of the narcotic analgesic and monitor patients closely at frequent intervals. Refer to the individual product label for more information Monitor Methadone-maintained patients closely for evidence of withdrawal effects and adjust the Methadone dose accordingly
Pulmonary hypertension agents (PDE5 inhibitors)	Sildenafil	↑ Sildenafil	Co-administration of Sildenafil with Paxlovid is contraindicated due to the potential for Sildenafil associated adverse events, including visual abnormalities, hypotension, prolonged erection, and syncope
Sedative/hypnotics	Triazolam, oral Midazolam	↑ Triazolam ↑ Midazolam	Co-administration contraindicated due to potential for extreme sedation and respiratory depression
Sedative/hypnotics	Buspirone, Clorazepate, Diazepam, Estazolam, Flurazepam, Zolpidem Midazolam (administered parenterally)	↑ Sedative/hypnotic ↑ Midazolam	A dose decrease may be needed for these drugs when co-administered with Paxlovid and monitoring for adverse events. Co-administration of Midazolam (parenteral) should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for Midazolam should be considered

Appendix 7: Agents Under Investigation for Treatment of COVID-19 & MIS-C

MIS-C Specific Treatment: Drugs	Dosing & Duration	Comments
IVIG (IV) • KD features and/or coronary artery changes	**Dosing:** 2g/kg (max dose 100g)[26]	**Adverse events:** • Infusion reactions • Anaphylaxis Transaminitis, Aseptic meningitis • Haemolysis
Corticosteroids (IV/PO) • Prednisone, Prednisolone, Methylprednisolone **Use** • High-risk KD features • MIS-C	**Dosing**[26] 2mg/kg/day divided every 8-12 hrs Pulse dosing[26] • 10mg/kg-30mg/kg/day divided followed by a taper • Determine based on patient severity	**Adverse events:** • Hypertension • Hyperglycaemia
Anakinra (SQ) • Non-formulary-limited supply • IL-1 inhibitor • Consider if fevers > 20 hrs post-steroids/IVIG or moderate/severe presentation ID consult required	**Discuss the dose with ID or Rheum** **Dosing:** • 2-4mg/kg/dose (Max 100mg/dose) SQ/IV BID [26,30] May ↑ to TDS or QID if poor response • Continue for 5-7 days **Dose adjustments:** • CrCl < 30mL/min, consider OD dosing • Not dialyzable	**Caution:** • Treatment with > 1 biologic is not recommended • Avoid live viral vaccines **Caution:** Converting from Tocilizumab to Anakinra **Adverse events:** • Anaphylaxis, Neutropaenia, Eosinophilia, Transaminitis, Immunosuppression • Short half-life (4-6 hrs) • MAY convert to Tocilizumab without concern • Clinical improvement expected in 1-3 days

Appendix 8: Flow Diagram Decision for Conscious Proning Process



Appendix 9: Timed Position Changes for Patients Undergoing Conscious Proning Process

Timed Position Changes:

If patient fulfils criteria for proning ask the patient to switch positions as follows. Monitor oxygen saturations 15 minutes after each position change to ensure oxygen saturation has not decreased. Continue to monitor oxygen saturations as per the Early Warning Score (NEWS)

30 minutes to 2 hours lying fully prone (bed flat)

30 minutes to 2 hours lying on right side (bed flat)

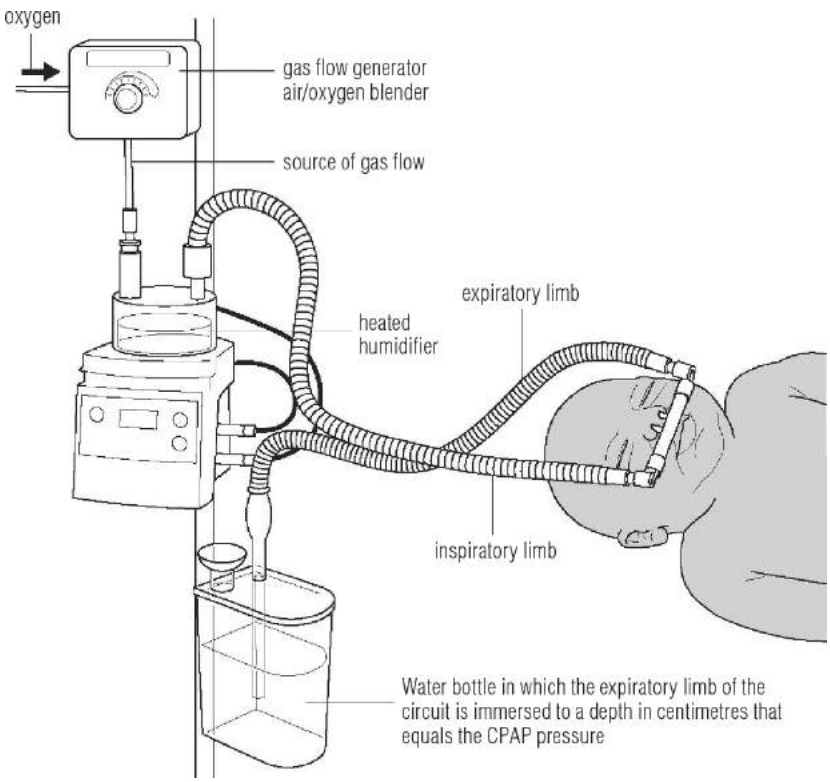
30 minutes to 2 hours sitting up (30-60 degrees) by adjusting head of the bed

30 minutes to 2 hours lying on left side (bed flat)

30 minutes to 2 hours lying prone again

Continue to repeat the cycle…….

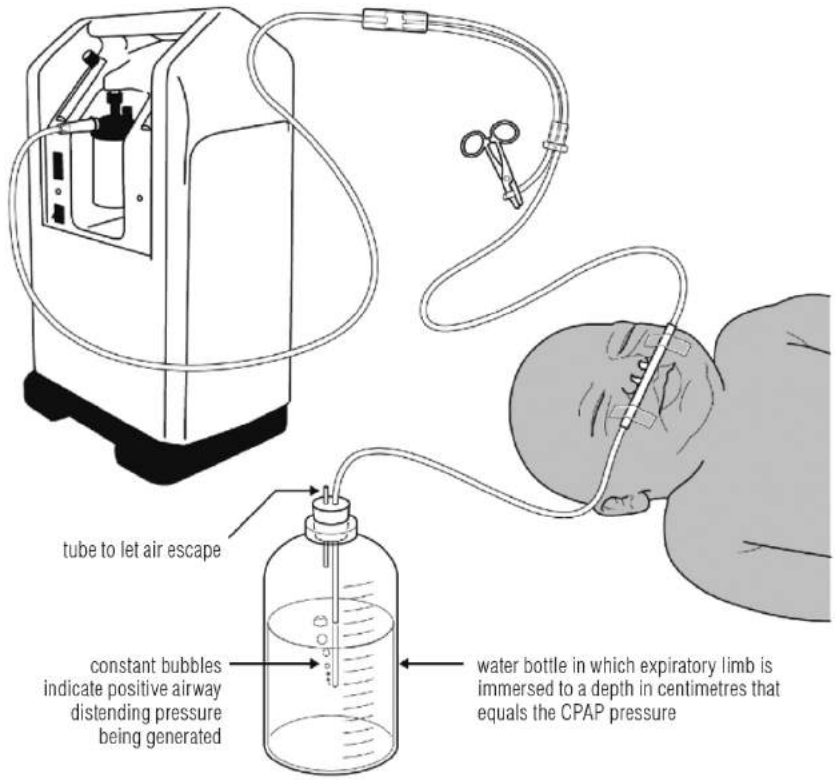
Appendix 10: Bubble CPAP in Children



Recommended Continuous oxygen/air flow
5-10L/min

In the absence of a heated humidifier, an ordinary humidifier will do with flow 5-8L/min

Improvised CPAP using nasal prongs circuit and clean bottle with a lid



Source: WHO; Oxygen Therapy in Children

Appendix 11: Paediatric Respiratory Rate and Heart Rate Ranges

Paediatric Respiratory Rate and Heart Rate Lower Limit, Normal Range, and Upper Limit by Age*

Age	Respiratory Rate (breaths/minute)			Heart Rate (beats/minute)		
	Lower limit (1st percentile)	Normal range (10th to 90th percentile)	Upper limit (99th percentile)	Lower limit (1st percentile)	Normal range (10th to 90th percentile)	Upper limit (99th percentile)
0 to 3 months	25	34 to 57	66	107	123 to 164	181
3 to < 6 months	24	33 to 55	64	104	120 to 159	175
6 to < 9 months	23	31 to 52	61	98	114 to 152	168
9 to < 12 months	22	30 to 50	58	93	109 to 145	161
12 to < 18 months	21	28 to 46	53	88	103 to 140	156
18 to < 24 months	19	25 to 40	46	82	98 to 135	149
2 to < 3 years	18	22 to 34	38	76	92 to 128	142
3 to < 4 years	17	21 to 29	33	70	86 to 123	136
4 to < 6 years	17	20 to 27	29	65	81 to 117	131
6 to < 8 years	16	18 to 24	27	59	74 to 111	123
8 to < 12 years	14	16 to 22	25	52	67 to 103	115
12 to < 15 years	12	15 to 21	23	47	62 to 96	108
15 to 18 years	11	13 to 19	22	43	58 to 92	104

*The respiratory and heart rates provided are based upon measurements in awake, healthy infants and children at rest. Many clinical findings besides the actual vital sign measurement must be taken into account when determining whether or not a specific vital sign is normal in an individual patient. Values for heart rate or respiratory rate that fall within normal limits for age may still represent abnormal findings that are caused by underlying disease in a particular infant or child

Source: uptodate.com

Appendix 12: Comprehensive Mental Health Assessments

DEFINITIONS:
Mental Health Specialist: Refers to psychiatrist, clinical officer psychiatry, licentiate psychiatry and mental health nurse.

I. **Relaxation Exercise: Relaxation Technique. Progressive Muscle Relaxation Script**

Progressive muscle relaxation is an exercise that reduces stress and anxiety in your body by having you slowly tense and then relax each muscle. This exercise can provide an immediate feeling of relaxation, but it's best to practice frequently. With experience, you will become more aware of when you are experiencing tension and you will have the skills to help you relax. Duringthis exercise, each muscle should be tensed, but not to the point of strain. If you have any injuries or pain, you can skip the affected areas. Pay special attention to the feeling of releasing tension in each muscle and the resulting feeling of relaxation. Let's begin

- Sit back or lie down in a comfortable position. Shut your eyes if you're comfortable doing so
- Begin by taking a deep breath and noticing the feeling of air filling your lungs. Hold your breathfor a few seconds
  (brief pause)
- Release the breath slowly and let the tension leave your body.Take in another deep breath and hold it *(brief pause)*
- Again, slowly release the air
- Even slower now, take another breath. Fill your lungs and hold the air *(brief pause)*
- Slowly release the breath and imagine the feeling of tension leaving your body
- Now, move your attention to your feet. Begin to tense your feet by curling your toes and the archof your foot. Hold onto the tension and notice what it feels like. *(5 second pause)*
- Release the tension in your foot. Notice the new feeling of relaxation
- Next, begin to focus on your lower leg. Tense the muscles in your calves. Hold them tightly andpay attention to the feeling of tension. *(5 second pause)*
- Release the tension from your lower legs. Again, notice the feeling of relaxation. Remember to continue taking deep breaths
- Next, tense the muscles of your upper leg and pelvis. You can do this by tightly squeezing yourthighs together. Make sure you feel tenseness without going to the point of strain. *(5 second pause)*
- And release. Feel the tension leave your muscles
- Begin to tense your stomach and chest. You can do this by sucking your stomach in. Squeezeharder and hold the tension. A little bit longer. *(5 second pause)*
- Release the tension. Allow your body to go limp. Let yourself notice the feeling of relaxation.Continue taking deep breaths. Breathe in slowly, noticing the air fill your lungs, and hold it *(brief pause)*
- Release the air slowly. Feel it leaving your lungs
- Next, tense the muscles in your back by bringing your shoulders together behind you. Hold themtightly. Tense them as hard as you can without straining and keep holding. *(5 second pause)*
- Release the tension from your back. Feel the tension slowly leaving your body, and the newfeeling of relaxation. Notice how different your body feels when you allow it to relax
- Tense your arms all the way from your hands to your shoulders. Make a fist and squeeze all theway up your arm. Hold it. *(5 second pause)*
- Release the tension from your arms and shoulders. Notice the feeling of relaxation in yourfingers, hands, arms, and shoulders. Notice how your arms feel limp and at ease
- Move up to your neck and your head. Tense your face and your neck by distorting the musclesaround your eyes and mouth. *(5 second pause)*
- Release the tension. Again, notice the new feeling of relaxation

- Finally, tense your entire body. Tense your feet, legs, stomach, chest, arms, head, and neck. Tense harder, without straining. Hold the tension. *(5 second pause)*
- Now release. Allow your whole body to go limp. Pay attention to the feeling of relaxation, andhow different it is from the feeling of tension
- Begin to wake your body up by slowly moving your muscles. Adjust your arms and legs. Stretch your muscles and open your eyes when you're read. © 2017 Therapist Aid

II. Depression Inventory PHQ9[35]

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is the depression screening tool, which scores each of the 9 criteria as "0" (not at all) to "3" (nearly every day).

Over the last 2 weeks, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things?
2. Feeling down, depressed, or hopeless?
3. Trouble falling or staying asleep, or sleeping too much?
4. Feeling tired or having little energy?
5. Poor appetite or overeating?
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down?
7. Trouble concentrating on things, such as reading, listening to radio/someone or watching something such as TV?
8. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual?
9. Thoughts that you would be better off dead, or of hurting yourself in some way?

Total= /27

Depression Severity: 0-4 None. 5-9 Mild depression. 10-14 Moderate depression. 15-19 Moderately severe depression. 20-27 Severe depression.

III. Generalised Anxiety Disorder Inventory GAD7.[36]

Over the last 2 weeks, how often have you been bothered by the following problems?

0 - Not at all 1 - Several days 2 - More than half the days 3 - Nearly every day

1. Feeling nervous, anxious or on edge?
2. Not being able to stop or control worrying?
3. Worrying too much about different things?
4. Trouble relaxing?
5. Being so restless that it is hard to sit still?
6. Becoming easily annoyed or irritable?
7. Feeling afraid as if something awful might happen?

Generalised Anxiety Disorder - 7 Anxiety = Total Score _____

GAD - 7 total score for the seven items ranges from 0 to 21. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively.

Anxiety Severity: 0-5 mild 6-10 moderate 11-15 moderately severe anxiety 15-21 severe anxiety.

---

[35] *The copyright for the PHQ-9 was formerly held with Pfizer, who provided the educational grant for Drs. Spitzer, Williams and Kroenke who originally designed it. This is no longer the case and no permission is required to reproduce, translate, display or distribute the PHQ-9.*

[36] The GAD-7 originates from Spitzer RL, Kroenke K, Williams JB, et al; A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 May 22;166(10):1092-7. GAD-7 © Pfizer Inc. all rights reserved.

IV. AUDIT Questionnaire [37]

Circle the answer that is correct for you

1. How often do you have a drink containing alcohol?
   * Never * Monthly or less * 2-4 times a month * 2-3 times a week * 4 or more times a week
2. How many standard drinks containing alcohol do you have on a typical day when drinking?
   * 1 or 2 * 3 or 4 * 5 or 6 * 7 to 9 * 10 or more
3. How often do you have six or more drinks on one occasion?
   * Never * Less than monthly * Monthly * Weekly * Daily or almost daily
4. During the past year, how often have you found that you were not able to stop drinking once you had started?
   * Never * Less than monthly * Monthly * Weekly * Daily or almost daily
5. During the past year, how often have you failed to do what was normally expected of you because of drinking?
   * Never * Less than monthly * Monthly * Weekly * Daily or almost daily
6. During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session?
   * Never * Less than monthly * Monthly * Weekly * Daily or almost daily
7. During the past year, how often have you had a feeling of guilt or remorse after drinking?
   * Never * Less than monthly * Monthly * Weekly * Daily or almost daily
8. During the past year, have you been unable to remember what happened the night before because you had been drinking?
   * Never * Less than monthly * Monthly * Weekly * Daily or almost daily
9. Have you or someone else been injured as a result of your drinking?
   * No * Yes, but not in the past year * Yes, during the past year
10. Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?
    * No * Yes, but not in the past year * Yes, during the past year

Scoring the AUDIT

Scores for each question range from 0 to 4, with the first response for each question (e.g., never) scoring 0, the second (e.g., less than monthly) scoring 1, the third (e.g., monthly) scoring 2, the fourth (e.g., weekly) scoring 3, and the last response (e.g., daily or almost daily) scoring 4. For questions 9 and 10, which only have three responses, the scoring is 0, 2 and 4 (from left to right).

A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

[37] Saunders JB, Aasland OG, Babor TF et al. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption — II. Addiction 1993, 88: 791–803

Appendix 13: Mpox Epidemiology, Clinical Guidance, infection Prevention and Control

COVID-19 Pandemic has shown the importance of Emergency Health Response to threats to Global Health Security. A massive increase in globalisation and connectivity has meant that a virus can spread from one side of the world to another in mere hours. Emerging and re-emerging infections are on the increase, and it is important for clinicians and health systems alike to be aware and ready to respond within the shortest notice. Mpox is one such re-emerging infectious disease that was declared a **Public Health Emergency of International Concern (PHEIC)** by the WHO on 23rd July 2022[38]. A PHEIC is "an extraordinary event which is determined to constitute a public health risk to other WHO member states through the international spread of diseases and to potentially require a coordinated international response." This appendix will cover pertinent clinical presentations, treatment options and preventative measures that must be undertaken.

Background

In 1980, following the eradication and cessation of smallpox, Mpox had emerged subsequently. The same year, it was noticed that persons younger than 40 years and not vaccinated against smallpox were susceptible to get infected by Mpox. Mpox is considered the most potentially life-threatening orthopoxviral, with a case fatality rate historically noted between 3-6%. Since May 2022, the WHO reports more than 57,000 Monkeypox cases in more than 100 countries across six continents[39]. The virus is transmitted both through animal-to-human contact (primary transmission) and from human to human (secondary transmission). That disease develops 4 to 14 (up to 21 days) days following exposure, although most people recover within weeks. Severe complications and sequelae have been reported to be more common among those unvaccinated for smallpox compared with those vaccinated[40].

Children under the age of 10 years accounted for all Mpox deaths in the 1970s to 1990s, and more than a third of such deaths since then. Outside of Africa, this current Mpox outbreak is disproportionately affecting generally young and healthy men who have sex with men, suggesting amplification for transmission through sexual networks. Access to care is also important as bacterial superinfection is a leading cause of morbidity and death related to Mpox. Additional reports show a high prevalence of HIV and other STIS in the current Mpox outbreak[41]. Concurrent HIV infection has been associated with poor Mpox clinical outcomes[42]. Compared with persons without HIV infection, a higher proportion of persons with HIV infection were hospitalised. It is important that public health

[38] https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-covid-19-media-briefing--27-july-2022 accessed 12.09.22

[39] https://www.cdc.gov/poxvirus/mpox/response/2022/world-map.html accessed 12.09.22

[40] World Health Organization.Mpox Fact sheets.19 May 2022.https://www.who.int/news-room/fact-sheets/detail/monkeypox.

[41] Curran et al 2022 Morbidity and Mortality Weekly Report Weekly / Vol. 71 / No. 36

[42] Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. Clin Infect Dis 2020;71:e210–4.PMID:32052029 https://doi.org/10.1093/cid/ciaa143

officials leverage systems for delivering HIV and STI care and prevention to reduce Mpox incidence in this population. Consideration should be given to prioritising persons with HIV infection and STIs for vaccination against Mpox. HIV and STI screening and other recommendations[43]. Zambia has an opportunity to leverage on already existing systems of providing HIV care and those created during the COVID-19 pandemic, as we have previously shown success that there is strength in numbers, in partnerships, in using data and strong leadership[44].

Epidemiology of Mpox

Causative agent: Mpox is a sylvatic zoonosis with incidental sporadic cases occurring among humans mostly in tropical rainforest regions of Central and Western Africa[45]. The disease is caused by an enveloped double-stranded DNA virus that belongs to the Orthopoxvirus genus in the family Poxviridae. There are two main known Mpox clades

Clade I: Previously known as the Congo basin clade (Central African) (CFR, up to 11%)

Clade II: Previously known as the West African clade (CFR, up to 6%)

Mpox Modes of Transmission

1. Contact and droplet exposure via exhaled large droplets
2. Animal-to-human transmission through
    a. Direct contact with the blood
    b. Bodily fluids
    c. Cutaneous or mucosal lesions of infected animals
3. Human-to-human transmission can be transmitted through
    a. Contact with bodily fluids
    b. Skin lesions or on internal mucosal surfaces, such as in the mouth, anus or throat,
    c. Respiratory droplets (usually requires prolonged face-to-face contact
    d. Contaminated objects
    e. Via the placenta from mother to foetus (which can lead to congenital Mpox)

Note: The longest documented chain of transmission in a community has risen in recent years from 6 to 9 successive person-to-person infections. While the Mpox virus has been found in semen, it is currently not known whether Mpox can be spread through semen or vaginal fluids.

[43] Curran et al 2022 Morbidity and Mortality Weekly Report Weekly / Vol. 71 / No. 36

[44] https://www.who.int/news-room/feature-stories/detail/strength-in-numbers-data-partners-and-leadership-create-resilient-hiv-services-during-covid-19-in-zambia

[45] World Health Organization (16 May 2022). Disease Outbreak News; Monkeypox– United Kingdom of Great Britain and Northern Ireland. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON381

Risk Factors for acquiring Mpox Virus[46]

i) Close contact with a person with Mpox
ii) Caring for someone who has monkeypox without wearing gloves and a well-fitting mask
iii) Coming in contact with infected animals
iv) Men having sex with men or having multiple/casual sexual partners
v) Children, pregnant women and the immunocompromised
vi) Health workers and laboratory personnel within with Orthopoxvirus

WHO Case Definitions[47]

Confirmed Case: Laboratory confirmed MPXV detection by PCR or sequencing

Suspected case: Person who is a contact with a probable or confirmed Mpox case in the 21 days before the onset of signs or symptoms, and who presents with any of the following: acute onset of fever (> 38.5°C), headache, myalgia (muscle pain/body aches), back pain, profound weakness or fatigue.

OR

A person presenting since 01 January 2022 with an unexplained acute skin rash, mucosal lesions or lymphadenopathy (swollen lymph nodes).

AND

for which the following common causes of acute rash or skin lesions do not fully explain the clinical picture: Varicella zoster, Herpes zoster, measles, Herpes simplex, bacterial skin infections, disseminated gonococcus infection, primary or secondary Syphilis, chancroid, Lymphogranuloma venereum, Granuloma inguinale, Molluscum contagiosum, allergic reaction (e.g., to plants); and any other locally relevant common causes of papular or vesicular rash.

Probable case: A person presenting with an unexplained acute skin rash, mucosal lesions or lymphadenopathy (swollen lymph nodes). The skin rash may include single or multiple lesions in the anogenital region or elsewhere on the body.

AND

One or more of the following:

- Has an epidemiological link to a probable or confirmed case of Mpox in the 21 days before symptom onset
- Identifies as gay, bisexual or other man who has sex with men
- Has had multiple and/or casual sexual partners in the 21 days before symptom onset
- Has detectable levels of anti-orthopoxvirus (OPXV) IgM antibody; or a four-fold rise in IgG antibody titer based on acute (up to day 5-7) and convalescent (day 21 onwards) samples;

[46] World Health Organization (16 May 2022). Disease Outbreak News; Monkeypox– United Kingdom of Great Britain and Northern Ireland. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON381

[47] World Health Organization.Monkeypox Surveillance.https://www.who.int/publications/i/item/WHO-MPX-Surveillance-2022.2

in the absence of recent smallpox/Mpox vaccination or other known exposure to OPXV (during the period of 4 to 56 days after rash onset)

- has a positive test result for orthopoxviral infection (e.g., OPXV-specific PCR without MPXV-specific PCR or sequencing)

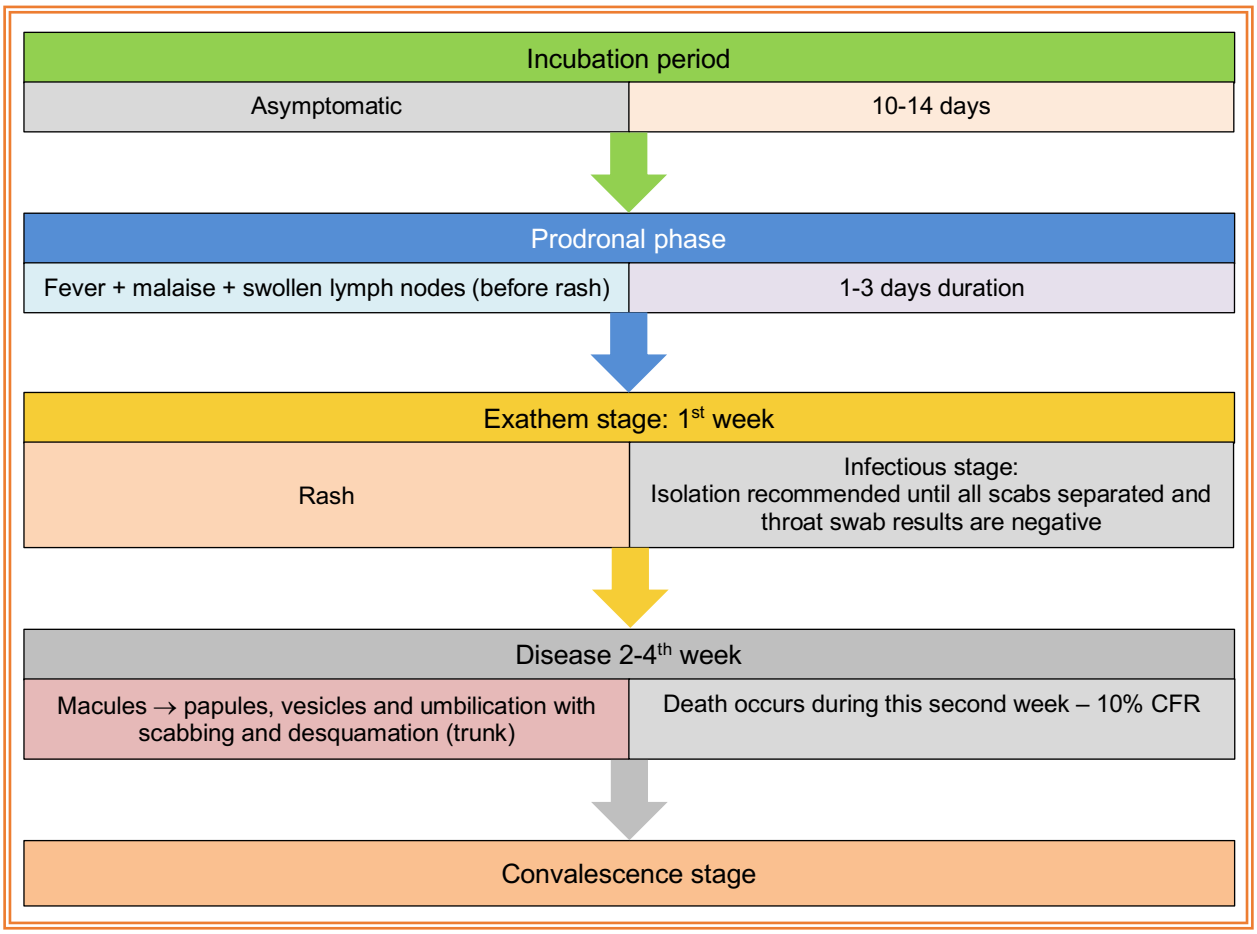


Figure 19: Clinical Progression and Pathogenesis of Mpox

Figure 20: Disease Progression by Rash Stage

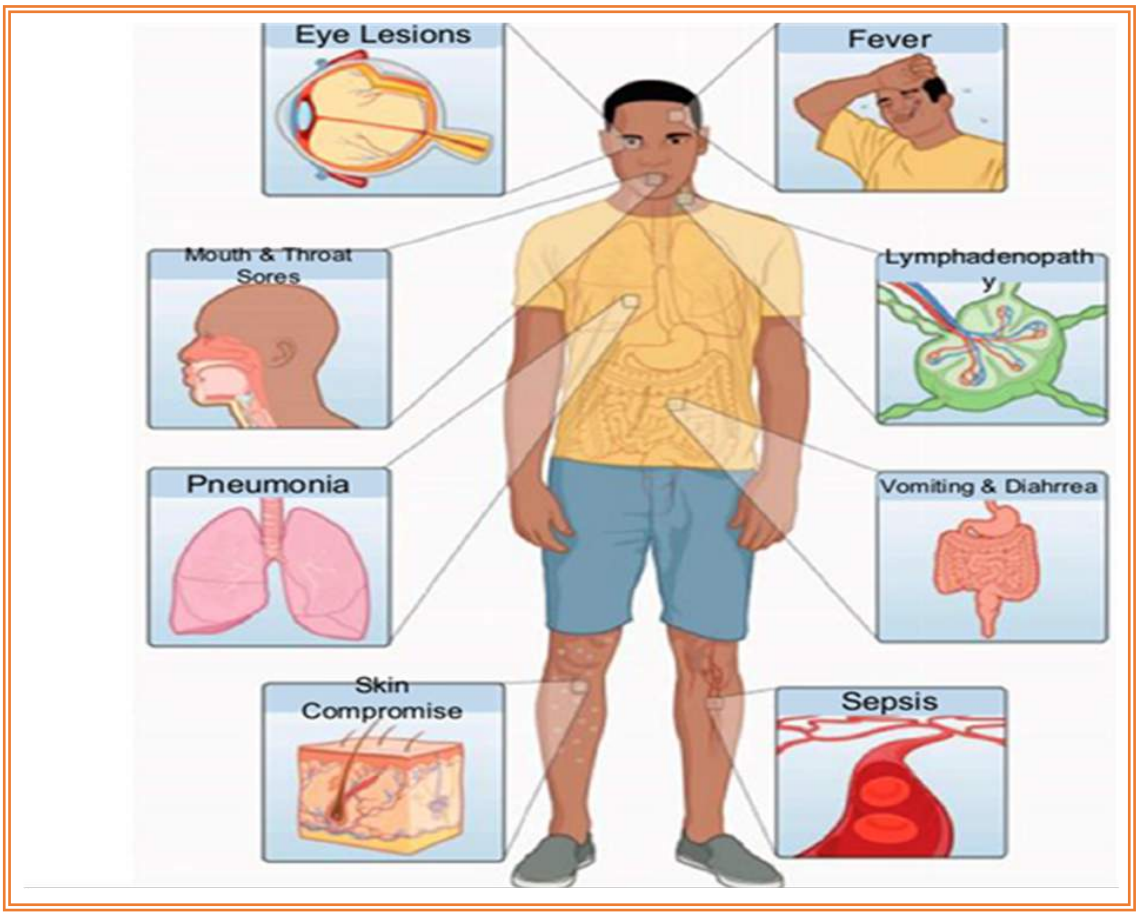


Figure 21: Extracutaneous Manifestations of Mpox

Danger Signs:

- Loss of vision
- Delirium, loss of consciousness, convulsions
- Respiratory distress
- Bleeding, inability to produce urine
- Signs of sepsis

Long-term sequelae/complications:

- Pockmarks, scarring or loss of pigmentation
- Corneal ulcers and blindness
- Superimposed bacterial infections on the skin lesions causing sepsis
- Severe dehydration
- Electrolyte abnormalities
- Retropharyngeal abscess
- Encephalitis
- Secondary Systemic Sexually transmitted infection

Atypical Presentation of Mpox:

Non-typical presentations of the disease had been reported among individuals:

- Anal pain and rectal bleeding
- Ocular lesions (Scarring, reduced skin pigmentation, blindness)
- Sudden (fewer or even single) rashes on any part of the body
- Close mimic of many STIs: Since Mpox can present with genital ulcers or a macular rash on the palms and soles, other sexually transmitted infections should be considered (e.g., secondary Syphilis, *Lymphogranuloma venereum*, Chancroid)

Disease Severity Stratification

Skin lesion severity score	• From smallpox experience *(28, 94)*: – Mild (< 25 skin lesions) – Moderate (25–99 skin lesions) – Severe (100–250 skin lesions) – Very severe (> 250 skin lesions)

Mpox Cases in Special Population

Data are still limited across all susceptible populations.

1. **Mpox and HIV**:

Compared to HIV-negative cases, HIV-1–infected cases were significantly more likely to have skin rashes ≥ 2cm, genital ulcers, secondary bacterial skin infection, and a longer duration of illness[48]. However, the CDC doesn't know if having HIV increases the likelihood of getting Mpox.

2. **Mpox and Pregnancy:** increase occurrence of adverse pregnancy outcomes such as

- Spontaneous pregnancy loss
- Stillbirth
- Sreterm delivery
- Neonatal Mpox infections have also been reported. Note that the frequency and risk factors for severity and adverse pregnancy outcomes are not known.

3. **Mpox in Children and Adolescents**

Evidence from patients infected with Clade I of Mpox virus that the disease is more likely to be severe in children under 8 years anyone with immunocompromising conditions or certain skin conditions, such as eczema, is at risk of severe Mpox disease.

Additional clinical presentations:

- Difficulty swallowing, or coughing may occur when oropharyngeal lesions
- Intraocular lesions, eyelid swelling, or eyelid crusting may occur when there are lesions near or in a patient's eye, which can occur when a patient touches these sites with their hand after touching a lesion

Mpox Skin Lesions Differentiation

Mpox can clinically resemble various rash illnesses which need to be considered during differential diagnosis. Below are some examples:

- Measles
- Chickenpox
- Scabies
- Bacterial; skin infection
- Sexually transmitted for infection
- Medicated associated allergies
- Molluscum
- Other novel Orthopoxvirus infections can also be considered
- Pruritic urticarial papules and plaques of pregnancy
- Molluscum

[48] World Health Organization.Monkeypox: Epidemiology, preparedness and response for African outbreak contexts,29 August 2022.https://openwho.org/courses/monkeypox-intermediate

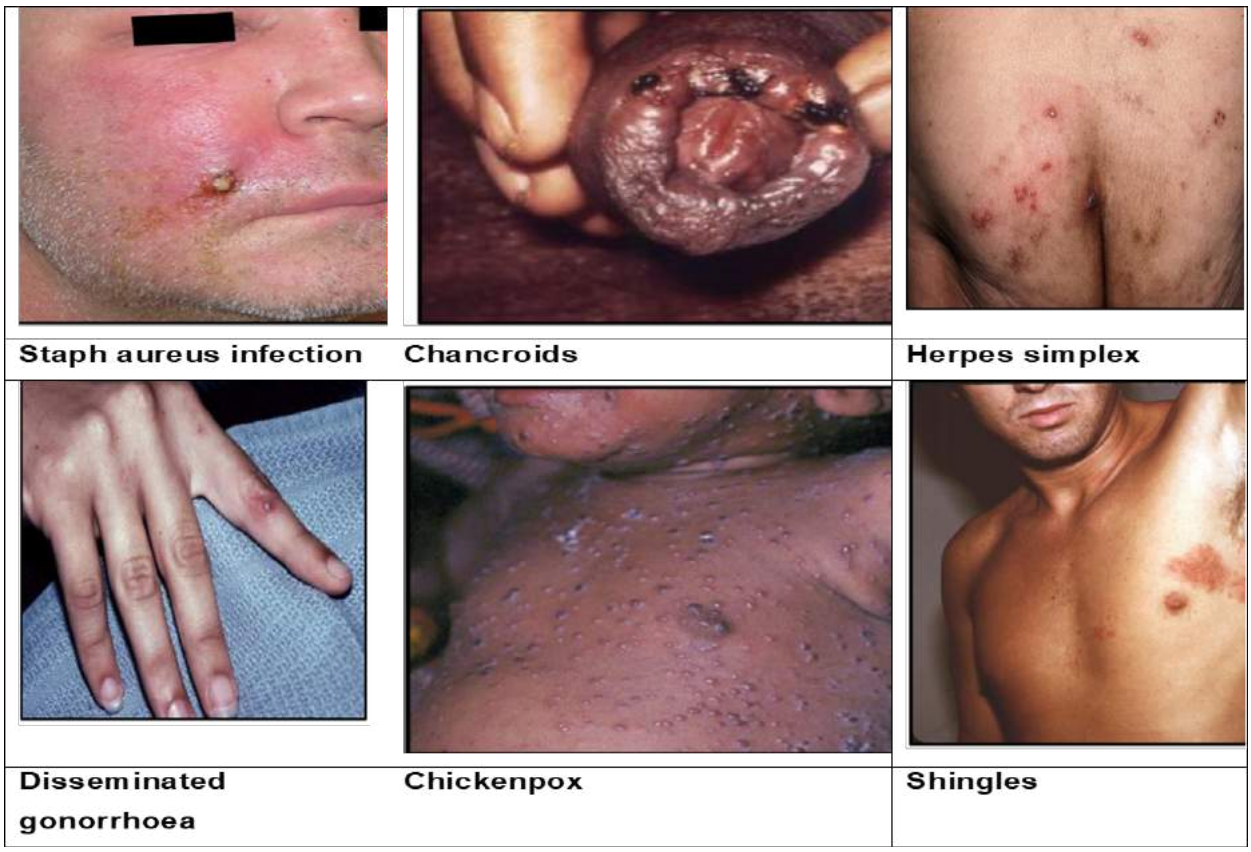


Figure 22: Comparing Mpox and other Vesicular Skin Lesions

Table 22: Comparison between Mpox, Chickenpox and Measles[49]

		Monkeypox	Chickenpox	Measles
Symptoms	Fever	1-3 days before rash	1-2 days before rash	3-5 days before rash
	Rash appearance	Lesions often in one stage of development	Lesions often in multiple stages of development	Lesions often in multiple stages of development
	Rash development	Slow	Rapid	Rapid
	Rash distribution	More dense on face; present on palms and soles	More dense on trunk; Absent on palms and sole	Starts on face and spreads, sometimes reaching hands and feet
	Lymphadenopathy	Present	Absent	Occasional
	Death	Up to 10%	Rare	Varies widely

[49] World Health Organization.Monkeypox: Epidemiology, preparedness and response for African outbreak contexts,29 August 2022.https://openwho.org/courses/monkeypox-intermediate

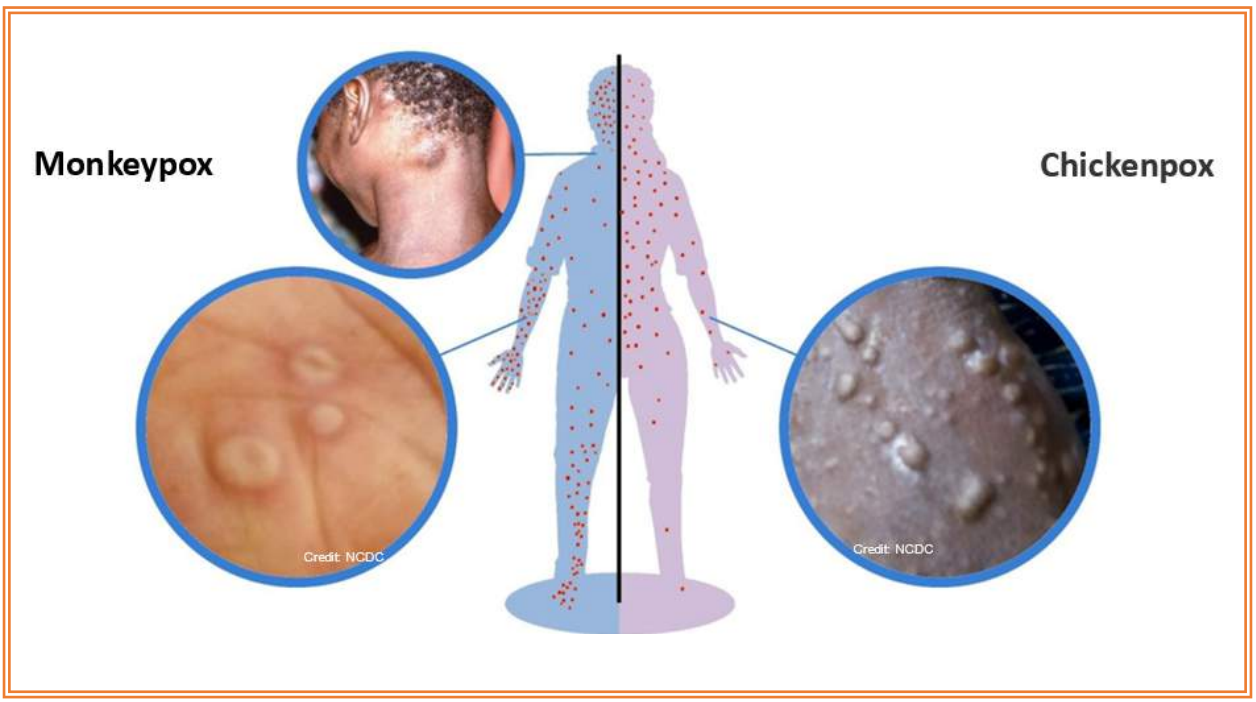


Figure 23: Pattern of Rash in Mpox vs Chickenpox

Diagnosis

1. Medical history. This includes travel history, and sexual practices
2. Lab tests for polymerase chain reaction (PCR) test skin lesion swabs
    - Specimen type Recommended specimen type is skin lesion material Swab of a lesion from any part of the body is acceptable if there is a visible lesion
    - Specimen collection Use two sterile synthetic swabs per lesion
    - Swab each lesion vigorously to collect adequate DNA
    - It is not necessary to de-roof the lesion before swabbing
3. Approximately 3 lesions per patient are suggested from different locations on the body or from lesions which differ in appearance
4. Biopsy. A biopsy involves removing a piece of skin tissue and testing it for the virus (Ballooning degeneration of keratinocytes, prominent spongiosis, dermal oedema, and cute inflammation)
5. Electron microscopy (Brick shape)
6. Anti Orthopoxvirus IgG and IgM

Severity Stratification and Assessment for Treatment

Uncomplicated Cases:

Majority will have a clinical course that is asymptomatic or only mildly symptomatic and need only supportive care.

- Antiviral Therapy not indicated for uncomplicated cases, but can provide symptomatic treatment
- Treat conditions affecting nutrition (mouth sores, vomiting, diarrhoea)
- Ensure patients eat and drink liquids: water, soups, teas, oral rehydration solution intravenous fluids if needed (Consider oral vitamin A, breast feeding, breast milk or infant formula according to the situation caregiver precautions, masks, hygiene for young patients)
- Ensure patient receives screening for HIV and other STIs
- Inform the patient of danger signs and when to seek urgent care
- Offer non-intrusive practical help to calm patient and family, keep them informed to know what to know, what to expect, how to care for themselves and how to take precautions

Complicated Cases or susceptible populations with risks for progression:

- Persons with severe disease (e.g., haemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalisation)
- Persons who may be at high risk of severe disease:
    - People with immunocompromising conditions (e.g., HIV/AIDS, leukaemia, lymphoma, chronic steroid use, malignancy, etc.)
    - Paediatric populations, particularly patients younger than 8 years of age
    - Pregnant or breastfeeding women
    - People with a history or presence of atopic dermatitis, people with other active exfoliative skin conditions
    - People with one or more complications
    - Persons with Mpox virus aberrant infections that include its accidental implantation in eyes, mouth, or other anatomical areas where Mpox virus infection might constitute a special hazard (e.g., the genitals or anus)

Table 23: Supportive Management for Patients with Mpox

Condition	Treatment objective	Treatment and care	Monitoring
Fever	Prevent and treat	External cooling or Antipyretic medications like paracetamol	Regular temperature monitoring
Skin infections	Prevent or treat secondary bacterial infections Promote lesion healing	Oral or intravenous antibiotics; incision and drainage Advanced wound management	Fever, pain, tenderness, erythema, oedema, exudate, warmth
Exfoliation, skin compromise	Avoid scratching Minimize insensible fluid loss Promote lesion healing	Wash with soap and water or Povidone-Iodine solution Moist dressings and topical antibiotics (e.g., Silver Sulfadiazine or Gentian violet) Surgical debridement, skin grafts	Lesion count/rash burden Skin turgor in non-affected areas Body weight Fluid intake/output
Eye infection	Prevent corneal scarring and visual impairment	Vitamin A supplementation Ophthalmic antibiotics/antivirals	Repeat examination and vision testing Slit lamp examination
Mouth and throat Sores	Minimize mucosal pain Encourage food intake Promote lesion healing	Oral/topical analgesic medications	Lesion burden Pain scale Food and fluid intake/output
Vomiting and diarrhoea	Minimize fluid loss Maintain nutrition	Oral or intravenous rehydration Oral or intravenous antiemetic Antidiarrheal medication	Frequency and volume of emesis and diarrhoea, body weight, skin turgor Food and fluid intake/output
Lymphadenopathy	Minimize pain Reduce swollen lymph nodes	An oral or intravenous analgesic or anti-inflammatory Medications	Size of lymph nodes Pain/tenderness
Respiratory symptoms or distress	Maintain open airways Prevent and treat infection Prevent and manage respiratory distress	Suctioning of nasopharynx and airways Incentive spirometry, chest physiotherapy Bronchodilation, nebulizer treatments Oral/intravenous antibiotics Oxygen, non-invasive ventilation (e.g., BiPAP or CPAP) Intubation and ventilation	Respiratory rate and other vital signs Signs of distress such as indrawing, shortness of breath Pulse oximetry
Sepsis	Restore haemodynamic stability	Oral/intravenous antibiotics Intravenous fluid hydration, vasopressors Supplemental Oxygen, Corticosteroids, Insulin	Pulse, blood pressure Fluid status

Targeted Management

Currently there is no treatment approved specifically for Mpox virus infections. However, antivirals developed for use in patients with smallpox may prove beneficial against Mpox. The following medical countermeasures are available

I. **Specific Treatment**
   a. Tecovirimat
   b. Vaccinia Immune Globulin Intravenous (VIGIV)
   c. Cidofovir
   d. Brincifovir
   e. Trifluridine and vidarabine eye drop/ ointments

Table 24: Targeted Therapeutics under Emergency Use Authorization for Mpox

Drugs	Tecovirimat (TPOXX Or ST-246)	Vaccinia Immune Globulin Intravenous (VIGIV)	Cidofovir
Route	Oral or IV	IV	IV
Current Use	Inhibits viral spread to uninfected cells by directly and specifically targeting the Orthopox virus protein F13 (VP37) which is involved in producing extracellular enveloped virions. Tecovirimat is available as a pill or an injection. For children who weigh less than 28.6 pounds, the capsule can be opened, and medicine mixed with semi-solid food	Currently licensed for complications due to vaccinia vaccination, including Eczema vaccinatum, VIG can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function for which smallpox vaccination following exposure to Mpox virus is contraindicated	Approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS)

II. Vaccination

JYNNEOS and ACAM2000 (JYNNEOS vaccine are the only vaccines approved)

Post-Exposure Vaccination (PEPV) Strategies[50]

- There are no efficacy data on PEPV with JYNNEOS for the current outbreak
- Vaccination may: prevent disease if given within 4 days of exposure
- Reduce disease severity if given between 4-14 days of exposure

[50] World Health Organization . Vaccines and immunisation for monkeypox: Interim guidance, 24 August 2022. https://www.who.int/publications/i/item/WHO-MPX-Immunization-2022.2-eng

Indications for Post Exposure Vaccine Strategies

- For people with confirmed exposure to Mpox through public health investigation, contact tracing, or risk exposure assessments
- For people with presumed exposure to Mpox such as a known sexual partner who was diagnosed with Mpox within the past 14 days
- Have had multiple sex partners in the past 14 days in an area with Mpox

JYNNEOS

- Replication-deficient Vaccinia virus licensed as a series of two subcutaneous injections, 4 weeks apart. Recommended as pre-exposure prophylaxis for laboratory and other personnel with occupational exposure to Orthopoxvirus. Booster doses are recommended every 2 years for those with exposure to Mpox. The only contraindication is a severe allergy to a vaccine component. Side effects include injection site reactions; serious side effects are rare. The vaccine can be given to people with HIV and immunocompromising conditions

ACAM200

- Live vaccine approved for smallpox. Given subcutaneously as two doses given 28 days apart. Yet to be approved by WHO for emergency use authorisation

Primary Preventive (pre-exposure) Vaccine (PPV)[51]

People who should get primary prevention vaccine include:

1. Clinical laboratory personnel who perform testing to diagnose Orthopoxviruses, including those who use polymerase chain reaction (PCR) assays for diagnosis of Orthopoxviruses, including Mpox virus
2. Research laboratory workers who directly handle cultures or animals contaminated or infected with Orthopoxviruses that infect humans, including Mpox virus, replication-competent Vaccinia virus, or recombinant Vaccinia viruses derived from replication-competent Vaccinia virus strains
3. Certain healthcare and public health response team members designated by public health authorities to be vaccinated for preparedness purposes

[51] World Health Organization. Vaccines and immunisation for monkeypox: Interim guidance, 24 August 2022. https://www.who.int/publications/i/item/WHO-MPX-Immunization-2022.2-eng

Mpox Prevention[52]

1. **Avoid close, skin-to-skin contact with people who have a rash that looks like Mpox**
   - Do not touch the rash or scabs of a person with Mpox
   - Do not kiss, hug, cuddle or have sex with someone with Mpox
2. **Avoid contact with objects and materials that a person with Mpox has used**
   - Do not share eating utensils or cups with a person with Mpox
   - Do not handle or touch the bedding, towels, or clothing of a person with Mpox
3. **Wash your hands often**
   - Wash your hands often with soap and water or use an alcohol-based hand sanitizer, especially before eating or touching your face and after you use the bathroom
4. **Avoid contact with animals that can spread the Mpox Virus**
   - Usually, rodents and primates
   - Avoid also sick or dead animals, as well as bedding or other materials they have touched

Infection Prevention and Control at Health Facilities

Implementation of appropriate IPC measures is essential to mitigate and control risks of transmission of Mpox in health care and community settings. It is critical to ensure that basic IPC standards are put in place at the national and health facility level to provide minimum protection to patients, health workers, caregivers and visitors and thereby protect the community. Health workers should always follow standard precautions and perform a risk assessment to evaluate the need to use additional transmission precautions.

Standard precautions include:

- Hand hygiene
- Respiratory hygiene and cough etiquette patient placement
- Personal protective equipment aseptic technique

Safe injections and sharps injury prevention environmental cleaning and disinfection handling of laundry and linen

- Decontamination and reprocessing or reusable patient care items
- Equipment waste management
- Use of condoms

52 CDC.2022.Monkeypox prevention. https://www.cdc.gov/poxvirus/monkeypox/prevention/protect-yourself.html.July 2022.

IPC considerations for suspected patients with Mpox

Contact and droplet precautions should be implemented for any suspected Mpox patients. In addition to contact and droplet precautions, airborne precautions should be implemented if varicella zoster virus (i.e. chickenpox) is suspected and until it is excluded.

Key issues:

- Health workers should perform hand hygiene according to the WHO Your 5 moments for hand hygiene, including prior to putting on and after removing PPE
- If varicella zoster virus (i.e. chickenpox) is suspected, place the patient in an airborne infection isolation room with a dedicated bathroom or toilet
    - If an airborne infection isolation room is not available, place patient in a well-ventilated single room with a dedicated bathroom or toilet and keep the door closed
    - Health workers should wear the following PPE: gloves, gown, respirator (e.g., N95, FFP2) and eye protection
    - Isolation room/area should have signage posted at the entrance indicating that patient is under contact/droplet/airborne precautions and the required PPE in the correct order for health workers
    - When varicella zoster virus (i.e. chickenpox) is not suspected, place a patient in a well-ventilated single room with a dedicated bathroom or toilet
    - Health workers should wear PPE according to the PPE recommendation for confirmed patients (gown, gloves, respirator (e.g., N95, FFP2) and eye protection)
- Health workers should be trained on procedures for safe putting on and removing PPE
- Use dedicated footwear that can be decontaminated Disposable shoe covers are not recommended
- Instruct the patient to wear a well-fitting medical mask and follow respiratory hygiene and cough etiquette when transport is necessary
- Avoid unnecessary movement of suspect patients. If the suspect patient must be moved or transported within or beyond the facility, ensure transmission-based precautions are maintained (droplet/contact/airborne), place a well-fitting medical mask on the patient and cover lesions
- The receiving facility/ward/unit should be aware that transmission-based precautions are required and, pending arrival, the need to prepare the isolation or designated area

IPC considerations for confirmed patients with Mpox

Contact and droplet precautions be implemented for any confirmed patient with Mpox. In addition to contact and droplet precautions, respirators should be used.

Remarks:

- Place patient in a well-ventilated, single-patient room with a dedicated bathroom or toilet
- Isolation room/area should have signage posted at the entrance indicating contact/droplet precautions Wear PPE including gloves, gown, a respirator (e.g., N95, FFP2) and eye protection
- If single patient rooms are not available, consider cohorting confirmed cases, maintaining a distance of at least 1m between patients
- Use dedicated footwear that can be decontaminated Disposable shoe covers are not recommended Health workers should be trained on procedures for safe donning and doffing of PPE
- Cover exposed lesions when others are in the room and if the patient can tolerate
- Avoid unnecessary movement of confirmed patients. If the patient must be moved or transported within or beyond the facility, ensure transmission-based precautions are maintained, place a well-fitting medical mask on the patient and cover lesions (provided the patient is able to tolerate)
- The receiving facility/ward/unit should be aware that transmission-based precautions are required and, pending arrival, the need to prepare the isolation or designated area
- Precautions should remain in place until lesions have crusted, scabs have fallen off and a fresh layer of skin has formed underneath
- Severe cases (including immunosuppressed) who may experience prolonged viral shedding from the upper respiratory tract may require clinical evaluation to determine when transmission-based precautions may be discontinued

Airborne precautions must be implemented if aerosol-generating procedures (AGPs) are performed. **Important:** AGPs should be performed in an Airborne Infectious Isolation room. If this room is not available or if it is not feasible, perform AGPs in a well-ventilated, single-patient room with the door closed. Health workers should wear a respirator (e.g., N95, FFP2) as well as eye protection, a gown and gloves when performing AGPs

IPC Considerations in the Community

Patients with mild, uncomplicated Mpox cared for at home should be isolated in an area separate from other household members and away from shared areas of the home (i.e. a separate room, or area with a curtain or screen).

Key issues:

- Patients at home with should be able to manage their self-care Clinical follow up should be conducted using methods other than in-person visits (e.g., telemedicine, telephone)
- Designate one person to facilitate the self-care of the patient with mild, uncomplicated Mpox: preferably someone who is in good health, has no underlying chronic conditions and has had previous smallpox vaccination or Mpox virus infection
- The patient with Mpox should stay in a dedicated, well-ventilated room (e.g., with windows that can be opened frequently) separate from others in the household
- Household members and patients with Mpox should clean their hands with soap and water or an alcohol-based hand sanitizer frequently. In addition, household members should avoid entering the room
- If the designated person that is facilitating self-care needs to enter the isolation area, they should maintain a distance of at least 1m from the patient When distance cannot be maintained, the designated person is to wear a well-fitting medical mask and disposable gloves. They should practice standard precautions at all times

Caution should be taken when handling and cleaning linens, and household surfaces and during waste disposal.

Laboratory Guidance

Interim guidance on sample collection - Collect these 4 sample types per patient:

1. Lesion fluid on a swab
2. Scabs/roofs of the lesions as tissue, (2 lesions of the same type, preferably from different locations on the body and which differ in appearance, should be collected in one (1) single tube)
3. EDTA blood, 4ml. Where possible or if delay in transportation is anticipated, this can be centrifuged to obtain plasma. Team can also collect and send serum if EDTA tube not available
4. Urine whenever this is practical. Urine samples should be collected using aseptic technique into a sterile collection tube

NOTE:

- Sample types 1 & 2 should be placed in separate viral transport media tubes (the ones used for COVID-19)
- Swab the lesion vigorously to ensure adequate viral DNA is collected
- Lesions, crusts and fluids should not be mixed in the same tube

- Specimens collected for MPXV investigation should be refrigerated (2-8 deg C) or frozen (-20 or lower) within 1 hour after collection
- All samples being transported should have appropriate triple packaging, labelling and documentation (duly completed lab request form)
- Samples should be sent to the Zambia National Public Health Institute Reference Laboratory (ZNPHRL)
- Contact ZNPHRL prior to sample shipment and for further guidance on sample management

Packaging

Transport of infectious substances requires a basic triple packaging system. It consists of three layers as follows:

- Primary receptacle - a primary watertight leak-proof receptacle containing the specimen. The receptacle is packaged with enough absorbent material to absorb all fluid in case of breakage
- Secondary packaging - a second durable, watertight, leak-proof packaging to enclose and protect the primary receptacle(s). Several cushioned primary receptacles may be placed in one secondary packaging, but sufficient additional absorbent material shall be used to absorb all fluid in case of breakage
- Outer packaging - secondary packaging is placed in outer shipping packaging with suitable cushioning material. Outer packaging protects contents from outside influences, such as physical damage, while in transit

Each completed package is normally required to be marked, labelled and accompanied with appropriate shipping documents (as applicable)

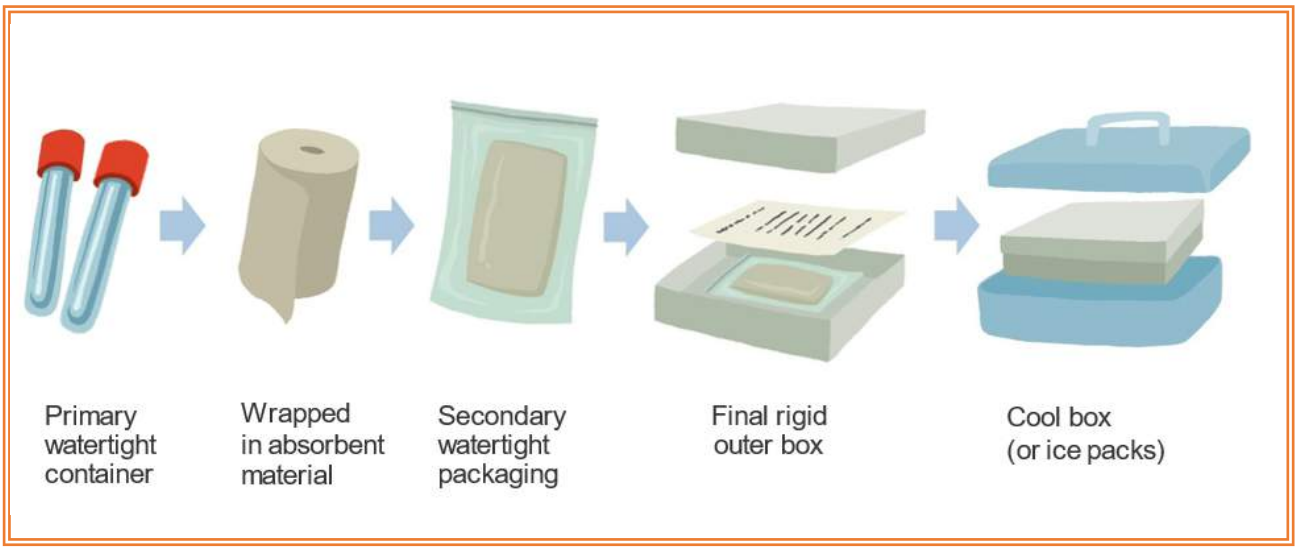


Figure 24: WHO Basic Triple Packaging

References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020 Jan 29.
2. Wei-jie Guan, Zheng-yi Ni, Yu Hu, Wen-hua Liang et al. Clinical characteristics of 2019 novel coronavirus infection in China. *New England Journal of Medicine* doi: 10.1056/NEJMoa2002032
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020 Jan 24.
4. Wang D, Hu B, Hu C, Zhu F, Liu X et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan. Published online February 7, 2020.
5. Chen N, Zhou M, Dong X, Qu J, Gong F. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020 Jan 30. [Epub ahead of print]
6. Chan JF, Yuan S, Kok K, To KK, Chu H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020 Jan 24. [Epub ahead of print]
7. Kate Feldman. Newborn baby diagnosed with Coronavirus in London. New York Daily News. Mar 15, 2020. 10:24 AM
8. Yaron Steinbuch. Chinese baby tests positive for coronavirus 30 hours after birth. New York Post. February 5, 2020. 09:22 AM
9. Chang D, Minggui L, Wei L, Lixin X, Guangfa Z et al. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan China. Published online February 7, 2020.
10. Zhu N, Zhang D, Wang W, Li X, Yang B, et al; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020 Jan 24. [Epub ahead of print]
11. Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT et al. Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. *N Engl J Med.*2020 Jan 28. doi: 10.1056/NEJMc2001272. [Epub ahead of print]
12. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020 Jan 31. doi: 10.1056/NEJMoa2001191. [Epub ahead of print] Huang C, Wang Y, Li X, Ren L, Zhao

J, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020 Jan 24. [Epub ahead of print]

13. Lei J, Li J, Li X, Qi X. CT Imaging of the 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiology*. 2020 Jan 31:200236. doi: 10.1148/radiol.2020200236. [Epub ahead of print]
14. Memish ZA, Assiri AM, Al-Tawfiq JA. Middle East respiratory syndrome coronavirus (MERS-CoV) viral shedding in the respiratory tract: an observational analysis with infection control implications. *Int J Infect Dis*. 2014 Dec; 29:307-8.
15. Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet*. 2015 Sep 5;386(9997):995-1007. doi: 10.1016/S0140-6736(15)60454-8. Epub 2015 Jun 3. Review.
16. Chan KH, Poon LL, Cheng VC, Guan Y, Hung IF et al. Detection of SARS coronavirus in patients with suspected SARS. *Emerg Infect Dis*. 2004 Feb;10(2):294-9.
17. Cheng PK, Wong DA, Tong LK, Ip SM, Lo AC et al. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. *Lancet*. 2004 May 22;363(9422):1699-700.
18. Hung IF, Cheng VC, Wu AK, Tang BS, Chan KH et al. Viral loads in clinical specimens and SARS manifestations. *Emerg Infect Dis*. 2004 Sep;10(9):1550-7.
19. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, et al; HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet*. 2003 May 24;361(9371):1767-72.
20. Liu W, Tang F, Fontanet A, Zhan L, Zhao QM et al. Long-term SARS coronavirus excretion from patient cohort, China. *Emerg Infect Dis*. 2004 Oct;10(10):1841-3.
21. Corman VM, Albarrak AM, Omrani AS, Albarrak MM, Farah ME, et al. Viral Shedding and Antibody Response in 37 Patients With Middle East Respiratory Syndrome Coronavirus Infection. *Clin Infect Dis*. 2016 Feb 15;62(4):477-483.
22. Al-Abdely HM, Midgley CM, Alkhamis AM, Abedi GR, Lu X, et al. Middle East respiratory syndrome coronavirus infection dynamics and antibody responses among clinically diverse patients, Saudi Arabia. *Emerg Infect Dis*. 2019 Apr;25(4):753-766.
23. Al-Abdely HM, Midgley CM, Alkhamis AM, Abedi GR, Tamin A et al. Infectious MERS-CoV Isolated From a Mildly Ill Patient, Saudi Arabia. *Open Forum Infect Dis*. 2018 May 15;5(6):ofy111
24. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and Chloroquine effectively inhibit the recently emerged novel coronavirus

(2019-nCoV) in vitro. *Cell Res*. 2020 Feb 4. doi: 1038/s41422-020-0282-0. [Epub ahead of print] PubMed PMID: 32020029.

25. Jianjun Gao, Zhenxue Tian, Xu Yang. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *BioScience Trends* advance publication. DOI:10.5582/bst.2020.01047
26. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, et al; Saudi Critical Care Trial Group. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med*. 2018 Mar 15;197(6):757-767.
27. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020 Feb 6; S0140-6736(20)30305-6.
28. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev 2016;3:CD010406.
29. Delaney JW, Pinto R, Long J, et al. The influence of corticosteroid treatment on the outcome of influenza A(H1N1pdm09)-related critical illness. Crit Care 2016;20:75.
30. Maitland K, et al. "Mortality after fluid bolus in African children with severe infection". *The New England Journal of Medicine*. 2011. 364(26):2483-2495. PubMed • Full text • PDF
31. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3: e343
32. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab and etesevimab. 2021. Available at: https://www.fda.gov/media/145802/download. Accessed February 17, 2021.
33. Dougan M, Nirula A, Gottlieb RL, et al. Bamlanivimab+etesevimab for treatment of COVID-19 in high-risk ambulatory patients. Conference on Retroviruses and Opportunistic Infections. 2021. Virtual. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/resources/2021/ vCROI-2021-Abstract-eBook.pdf.
34. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate COVID-19. *N Engl J Med*. 2021; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34260849.
35. Clinical management of COVID-19 INTERIM GUIDANCE. Accessed 28/05/2020. [Available at:https://apps.who.int/iris/bitstream/handle/10665/332196/WHO-2019-nCoV-clinical-2020.5-eng.pdf
36. Therapeutics and COVID-19: living guideline - World Health Organization (WHO): WHO/2019-nCoV/therapeutics/2021.2

37. Zeraatkar D, Cusano E, Diaz Martinez JP, Qasim A, Mangala S, Kum E, et al. Tocilizumab and Sarilumab alone or in combination with corticosteroids for COVID-19: a systematic review and network meta-analysis. 2021

38. The WHO Rapid Evidence Appraisal for COVID-19 Therapies [REACT] Working Group Association of administration of interleukin-6 antagonists with mortality and other outcomes among hospitalised patients with COVID-19: a prospective meta-analysis. JAMA 2021

39. World Health Organization. Monkeypox: Epidemiology, preparedness and response for African outbreak contexts,29 August 2022. https://openwho.org/courses/monkeypox-intermediate

40. CDC.2022.https://www.cdc.gov/travel/diseases/monkeypox#:~:text=Who%20is%20at%20risk%3F,higher%20risk%20of%20getting%20infected.

41. World Health Organization. Multi-country outbreak of monkeypox, External situation report #4 - 24 August 2022 https://www.who.int/publications/m/item/multi-country-outbreak-of-monkeypox--external-situation-report--4---24-august-2022

42. Monkeypox Outbreak: Global Trends. Geneva: World Health Organization, 2022. Available online: https://worldhealthorg.shinyapps.io/mpx_global/ (last cited: [12 September 2022]

43. World Health Organization.Monkeypox.4 August 2022. https://www.who.int/news-room/questions-and answers/item/monkeypox

44. World Health Organization. Monkeypox Surveillance https://www.who.int/publications/i/item/WHO-MPX-Surveillance-2022.

45. CDC.2022.Monkeypox prevention. https://www.cdc.gov/poxvirus/monkeypox/prevention/protect-yourself.html.July 2022.

46. N Engl J Med 2022; 387:679-691DOI: 10.1056/NEJMoa2207323

47. World Health Organization. Vaccines and immunization for monkeypox: Interim guidance, 24 August 2022. https://www.who.int/publications/i/item/WHO-MPX-Immunization-2022.2-eng